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Evaluation of Cyproheptadine Hydrochloride Effects on Weight Gain in Underweight Children with Anorexia; A Randomized Clinical Trial

Seyed Alinaghi Kazemi[1], Maedeh Khosravi Yekta[2], Ramazan Fallah[3], Diana Noemi Diaz[4], *Kambiz Eftekhari[5]

[1]Professor of Pediatric, Pediatric Department, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran. [2]Assistant of Pediatric, Pediatric Department, Mousavi Hospital, Zanjan University of Medical Science, Zanjan, Iran. [3]Biostatistics, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran. [4]Assistant Professor of Pediatric Surgery, Surgery Department, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran. [5]Assistant Professor of Pediatric Gastroenterology, Pediatric Department, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background: Cyproheptadine hydrochloride is an antihistaminic drug. Appetite stimulation is one of its secondary effects that can be of advantage in some diseases. In this study we investigated the effect of Cyproheptadine hydrochloride on weight gain in underweight children with anorexia at age group 2 to10 years old.

Materials and Methods: In this randomized clinical trial, we selected 2-10 year-old underweight children with anorexia who referred to Ayatollah Mousavi Hospital in Zanjan (Iran), during 2015. One hundred and thirty-six children were allocated at random in two groups. The Cyproheptadine - treated children group were given the drug orally; 0.1 mg/kg/dose three times per day for 8 weeks, while patients in placebo group received placebo with the same dose. After two months, weight gain was compared with the previous values in both groups.

Results: In this study, 86 patients (63.2%) were female. The average increase in weight in the cyproheptadine - treated group was significantly higher than in the placebo group (1.08 ± 0.67 kg and 0.22 ± 0.46 kg, respectively) (p=0.005). The average increase height in the Cyproheptadine -treated group was significantly higher than in the placebo group (1.60 ± 0.97 cm, and 0.86 ± 0.85 cm, respectively) (p=0.005). According to the parents of both groups, anorexia in the Cyproheptadine - treated group improved in 100%, and in the placebo group in 52.7%. This difference was statistically significant (p=0.005). No any side effects of Cyproheptadine hydrochloride were observed.

Conclusion: According to the finding of our study, there were no serious side effects of Cyproheptadine hydrochloride. Therefore considering the acceptable safety of Cyproheptadine hydrochloride for inducing growth in underweight children, we propose its administration with the aforementioned dose.

Key Words: Anorexia, Children, Cyproheptadine hydrochloride, Weight gain.

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Corresponding Author:

Kambiz Eftekhari, MD, Mailing Address: Pediatric department, Bahrami Children's Hospital, Tehran, Iran. Fax: +982177568809

Email: dr_k_eftekhary@yahoo.com

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1- INTRODUCTION

Cyproheptadine hydrochloride is an antihistamine drug, antagonist of histamine and serotonin (1). The drug was approved by Food and Drug Administration (FDA) for the treatment of allergic rhinitis, allergic conjunctivitis, urticaria, dermatographism and mild angioedema in children (1, 2). Clinicians used Cyproheptadine hydrochloride in some diseases due to its effects on appetite stimulation. Some studies described unexplained weight gain after ingestion of Cyproheptadine hydrochloride (3, 4). There is no objective method for assessing appetite in children yet (2). The cause of anorexia is probably multifactorial (2).

There is a lot of difference between appetite and weight gain among the general population (2, 3). However, it can be assumed that increased appetite causes weight gain (2). Stimulation of appetite is one way to deal with anorexia (2). Several articles depict that consumption of Cyproheptadine hydrochloride as an appetite stimulator was useful for patients with asthma, failure to thrive (FTT), short stature, anorexia nervosa, cystic fibrosis and some types of cancers (1, 4-7). Usually these types of antihistamines have not serious or life-threatening side effects. The most important side effect of them is transient drowsiness (4, 8).

The results on treatment of anorexia with Cyproheptadine hydrochloride in patients with acquired immune deficiency syndrome (AIDS) and asthma were different (9). Among the drugs used to treat anorexia in underweight children is Megestrol acetate (MA), Dronabinol, mirtazapine and Cyproheptadine hydrochloride (9, 10). Most studies were done on Megestrol acetate, showed a positive effect on weight gain, increasing appetite and fat mass (10). In 1993 Megestrol Acetate was approved for treat cachexia, loss of appetite or unexplained weight loss. However, it was demonstrated that is not a safe drug, with serious side effects including edema, thromboembolic events and sudden deaths (11). Other side effect of the drug is the suppression of the adrenal axis, impaired glucose regulation, mood disorders, hyperlipidemia and testicular damage (1, 10). Therefore Cyproheptadine hydrochloride is safer (8, 12- 14) and more effective than Megestrol acetate to treat cachexia in patients undergoing chemotherapy (10, 11).

There is limited knowledge on the mechanisms of action of Cyproheptadine hydrochloride and its side effects. Rerksuppaphol et al. investigated the effect of this drug in children with malnutrition. Theirs results showed that weight gain in the group treated with Cyproheptadine hydrochloride was significantly higher than in the control group. No significant difference was observed between the groups in terms of fat percentage. Some side effects were rarely observed, like mild drowsiness, nausea, diarrhea, abdominal pain and headache but serious side effects were not reported and the drug was well tolerated (15).

The Iranian study reported a significant effect of Cyproheptadine hydrochloride in children with malnutrition aged 24 to 64 months during 4 weeks treatment. In this study the average weight gain in children treated with the drug compared to placebo was 0.60 and 0.11 kg respectively (16).

Anorexia and growth disturbance are the common problems in children that referred to the pediatric gastroenterology clinic. Most appetite stimulants in children have serious side effects (1, 10). Therefore, we aimed to investigate the effect of Cyproheptadine hydrochloride on weight gain with low side effects (8, 12-14). The purpose of our study was to evaluate the effect of Cyproheptadine hydrochloride on weight gain in underweight children with anorexia (below the 50th percentile) aged

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2-10 years compared with the control group in Zanjan city, Iran.

2- MATERIALS AND METHODS

2-1. Study design and population

This study is a double blind cross over randomized clinical trial. Children from 2 to 10 years old participated in 2015. They had been brought to the pediatric gastroenterology clinic of Ayatollah Mousavi Hospital in Zanjan (Iran) because of anorexia and underweight (under 50th percentile). Anorexia was considered as valuable when accompanied by a weight less than 50% and only parents' complaint did not have enough.

2-2. Inclusion and Exclusion criteria

Inclusion criteria included: children aged 2-10- year-old with anorexia and underweight (below the 50th percentile), without a justifiable condition for proper growth retardation, including underlying gastrointestinal, cardiovascular, respiratory, endocrine and metabolic, neurological or renal diseases. Exclusion criteria include: Children that were not taking Cyproheptadine hydrochloride completely and regularly were withdrawn from the study; if adverse drug reactions occurred; if used another medication interacting with Cyproheptadine, and identification of underlying organic disease.

2-3. Measuring tools and measurement

Questionnaires were completed with the cooperation of parents, which included demographic information (age, gender, developmental status, positive findings in physical examination). The weight was measured using a digital column scale (Seca 769, made in Germany) with an up to 100 grams sensitivity and height measured using a wall-mounted metal height gauge, according to scientific principles. The assessment of children's appetite in the study was done by asking their parents.

2-4. Intervention

The Sample size was one hundred and thirty-six patients for both groups. Written informed consent was taken from parents to participate in the study. The demographic data and results of the study were collected and a questionnaire was prepared. The sample size was calculated according to following formula:

$$n = \frac{\left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right]^2 \left[\sigma_1^2 + \sigma_2^2 \right]}{d^2} = 68$$

σ_1^2 = 4 (the variance of the children's weight without any intervention),

σ_2^2 = 9 (the variance of the children's weight with intervention),

α = 0.05, β = 0.2, d = 1.5 (the difference of mean weight in two groups).

The patients were allocated by using a simple randomized method in two groups (68 patients in each group). The first group was Cyproheptadine - treated who received oral Cyproheptadine hydrochloride (named Trustorix manufactured by Tadbir Kalaye Jam, Iran [Tekaje]) during 8 weeks with a dose of 0.1 mg/kg (Equal to 0.25 cc/kg) 3 times a day. The second group was the placebo and received placebo with a dose of 0.25 cc/kg 3 times a day.

Dietary recommendations were given to all patients, including the use of high-protein and home-made foods avoiding snacks and industrial drinks. Weight, height and appetite condition in each child were measured at the end of each month, compared with their initial values and with the values obtained in the placebo group. After that, questionnaires that include weight, height, and appetite status before and after the study were filled. Parents were informed about the side effects of

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Cyproheptadine hydrochloride such as drowsiness, nausea, diarrhea, abdominal pain and headache and they were asked to contact the researcher if any of these effects appeared.

2-5. Data analysis

Data were analyzed by SPSS software (version 22.0). The descriptive results were expressed as frequency, percentage, mean and standard deviation. The results were analyzed used with chi-square tests and variances analysis of covariance (ANCOVA). The normality of the data was obtained using the Kolmogorov-Smirnov test. The *P* values less than 0.05 were considered statistically significant.

2-6. Ethical consideration

The study was approved by the ethics committee of Zanjan University of Medical Sciences on 2014 with Number ZUMS.REC.1392.192. Registry code in a clinical trial registry center (IRCT) is IRCT.2014101318971N3.

3- RESULTS

In this study participated 136 children aged 2-10 years old. Of these, 86 patients (63.2%) were female. Forty-four (51.2%) girls and 24 (48.0%) boys were in the intervention group. The groups were matched in gender and did not have a significant statistical difference ($p = 0.722$). All patients were followed up until the end of the study and none of them was excluded from the study.

The mean and standard deviation (SD) of age in the Cyproheptadine -treated and placebo groups were 4.7 ± 2.7 and 6.7 ± 2.7 years, respectively. The mean and standard deviation (SD) of primary weight in the Cyproheptadine -treated group and placebo group were 15.2 ± 5.7 and 18.9 ± 6.6, respectively. The mean and standard deviation (SD) of primary height in the Cyproheptadine -treated group and placebo group were 113.8 ± 17.3 and 100.9 ± 17.3, respectively. The mean age, primary weight and height of children (**Table.1**) were statistically different in the two groups ($p <0.05$).

In the study, according to **Table.2**, the mean and standard deviation (SD) of the children's weight difference in the Cyproheptadine -treated group were 1.08 and 0.67 kg, respectively and in the placebo group 0.22 and 0.46 kg, respectively. By controlling the age of children with using of covariance analysis (age of children was not match in two groups), this difference was statistically significant ($p <0.05$).

The mean and standard deviation of the children's height difference in the Cyproheptadine -treated group were 1.60 and 0.97cm, respectively and in the placebo group were 0.86 and 0.85cm, respectively. By controlling the age of children using covariance analysis, this difference was statistically significant ($p <0.05$). At the end of the study (two months later), anorexia in the Cyproheptadine -treated group improved in 100%, and in the placebo group in 52.7%. This difference was statistically significant ($p <0.05$).

According to the table, mean weight difference with normal appetite and SD were 1.14 and 0.80 kg respectively. The mean weight variation in the Cyproheptadine -treated group was greater than in the placebo group. This difference was statistically significant ($p=0.005$). No any side effects of Cyproheptadine hydrochloride were observed.

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Table-1: Comparison of mean age, primary weight and height of children in two groups

Variables	Groups	Number	Mean	Standard Deviation	P-value
Age	Cyproheptadine	68	4.7	2.7	< 0.05
	Placebo	68	6.7	2.7	
Primary weight	Cyproheptadine	68	15.2	7.5	0.001
	Placebo	68	18.9	6.6	
Primary height	Cyproheptadine	68	100.9	17.9	< 0.05
	Placebo	68	113.8	17.3	

Table-2: Comparison of children's weight and height difference in two groups with age control (covariance analysis).

Variables	Groups	Number	mean	Standard Deviation	P-value
Weight difference	Cyproheptadine	68	1.08	0.69	< 0.05
	Placebo	68	0.22	0.46	
Height difference	Cyproheptadine	68	1.60	0.97	< 0.05
	Placebo	68	0.86	0.85	

4- DISCUSSION

The aim of this study was to evaluate the effect of Cyproheptadine hydrochloride on weight gain in underweight children with anorexia (below the 50th percentile) aged 2-10 years. The study was followed up for 2 months after the intervention. In the study, children in the Cyproheptadine -treated group showed significant weight and height gain compared to the placebo group. Both groups were matched in terms of gender but not matched in terms of age. The confounding factor was removed using analysis of covariance. Similar to our study, Najib, found that Body Mass Index (BMI) was significantly higher in Cyproheptadine -treated group than placebo group after 8 weeks of treatment (16). The average weight gain was 0.60 kg, which is lower than our results (1.80 kg). Our sample size is larger than their, 136 and 77 people, respectively. On the other hand, the age range of children in our study was wider than Najib's et al., as they studied only children 24 to 64 months. Also due to the double-blind study the results were being less influenced by confounding factors. Rerksuppaphola and Rerksuppaphol treated 37 underweight children aged 6-15 years old randomly with Cyproheptadine hydrochloride for 8 weeks (15). In this study, definitive weight gain in the case group was coincident with our results (1.25 and 0.65 kg, respectively). But weight gain was slightly higher than our study. This difference can be attributed to differences in age range and race of participants. On the other hand, their sample size was lower than ours.

Homnick et al. performed a study on 16 children with Cystic fibrosis (CF) (4). Patients receiving Cyproheptadine hydrochloride had significantly higher weight gain than the other group (3.45 kg vs. 1.1 kg). Of course the dose of Cyproheptadine hydrochloride was 4 mg at 4 times a day and the results of weight gain were evaluated after 12 weeks. They did not record any side effect. We decided to be more conservative. Couluris et al. investigated the effect of Megestrol acetate and Cyproheptadine hydrochloride in 66 children with cachexia due to chemotherapy (1). They showed that Cyproheptadine hydrochloride was safer and more effective than Megestrol acetate

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to gain weight in these children. Megestrol acetate had some side effects such as decreased level of cortisol and hyperlipidemia. Compared with her study, our sample size was higher. Marchand and colleagues compared the therapeutic effect of Cyproheptadine hydrochloride with Megestrol acetate, demonstrating that Cyproheptadine hydrochloride is safe and had little side effects (17). This finding was consistent with our study. They studied malnourished CF patients (17). The average weight gain in the case group and control group was 3.05 kg and 0.3 kg, respectively. The patients benefited from Megestrol acetate treatment, gained weight and improved the results of the respiratory tests. Unfortunately some side effects appeared, such as adrenal suppression, glucose intolerance and diabetes mellitus

Since few researchers have evaluated the effect of Cyproheptadine hydrochloride on weight gain in children without underlying disease, no additional references are available to compare with the results of present study. Most of these studies have been done on underweight children with an underlying disease. The strength of this study is the novelty of the idea. It can be concluded that the use of Cyproheptadine hydrochloride for appetite stimulation produces significant increase in weight and height in children and have less side effects.

4-1. Limitations of the study

From the limitations of the study, which is one of its weaknesses were did not evaluate some factors such as duration of weight loss and previous treatments to improve growth.

5- CONCLUSION

According to the finding of our study, there were no serious side effects of cyproheptadine hydrochloride. Therefore due to the safety of it to promote weight gain in underweight children it can be used in appropriate dose for children under 50th percentile with anorexia.

6- CONFLICT OF INTEREST

The Authors had no conflict of interest. The study had no funding source and only was supported by Vice-Chancellor's Office for Research at Zanjan University of Medical Sciences, Zanjan, Iran.

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