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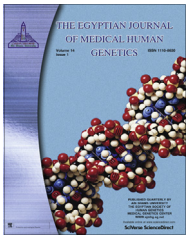

ORIGINAL ARTICLE

Conservative therapy versus intra-gastric balloon in treatment of Prader-Willi Syndrome morbid obesity

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KEYWORDS

Intra-gastric balloon;
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Abstract *Background and purpose:* Prader-Willi Syndrome (PWS) is a complex multisystemic disorder characterized by hyperphagia, severe obesity and muscular hypotonia. So, it is essential to seek an ideal program to help in solving such a widespread problem. The purpose of this study was to investigate the effect of conservative therapy (diet and exercises) versus intra-gastric balloon in PWS patients. Ten children born with PWS from both sexes ranging in age from 8 to 15 years were assigned into two groups of equal number. Study group I received conservative therapy in the form of diet regimen (a low caloric diet) and aerobic exercises on a stationary bicycle while study group II underwent intra-gastric balloon. Evaluation procedures in the form of initial evaluation and measurement of Body mass index (BMI) and lipid profile parameters were conducted for each child of the two groups before and after 6 months of treatment. The results revealed no significant difference when comparing the pre-treatment mean values of the two study groups (I and II), while significant improvement was observed in all the measuring variables of the two groups when comparing their pre- and post-treatment mean values. Significant difference was also observed when comparing the post-treatment results of the two groups in favor of the study group I. It concluded that conservative therapy could be the first choice of treatment of PWS morbid obesity, while BioEnterics Intra-gastric balloon (BIB) came in the second choice.

1. Introduction

Prader-Willi Syndrome (PWS) is a genetically determined disorder that affects approximately one in 14,000 people of both genders. The genetic basis is the absent expression of the paternally active genes in the PWS critical region on chromosome 15 [1]. It is characterized by muscular hypotonia, ligament laxity, hyperphagia, severe obesity, short stature, hypogonadism, and dysmorphic features. Both hypotonia and excessive body weight may affect the development of motor and functional skills of PWS individuals. A central feature of the syndrome is an excessive appetite, with overeating behavior apparent as early as 2 years of age. In addition, people with PWS usually require special help at school, due to the presence of mild learning disabilities, as well as having a short stature and other phenotypic characteristics [2]. A proposed pathophysiological

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explanation for the overeating behavior is hypothalamic dysfunction with failure of the feedback mechanism which would normally lead to feelings of fullness and loss of feelings of hunger after eating [3].

The most widely accepted definition of obesity relates to the body mass index (BMI): weight (kg)/height (m^2). Children above the 85th percentile are classified overweight and those above the 95th percentile, obese [4].

Caloric restriction has remained as the ministry of treatment of obesity. It improves most of the lipid abnormalities. One of the best ways to achieve healthier weight is to adopt a healthful diet with an energy intake that does not exceed expenditure, is low in fat, and provides adequate amounts of all food groups, including whole grains and cereals, fruits and vegetables [5].

Physical activity is recognized as an integral part of obesity treatment with other therapeutic means, Exercise is an activity requiring physical exertion done for the sake of health. Exercises use a variety of muscle groups continuously and rhythmically, increasing heart rate and breathing. Specific aerobic activities include walking, jogging, bicycling, swimming, tennis and cross-country skiing [6].

Surgical treatment of obesity is based on two techniques gastric – restricting technique (gastric band, stapling, and balloon) and gastric restricting and malabsorptive technique (Gastric bypass) [7].

BioEnterics Intra-gastric balloon (BIB). It is a liquid-filled, intragastric balloon model that decreases preprandial hunger, increases postprandial satiety, and promotes weight loss in the short term [8]. Additionally, the intra-gastric balloon is thought to help individuals to modify their eating habits by providing a self-education tool [9].

A clinical trial was conducted on PWS patients to compare between the effects of conservative therapy in the form of diet regimen (a low caloric diet) plus aerobic exercises on a stationary bicycle and intra-gastric balloon in reducing patients' weight.

2. Patients and methods and procedures

2.1. Patients

Ten PWS patients from both sexes were eligible for participation according to the following criteria: their ages ranged from 8 to 15 years, they had a body mass index more than 35. All patients were conscious and ambulant. Five PWS patients had the same surgical technique done by the same surgeon for the intra-gastric balloon group. Children were subsequently excluded for any of the following reasons: they had BMI < 30, esophagitis > grade 1, and hiatal hernia > 5 cm and medically unstable as determined by history or medical records, as cardiac patients.

Patients were classified into two equal groups; study group I, five patients received conservative therapy in the form of diet regimen (a low caloric diet) a well-balanced diet of 1.200 kcal/day and aerobic exercises on a stationary bicycle, while study group II, five patients underwent bioenterics intra-gastric balloon.

Evaluation procedures in the form of initial evaluation and measurement of BMI and lipid profile parameters were conducted for each child of the two groups before and after 6 months of treatment.

2.2. Methods

All procedures were explained to the parents and participants; the experimental protocol was explained in detail for caregivers of the children before the initial assessment. Each of them signed a consent form prior to participation.

2.2.1. Initial evaluation procedures

A diagnosis of PWS was made according to the Holm and Cassidy criteria and confirmed by genetic analysis using methylation test and/or fluorescence in situ hybridization (FISH) for chromosome 15 [10].

Each child was examined medically in order to exclude any abnormal medical problem.

2.2.2. Estimation of lipid profile

After fasting for at least 12 h, 3 ml of venous blood was extracted from the dorsal hand vein and allowed to clot at 37 °C in the water bath, then serum was separated using a centrifuge for the estimation of serum triglycerides and cholesterol level [11].

2.2.3. Measurement of body mass index

Weight and height scale: A valid and reliable weight and height scale was used. Then the body mass index was calculated: [Body mass index = body weight (kg)/height (m^2)]. It is plotted on percentile charts [12].

2.3. Treatment procedures

The procedures of this protocol were achieved under the following steps:

2.3.1. For study group I

Conservative therapy group (dieting and aerobic exercises).

2.3.1.1. Recommended diet regimen. Children received a low calorie diet. The caloric intake was below 1200 cal/day. This diet was used for 3 days at a time and followed by 4 days normal eating and then repeated for 6 months [13].

Day 1:

Breakfast: skimmed milk with tea, ½ grapefruit, 1 slice toast and 1 cup peanut butter.
Lunch: ½ cup tuna or 1 slice cheese, 1 slice toast.
Dinner: 2 slices of any type meat, 1 cup string beans and 1 small apple.

Day 2:

Breakfast: skimmed milk with tea, 1 egg, slice toast and ½ banana.
Lunch: 1 cup cottage cheese or ½ cup tuna, 5 saltine crackers.
Dinner: 1 cup broccoli or cabbage, ½ cup carrots, ½ bananas and 1 cup vanilla ice cream.

Day 3:

Breakfast: 5 saltine crackers, 1 slice cheddar cheese and 1 small apple.
Lunch: 1 boiled egg, 1 slice toast.
Dinner: 1 cup tuna, 1 cup carrot, 1 cup grains, 2 cup cantaloupe and ½ cup vanilla ice cream.

2.3.1.2. Program of aerobic training. Exercises were performed on the electronic bicycle ergometer as the following stages:

First stage (warming up):

Consisted of 5 min warming up in the form of pedaling at the speed of 60 revolutions per min without load.

Second stage (active stage):

Duration: 30 min.
Mode: pedaling at speed of 60 revolutions per min.
Load: adjusted load to achieve 60% of the predictive age maximal heart rate which was calculated by the following equation [14]:

$$\text{Maximal heart rate} = 220 - \text{age (years)}$$

$$\text{Moderate work load} = 60\% \text{ of maximal heart rate.}$$

The heart rate will be measured through a pulsometer attached to patient's ear.

Third stage (cooling down):

Consisted of 5 min cooling down in the form of pedaling at the speed of 60 revolutions per min without load [6].

Duration and frequency: 3 sessions per week for 6 months [6].

2.3.2. For study group II

2.3.2.1. Intra-gastric balloon group. Bioenterics intra-gastric balloon is an endoscopic device for temporary treatment of morbid obesity. It consists of a silicon smooth elastic balloon with self sealing radiopaque valve designed to remain in the gastric cavity for a period of 6 months. Its use is totally reversible and repeatable [15].

- Bioenterics intra-gastric balloons were implanted during the study period. Placement was performed with patients under sedation or general anesthesia, immediately after upper gastrointestinal endoscopy if this revealed no contraindication (e.g., potentially bleeding lesion, large hiatal hernia).
- The balloon was inflated with 500–650 ml of saline mixed with 10 ml of methylene blue. Patients were instructed:
  - To expect nausea, vomiting, and abdominal cramps during the following 72 h.
  - To take a liquid diet for 72 h, including protein-rich drinks (e.g., Clinutren; Nestlé, Vevey, Switzerland) and, starting at day 4, to progressively follow a personalized balanced-deficit diet of 1000 kcal per day less than their usual intake, with approximately 15% of energy derived from proteins, 30% or less from fats, and the remainder from carbohydrates [16].

3. Data analysis

The raw data were analyzed using the SPSS program to determine the mean ± standard deviation for each measuring variables of the two groups before and after 6 months of treatment. Tests included in this study were independent *t*-test and paired *t*-test.

4. Results

The collected data from this study represent the statistical analysis of the Body mass index and lipid profile parameters, which were measured before and after 6 months of treatment for the two groups. The raw data of the measured variables for the two groups were statistically treated to determine the mean and standard deviation. The Mann–Whitney test and the Wilcox signed Ranks test were then applied to examine the significance of the treatment conducted for each group.

The obtained results in this study revealed no significant differences when comparing the pre-treatment mean values of the two groups. Significant improvement was observed in all measuring variables of the two study groups (I and II), when comparing their pre and post-treatment mean values. After treatment significant differences were also observed when comparing the post-treatment results of the two groups in favor of the study group I.

As revealed from Table 1 and Fig. 1, significant reduction was observed in the mean values of Body mass index for the study group I at the end of treatment as compared with the corresponding mean values before treatment.

Also, Table 2 and Fig. 2, showed a significant reduction in the mean values of Body mass index for the study group II at the end of treatment as compared with the corresponding mean values before treatment.

No significant difference was observed when comparing the pre-treatment mean values of Body mass index of the two groups. While significant improvement was observed when comparing the post-treatment mean values of Body mass index of the two groups in favor of the study group I ($P < 0.05$) as shown in Fig. 3.

As revealed from Table 3 and Fig. 4, significant reduction was observed in the mean values of lipid profile parameters for the study group I at the end of treatment as compared with the corresponding mean values before treatment.

Also, Table 4 and Fig. 5, showed a significant reduction in the mean values of lipid profile parameters for the study group II at the end of treatment as compared with the corresponding mean values before treatment.

No significant difference was observed when comparing the pre-treatment mean values of lipid profile parameters of the two groups significant improvement was also observed when comparing the post-treatment mean values of lipid profile

Table 1 Study group I mean values of BMI before and after treatment in kg/m^2.

Variables	Study group I	
	Range	Mean ± SD
Before	43.5–52.6	48.96 ± 3.387
After	27.2–31.8	29.48 ± 1.77
Wilcox signed Ranks test	2.023	
Asymp. sig.	0.043	
Significant	*S*	
Percentage (%) of improvement	39.78%	

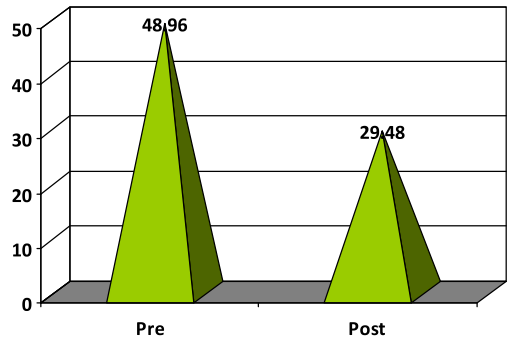

Figure 1 Pre and post values of BMI of study group I.

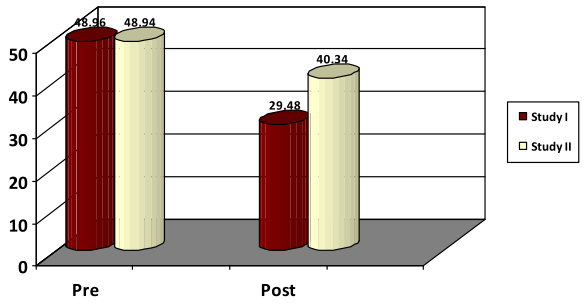

Figure 3 Pre and post values of BMI of both groups of the study.

Table 2 Study group II mean values of BMI before and after treatment in kg/m^2.

Variables	Study group II	
	Range	Mean ± SD
Before	43.5–52.6	48.94 ± 3.42
After	35.3–43.3	40.34 ± 3.14
Wilcox signed Ranks test	2.023	
Asymp. sig.	.043	
Significant	*S*	
Percentage (%) of improvement	17.6%	

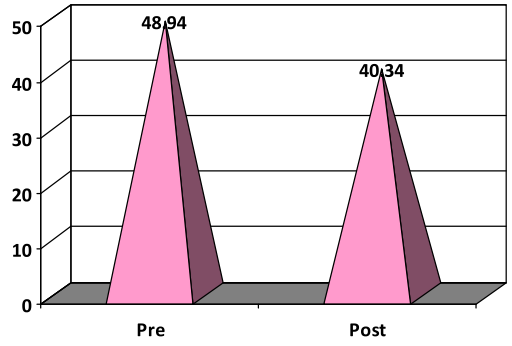

Figure 2 Pre and post values of BMI of study group II.

parameters of the two groups in favor of the study group I ($P < 0.05$) as shown in Fig. 6.

5. Discussion

Obesity associated with Prader-Willi Syndrome is likely to be progressive. Weight gain between the ages of 1 and 6 years, leads most PWS patients to develop morbid obesity, affecting the development of motor and functional skills. PWS patients are characterized by an increase in BMI which is demonstrated to be associated with an increase in functional impairment with further reductions in physical activity. Body weight reduction is mandatory to reduce the risk of cardio-respiratory and metabolic complication and to improve life expectancy.

In our study the pre-treatment mean values of BMI of our patients showed a significant increase in their values which indicated that those children had a significant feature of obesity, This comes in agreement with Capodaglio et al. [17] who demonstrated that, PWS patients presented with reduced lean body mass and increased fat to lean mass ratio not only when compared with lean patients but also in relation to obese patients. Menegoni et al. [18] also reported that obesity associated with PWS is often massive and many individuals exceed by more than 200% their ideal body weight. In addition to obesity and muscular hypotonia, PWS shows dysmorphic features that can affect the development of motor and functional skills.

The post-treatment results of the present study indicated that both groups induced significant reduction in BMI, serum cholesterol and triglycerides which was higher in the conservative therapy group than the intra-gastric balloon group. Group I who received a selected diet program, with aerobic exercise training, showed the highest significant reduction in BMI, serum cholesterol and triglycerides. This result reinforced the effectiveness of conservative therapy on improving metabolic activity. The same result was also reported by Scheimann et al. [19], as increase in the lipolytic responses to isoprenaline and dobutamine occur during the use of a hypocaloric diet [13]. Very low calorie diet also results in rapid loss, often 3–4 lb or more per week, and rapid medical improvement, such as significant reduction in blood pressure, decrease in serum cholesterol of 20–25% and dramatic lowering of glucose level in diabetics [5]. However, the more the restrictive diet, the more is the rapid weight loss, but the greater the risk of non compliance [20].

Aerobic high intensity exercise on obese women led to a decrease in body weight and body mass index after 2 months because exercise training is a major modifiable component of total daily energy expenditure [21]. But the significant effect was after 6 months of intervention [22]. Also exercise prevents weight gain and promotes weight loss [23]. An increase in exercise energy expenditure, without a compensatory increase in food intake, is also an effective means for achieving weight loss [24]. Low amounts of exercise at moderate or high intensity are associated with potentially beneficial changes in plasma lipid profile. However, higher levels of high intensity exercise resulted in more pronounced changes in lipoprotein and were required to increase the high density lipoprotein cholesterol level, without significant weight loss [25].

This improvement was also confirmed by Tall [26] who reported that the improvement in lipid profile variables and insulin sensitivity that are associated with habitual exercise is also seen after a single session of exercise. This finding could

Table 3 Study group I mean values of lipid profile parameters before and after treatment.

Variables	Study group I			
	Total cholesterol		Triglycerides	
	Range	Mean ± SD	Range	Mean ± SD
Before	231–253	241.8 ± 8.075	145–180	162.8 ± 14.44
After	179–201	192.2 ± 10.75	80–122	103.20 ± 19.22
Wilcox signed Ranks test	2.023		2.023	
Asymp. sig.	0.043		0.042	
Significant	*S*		*S*	
Percentage (%) of improvement	20.5%		36.6%	

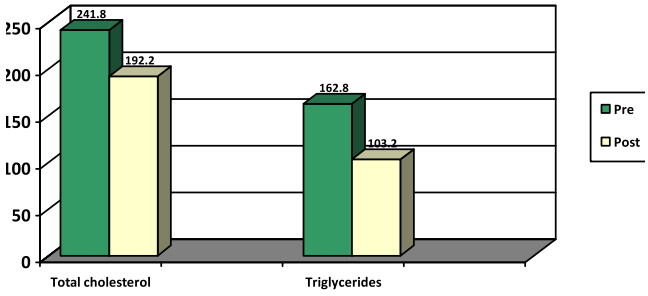

Figure 4 Pre and post values of lipid profile parameters of study group I.

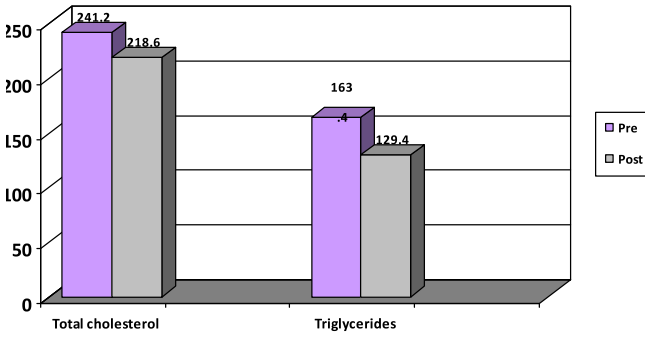

Figure 5 Pre and post values of lipid profile parameters of study group II.

indicate that the short term effects of exercise on insulin signaling in muscle are a fundamental mechanism underlying many of the observed changes in the lipid profile.

Exercise is associated with an increase in lipoprotein lipase activity in adipose tissue and muscles, which lowers LDL and chylomicron triglyceride levels and enhances the clearance of cholesterol-rich LDL and chylomicron remnant. LDL, and triglycerides are exchanged for cholesterol ester in LDL, and HDL, a process mediated by cholesteryl ester transfer protein, and the triglycerides in HDL, and LDL are then hydrolyzed by lipases, causing a decrease in the size of the particles. Exercise and weight loss also reduce the level of cholesteryl ester transfer protein perhaps because a fraction of this protein is made in adipose tissue [27].

Cycle ergometer leads to an increase in the energy expenditure. The total daily energy expenditure can be divided into several components: resting metabolic rate, which accounts for approximately 60–70% of 24 h energy expenditure; the energy cost of feeding approximately 10% of 24 h energy expenditure; and the thermal effect of physical activity or exercise, which is the most variable component and may vary from 15% of 24 h energy expenditure in sedentary people to even 400% in professional cyclists under extreme circumstances [28]. The body mass index and abdominal fat were decreased by training on a cycle ergometer for 3 days/week for 6 weeks because there was a decrease in total amount of stored calories. This decrease in energy stores is obviously the results of a negative energy balance so that exercise produces a decrease in energy intake leading to a reduction in weight [29]. Cycling is an effective form of exercise for improvements in the cardiovascular function [30].

Table 4 Study group II mean values of lipid profile parameters before and after treatment.

Variables	Study group II			
	Total cholesterol		Triglycerides	
	Range	Mean ± SD	Range	Mean ± SD
Before	231–255	241.2 ± 9.497	148–180	163.4 ± 15.043
After	209–230	218.6 ± 7.60	120–140	129.40 ± 7.335
Wilcox signed Ranks test	2.023		2.023	
Asymp. sig.	0.042		0.042	
Significant	*S*		*S*	
Percentage (%) of improvement	9.4%		20.8%	

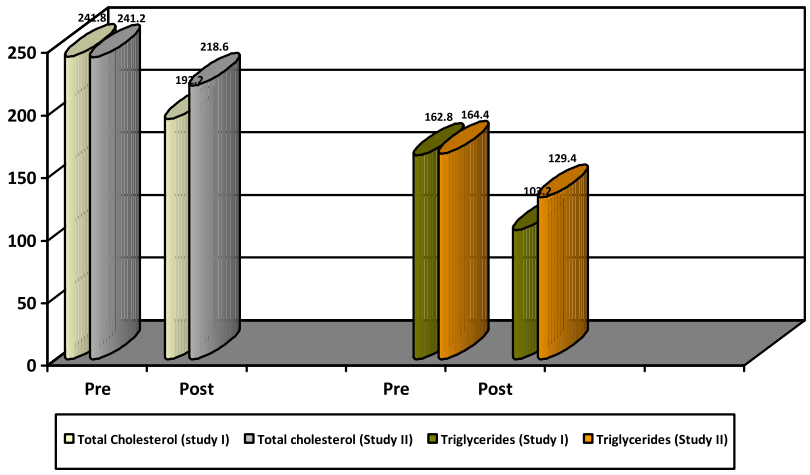

Figure 6 Pre and post values of lipid profile parameters of both groups of the study.

In the present study group II patients underwent intra-gastric balloon and showed a significant reduction in BMI and serum cholesterol and triglycerides.

The post-treatment results of the study group II was in agreement with Dhruva and Redberg [31] who suggested that 70% of intra-gastric balloon were successful in treatment of obesity and excellent in terms of weight loss maintaining or good weight loss results. Also 60% of patients were off medications for related diseases as hyperlipidemia after the removal of bioenterics intra-gastric balloon [32].

In another study on 30 patients with BMI 42.4, and hyperlipidemia, eight patients treated by BIB, four patients showed normal levels, two lowered levels and two unchanged values post operatively [33]. The early treatment may produce better results and minimize complication [34]. There was also improvement of some morbid conditions associated with obesity (hypertension, diabetes, hyperlipidemia), and reduction of mortality [35]. The estimate of BIB effectiveness at balloon removal came from 15 studies that summarized data from up to 3,608 patients. These estimates were 14.7 kg loss. Two studies provided data on maintenance of weight lost 1 year after treatment [36]. The inflated balloon occupies a portion of the gastric volume and theoretically reduced the capacity for food. This method is far less invasive than gastric surgery for reducing stomach capacity [37].

In conclusion, both conservative therapy and intra-gastric balloon are effective in treatment of PWS morbid obesity with high recommendation for using conservative therapy.

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