Short-term use of liraglutide in the management of patients with weight regain after bariatric surgery

Tratamento de curto prazo com liraglutide no reganho de peso após cirurgia bariátrica

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A B S T R A C T

Objective: To evaluate the results of the use of Liraglutide in a group of patients undergoing surgical treatment of morbid obesity with unsatisfactory weight loss or regain of more than 15% of minimum reached weight. **Methods**: The authors conducted a retrospective analysis of 15 operated patients who had excess weight loss <50% after two years of follow-up or regained weight more than 15% of the minimum reached weight. We included only patients who had the expected "surgical anatomy", assessed by contrast radiography and endoscopy. Mean age was 47.2 ± 12.5 years, and patients received liraglutide at doses from 1.2 to 3.0 mg/day for eight to 28 weeks follow-up. **Results**: Surgical treatment induced a weight loss of 34.1 ± 16.5 kg. The average weight regain after 5.3 ± 3.3 years was 14.2 ± 12.1 Kg. The average weight was significantly reduced after treatment with liraglutide (100.9 ± 18.3 kg. vs Kg 93.5 ± 17.4, p <0.0001). Six patients had nausea and two discontinued therapy due to the cost of medication. **Conclusion**: medical treatment directed to the control of satiety using liraglutide may be an alternative treatment of patients with poor weight loss or weight regain after surgery when no technical problem has been identified.

Key words: Obesity. Bariatric surgery. Drug utilization. Anti-obesity agents. Glucagon.

INTRODUCTION

Bariatric surgery is the most effective method of treating severe obesity. Weight loss ranges from 20 to 40% of the initial weight, or 60 to 80% overweight, depending on the surgical method employed, which can be purely restrictive, mixed with more restrictive component, or malabsorptive [1].

Maximum weight loss occurs between 18 and 24 months postoperatively, but over the years a regain of 10 to 15% of the minimum weight reached is considered normal [2].

More pronounced weight regains are considered "pathological", especially if there is return of previously controlled comorbidities, or if the patient is not able to maintain at least 50% loss of their excess weight [3].

The causes of weight regain may be related to the surgical method employed, especially those purely restrictive, to technical failure of the operation, whatever the method, or to the patient's eating behavior (excess carbohydrates, frequent snacks, alcohol binge drinking), influenced or not by factors of mental health, such as anxiety, depression and eating compulsion [4]. It is stated that possible flaws in entero-hormonal stimulation influencing the loss of satiety could be involved [5].

Treatment of weight regain is made with dietary counseling and physical activity. In cases of excessive regained, and depending on the surgical method initially used, revisional operations may be indicated for the correction of technical failures or technical change, eg change of adjustable gastric banding to gastric bypass [6].

The use of drugs as an aid in the treatment of weight regain has been described in uncontrolled studies, with mixed results [7,8]. Although the association of antiobesity drugs in patients with weight regain is a common practice in the offices of endocrinologists [9], there are few data on the long-term results of this kind of approach.

Liraglutide is a synthetic analogue of the hormone GLP-1 (glucagon like peptide-1), secreted by the intestine, used to treat type II diabetes [10].

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It is known that gastrojejunal bypass operations (gastric bypass) or biliopancreatic diversions increase secretion of GLP-1, which stimulates the hyperplasia of pancreatic beta cells and insulin production (incretin action) and satiety [11]. For its satiating effect, the Liraglutide has also been used as an anti-obesity medication [12].

The aim of this study was to evaluate the results of the use of Liraglutide in a group of patients undergoing surgical treatment of morbid obesity and who had, throughout its evolution, unsatisfactory weight loss or gain of more than 15% of their minimum weight reached.

METHODS

We retrospectively studied 15 patients (four men and 11 women), aged 27-74 years undergoing different surgical techniques for the treatment of severe obesity and who had weight loss less than 50% of excess weight after at least two years of follow-up, or regained at least 15% of the minimum weight reached.

The patients studied had received dietary counseling and antiobesity medication prescription (Sibutramine) or to control binge eating (fluoxetine, sertraline or Topiramate), without success.

Patients were treated with Liraglutide with doses ranging from 1.2 to 1.8 mg / day by subcutaneous injection, beginning with the dose of 0.6 mg / day and increased to 1.2 mg after one week. The dose escalation was performed according to clinical response and most of the patients received the dose of 1.8 mg (53.3%). All patients received dietary guidance. They were followed for an average of 4.2 months (three to seven months) and re-evaluated for weight loss.

Endoscopy and contrast radiography were performed in all patients to rule out possible surgical causes that could cause weight regain.

Data are expressed as mean ± SD for continuous variables and as percentages for categorical data. The percentage of excess weight loss (%EWL) was calculated using the formula: %EWL = (preoperative weight - current weight) x100 / preoperative weight - ideal weight (for BMI 25 kg/m2). We used the t-test to evaluate weight loss and percentage loss of excess weight, comparing the means of two variables in a single group at different times during follow-up. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Of the 15 patients studied, four were submitted to gastric banding (26.6%), nine to Roux-en-Y gastric bypass (60%), one to duodenal switch biliopancreatic diversion (6.7%) and one to longitudinal gastrectomy (6.7%). The mean postoperative period was 5.6 years (two to 13 years). Baseline characteristics of the patients are shown in Table 1.

Weight loss after surgery was statistically significant (preoperative mean weight = 120.8 ± 22.1 kg vs. postoperative mean weight 86.7 ± 14.4 kg, $p < 0.0001$), with a reduction in mean weight of 34.1 kg (95% CI: 24.9-43.22). The average excess weight loss was 66.7 ± 22.4% (41.4-112.9%). The regained weight during the follow-up of 5.3 ± 3.3 years was statistically significant (minimum weight = 86.7 ± 14.4 kg vs. weight before liraglutide use = 100.9 ± 18.3 kg, $p < 0.0005$) with a weight regain of 14.2 kg (95% CI 4.9 to 43.2 kg).

Liraglutide was used during 12.5 ± 4.7 weeks (range: 8-28). During the use of the drug, all patients reported improvement of satiety and displayed weight loss, ranging from 2 to 18 kg (-7.5 ± 4.3 kg) (Figure 1). Nausea occurred in six patients (40%), three with gastric banding and three with gastric bypass. There were no other adverse events. Four patients discontinued medication (26.6%) on their own, whether due to the high cost or because they felt they were not showing the expected result. The full results of the patients are shown in table 2.

DISCUSSION

Weight regain in patients undergoing bariatric surgery represents a huge challenge for surgeons and endocrinologists.

The sense of frustration and fear that often reaches these patients can trigger compulsion, increasing the intake of sugar and carbohydrates, markedly worsening dietary patterns, which aggravates the problem. These patients often come for surgical alternatives that have high risk, results sometimes disappointing and are costly, benefiting a minority. Better understanding of the causes of weight regain is an important step to be able to treat it.

The problems caused by purely restrictive surgery, by the very wide pouches and anastomosis or by great alimentary distortions are easily diagnosed. However, on many occasions the patient states that hunger returned and no satiety is no longer strong as before, despite intact surgical anatomy.

The loss of the appetite regulatory mechanism may be associated with lower levels of secretion of intestinal peptides (PYY), as shown in rats [5]. This may be a key to long-term weight control.

GLP-1 is a potent inhibitor of food intake, due to its delaying effect on gastric emptying and also its action in the hypothalamus, suppressing appetite.

Liraglutide is an GLP-1 agonist, launched for the treatment of type II diabetes [11]. In a prospective randomized study that evaluated its use in obese patients with a BMI of 30 40Kg/m2 though, the average weight loss after 20 weeks

Table 1 - Basal characteristics of the patients with weight regain.

Variable	Total (n=15)
Age (years)	47.2 ± 12.5
Gender (%)	
Male	33.3
Female	66.7
Preoperative Weight (kg)	
Average ± Standard Deviation	120.8 ± 22.1
Range	(82 - 150)
RangeBody Mass Index (kg/m^2)	
Average ± Standard Deviation	42.4 ± 4.1
Range	(33.3 - 48.4)
Surgical technique (%)	
Rou-en-Y Gastric Bypass	60.0
Adjustable Gastric banding	26.6
Longitudinal Gastrectomy	6.7
Biliopancreatic Diversion	6.7
% EWL	
Average ± Standard Deviation	64.4
Range	(33 - 105)
Interval between surgery and use of Liraglutide (years)	
Average ± Standard Deviation	5.3 ± 3.3
Range	(1 - 11)

%EWL: Percentage of Excess Weight Loss (considering the minimum of reached weight).

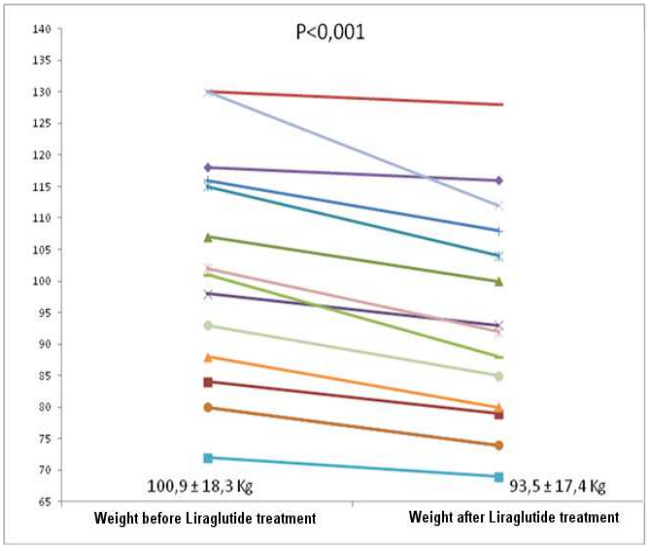

Figure 1 - *Result of the short term use of Liraglutide due to poor weight loss or weight regain after bariatric surgery.*

of treatment ranged from 4.8 to 7.2 kg, depending on the dose used (1.2 to 3.0 mg per day) and superior to placebo [12]. Other GLP-1 receptor agonist, exenatide, has been tested as an adjunctive treatment in patients with adjustable gastric band, with good results [13].

The use of these medications may be limited by their side effects, nausea, vomiting and hyperamylasemia, and their cost. In the present study, six patients had nausea, but were well controlled with temporary dose reduction of the medication. In Brazil, the average monthly cost of treatment with liragluitde is US$ 250 (1.8 mg / day), which limits its prolonged use to many patients and was the reason for discontinuation of treatment in two patients in the series presented.

Despite the various biases of this study (type of surgery, variability in weight loss and in the observation period), the observed good results open a new perspective for further studies to determine the role of this drug in the treatment of weight regain in patients undergoing surgical treatment of obesity.

In conclusion, drug therapy directed to the control of satiety, by use of Liraglutide, can be an alternative for the treatment of poor weight loss or of weight regain after bariatric surgery when no technical problem has been identified.

Table 2 - Clinical data of the patients included in the analysis.

Patient	Surgical Technique	Weight (Kg) before surgery	Minimum weight (Kg) after surgery	Weight (Kg) before Liraglutide use	Weight (Kg) after Liraglutide	Duration Liraglutide treatment (weeks)
1	GBP	112	72	80	74	8
2	GBP	93	70	84	79	8
3	GBP	122	92	107	100	28
4	GBP	113	67	98	93	8
5	LG	145	105	115	104	12
6	AGB	88	74	80	74	12
7	GBP	121	90	116	108	12
8	GBP	150	95	130	128	12
9	BPD	145	72	101	88	12
10	GBP	140	99	118	116	12
11	AGB	82	72	72	69	12
12	GBP	110	88	88	80	12
13	AGB	150	110	130	112	12
14	AGB	120	102	102	92	16
15	GBP	121	93	93	85	12

GBP (Gastric Bypass), AGB (Adjusted Gastric Banding), LG (Longitudinal Gastrectomy), BPD (Biliopancreatic diversion)

RESUMO

Objetivo: *avaliar os resultados da utilização do liraglutide em um grupo de pacientes submetidos ao tratamento cirúrgico da obesidade mórbida com perda insatisfatória de peso ou ganho de mais de 15% do seu peso mínimo atingido.* ***Métodos:*** *realizou-se análise retrospectiva de 15 pacientes operados que tiveram perda de excesso de peso <50% após dois anos de seguimento ou reganho de peso de mais de 15% do peso mínimo atingido. Foram incluídos apenas pacientes que apresentavam a "anatomia cirúrgica" normal avaliada por radiografia contrastada e endoscopia digestiva alta. A média de idade foi 47,2±12,5 anos e os pacientes receberam liraglutide na dose de 1,2 a 3,0mg/dia por oito a 28 semanas de seguimento.* ***Resultados:*** *o tratamento cirúrgico induziu uma perda de peso de 34,1± 16,5Kg. A média de reganho de peso após 5,3 ±3,3 anos foi 14,2±12,1Kg. A media de peso reduziu significativamente após o tratamento com liraglutide (100,9±18,3Kg* vs. *93,5±17,4Kg; p<0,0001). Seis pacientes apresentaram náuseas e dois descontinuaram o tratamento em decorrência do custo da medicação.* ***Conclusão:*** *o tratamento clínico medicamentoso dirigido para o controle da saciedade com o uso do liraglutide pode ser uma alternativa para manejo dos pacientes com reganho de peso ou perda insuficiente após o tratamento cirúrgico, quando nenhum problema técnico tenha sido identificado.*

Descritores: *Obesidade. Cirurgia bariátrica. Uso de medicamentos. Fármacos antiobesidade. Glucagon.*

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