Original Article

Does Combining Liraglutide with Intragastric Balloon Insertion Improve Sustained Weight Reduction?

Mahmoud M. Mosli, Moaiad Elyas[1]

Department of Medicine, King Abdulaziz University, Jeddah, [1]Department of Gastroenterology and Hepatology, Saad Specialist Hospital, Al-Khobar, Kingdom of Saudi Arabia

Address for correspondence: Mahmoud M. Mosli, Department of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. E-mail: Mahmoud.Mosli@RobartsInc.com

ABSTRACT

Background/Aim: Intragastric balloon (IGB) is an effective and safe method of weight reduction. However, IGBs have been associated with a high rate of weight regain post removal. Accordingly, ways to improve sustained weight reduction including concomitant treatment with Glucagon-like peptide 1 (GLP-1) agonists have been proposed. This study aims to evaluate the effect of adding Liraglutide to IGB insertion on sustained weight reduction. **Patients and Methods:** A retrospective analysis of all cases treated with IGB with or without Liraglutide was performed. Outcomes were statistically compared. **Results:** A total of 108 patients were included; 64 were treated with IGB alone and 44 with IGB + Liraglutide. Six months after removing IGB, patients treated with IGB + Liraglutide had a higher mean weight loss post treatment completion (10.2 ± 6.7 vs. 18.5 ± 7.6, P = <0.0001) than those treated with IGB alone. After adjusting for covariates, patients treated with IGB alone demonstrated a higher mean body weight loss at the time of IGB removal (coefficient 7.71, 95% CI = 4.78–10.63), and a higher odds of treatment success 6 months post IGB removal (OR = 5.74, 95% CI = 1.79–188.42). Baseline body mass index appeared to be a significant predictor of mean body weight loss at the time of balloon removal. **Conclusions:** Adding Liraglutide to IGB does not appear to decrease the risk of weight regain 6 months post IGB removal.

Key Words: Glucagon-like peptide 1, obesity, weight change

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Obesity has become one of the leading comorbidities worldwide with an age standardized prevalence of 10.8% (9.7–12.0) in men, and 14.9% (13.6–16.1) in women.[1] Several health conditions have been associated with obesity such as the development of type 2 diabetes mellitus (DM-2), hypertension (HTN), coronary artery disease (CAD), obstructive sleep apnea (OSA), gallstones, fatty liver, and dyslipidemia.[2,3] Obesity has been linked with decline in the quality of life and early mortality.[4-6] Weight reduction has, therefore, been recommended by the American College of Cardiology and American Heart Association Task Force for all patients with a body mass index (BMI) above 30 or above 25 with risk factors for CAD.[7]

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Lifestyle modification through exercise and dietary restriction are considered the first line of treatment for obesity but frequently fail to reduce weight.[8,9] Surgical gastric volume reduction through sleeve or partial gastrectomy is associated with multiple potential side effects such as immediate postoperative complications and late onset vitamin deficiencies.[10] Conversely, endoscopic intragastric balloon (IGB) insertion is a noninvasive method that produces weight reduction in up to 35% of patients according to randomized controlled trials.[11,12] Liraglutide (Victoza®, Novo Nordisk, Bagsvaerd, Denmark), a parenteral glucagon-like peptide type 1 (GLP-1) agonist used to treat DM-2 that has a weight reducing effect, was approved by the food and drug administration (FDA) in 2013 for the treatment of DM-2 and in 2014 for weight reduction (www.fda.gov). Liraglutide is considered an expensive medication with an average monthly cost of 500$ for those without medical insurance. Furthermore, the effect of combining endoscopic IGB insertion with Liraglutide on weight reduction remains unknown.

This study aims to evaluate the effect of adding the GLP-1 agonist Liraglutide to endoscopic IGB insertion on weight reduction.

PATIENTS AND METHODS

We performed a retrospective study of data collected prospectively between January 2014 and October 2015. The institutes departmental ethics committee approved this study. All consecutive adult patients who electively presented to the First Gastroenterology outpatient clinic in Jeddah, Kingdom of Saudi Arabia, a private community specialized gastroenterology clinic, requesting endoscopic IGB insertion for weight reduction were recruited. Baseline data, including complete history and physical examination, initial weight and height, and BMI was collected. Demographics and clinical data were then entered into a standard data extraction sheet.

Interventions

Intragastric balloon insertion

All patients were scheduled for outpatient endoscopic insertion of elastic spherical IGB (ORBERA©, Apollo Endosurgery Inc., Austin, United States of America) made from silicone and filled with approximately 500–700 ml of saline, within 2 weeks of recruitment. A single board certified experienced gastroenterologist performed all IGB insertions and removals.

Procedure: Insertion and removal

The deflated balloon comes preloaded on a catheter, which is blindly advanced transorally into the stomach. The preloaded system contains a guide wire. An endoscope is then advanced alongside it to ensure accurate placement of the balloon in the antrum. The guide wire is removed, and under direct visualization, the balloon is then inflated by injecting saline solution mixed with methylene blue through the external portion of the catheter.

All IGBs were removed 6 months post insertion or earlier in cases where persistent adverse events (AEs) developed.

During removal, balloons are initially punctured by an aspiration needle, which is specifically designed for this purpose. The needle allows for threading of a sheath deep into the balloon to fully deflate the balloon. The sheath is threaded 5 cm into the balloon (that would be the center), and then connected to suction to empty the saline out of it. This is critically important because any residual fluid will pool at the trailing edge of the extracted balloon making the diameter of the balloon too large to safely pass through the esophagus upon removal. After the balloon is fully deflated, it is grasped for extraction using a specifically designed grasper and withdrawn.

Liraglutide

After discussing common potential AEs such as diarrhea, nausea, constipation and headache occurring in less than 5% of patients and less common AEs such as acute pancreatitis, low blood sugar, acute renal failure, and allergic reactions (www.drugwatch.com/victoza/), all patients were routinely offered to receive the GLP1 agonist Liraglutide. The starting dose was typically 0.6 mg per day administered subcutaneously in the abdomen, thigh, or upper arm at any time independent of meals. After 1 week at 0.6 mg per day, patients were instructed to increase the dose to 1.2 mg per day. In diabetics, if the 1.2 mg dose did not result in acceptable glycemic control, the dose would have been increased to 1.8 mg per day post IGB insertion. The drug was started 1 month after IGB insertion and discontinued 1 month following removal.

Lifestyle changes

All patients were advised to implement lifestyle changes post IGB insertion in the form of exercising 3 times a week, reducing daily caloric intake to 1500 to 2000 kcal, and dividing meals into 4 to 5 small amount portions. This was performed during an independent counseling session with a specialized dietitian over 30 minutes, and separate printed educational materials were provided to further instruct patients.

Follow up

Patients were followed up at 3 and 6 months post insertion. At the time of follow up, patients underwent complete history and physical examination and were evaluated for post-procedural AEs such as pain, nausea, vomiting, gastroesophageal reflux disease (GERD), small bowel obstruction (SBO) due to IGB migration, gallstones, and acute pancreatitis, which are previously reported complications of IGB insertion.[13] Laboratory investigations such as electrolytes, kidney function, lipase, and liver enzymes were requested for cases of persistent pain or vomiting, but otherwise were not routinely performed. Abdominal computed tomography (CT) scan was only requested if SBO due to balloon migration was suspected.

Outcomes

Mean body weight reduction in kilograms (kg) 6 months post treatment was considered the primary outcome. Mean body weight and BMI at the time of IGB removal, overall success of therapy, defined as any weight decline compared to baseline weight that persisted 6 months after treatment completion, and AE's were secondary outcomes.

Statistical analysis

Descriptive statistics including means and standard deviations (SD) for continuous variables and frequencies for categorical variables were estimated. Standard *t*-test and Chi-square tests were used to compare means and frequencies, respectively.

To adjust for imbalances between groups, multiple linear regression analysis was used to identify the predictors of continuous outcomes. For dependent binary categorical outcomes, such as overall treatment success, multiple logistic regression testing was used to examine their association with independent variables. Multinomial regression was used for categorical outcomes where appropriate. Model selection using forward and backward elimination was performed. Regression coefficients and odds ratios (OR) with 95% confidence intervals (CI) were estimated. STATA 12.1 (Stata Corp, Texas, USA) was used. A P value of < 0.05 was considered statistically significant.

RESULTS

Patient population

A total of 108 patients were included in this study. Sixty-four patients were treated with IGB and 44 received IGB and Liraglutide. No significant differences were seen between the two groups at baseline [Table 1].

Outcomes

On hypothesis testing, patients treated with IGB and Liraglutide lost more weight 6 months after treatment completion than those treated with IGB alone (4.7 ± 6 vs. 2.7 ± 4.10, P = 0.019). Similarly, mean weight loss at the time of balloon removal was higher in patients treated with IGB and Liraglutide than patients receiving IGB alone (18.5 ± 7.6 vs. 10.2 ± 6.7, P =<0.0001). Mean BMI post treatment completion (33 ± 5.5 vs. 31.3 ± 5.9, P = NS), and mean weight in kg post treatment completion (88.6 ± 18.3 vs. 85.3 ± 18.4, P = NS) did not differ between the two groups [Table 2].

Adjusting for confounders

After adjusting for all clinically relevant baseline and follow-up covariates using multiple linear [Tables 3 and 4] and logistic [Table 5] regression analysis, patients treated with IGB alone demonstrated a higher mean body weight loss at the time of IGB removal (coefficient = 7.71, 95% CI = 4.78–10.63), and higher odds of treatment success 6 months post IGB removal (OR = 5.74, 95% CI = 1.79–188.42) compared to those treated with IGB and Liraglutide. Baseline BMI appeared to be a significant predictor of mean body weight loss at the time of balloon removal.

Model selection

Forward and backward elimination identified intervention (IGB vs. IGB plus Liraglutide) (P = 0.003)

Table 1: Baseline characteristics

	Balloon (*n*=64)	Balloon/ Liraglutide (*n*=44)	*P*
Age (mean±SD)	34.9±9.8	32.5±8.4	NS
Gender (%)			
Female	47 (61)	30 (39)	NS
Male	17 (55)	14 (45)	
Nationality (%)			
Saudi	55 (59)	39 (41)	NS
Non Saudi	9 (64)	5 (36)	
Pre treatment BMI (mean±SD)	37±5.9	38.5±6.1	NS
Pre treatment weight in kg (mean±SD)	99.3±19.9	103.8±19.1	NS
Pre BMI category (%)			
1	0	0	NS
2	7 (70)	3 (30)	
3	17 (71)	7 (29)	
4	23 (52)	21 (48)	
5	17 (57)	13 (43)	

SD: Standard deviation, BMI: Body mass index, *NS: Non significant, P>0.05

Table 2: Response to therapy

	Balloon (*n*=64)	Balloon/ Liraglutide (*n*=44)	*P*
Post treatment BMI (mean±SD)	33±5.5	31.3±5.9	NS
Post treatment weight (mean kg±SD)	88.6±18.3	85.3±18.4	NS
Post BMI category (%)			
1	3 (33)	6 (67)	NS
2	13 (46)	15 (54)	
3	25 (64)	14 (36)	
4	15 (79)	4 (21)	
5	5 (38)	8 (62)	
Mean Body Weight lost at IGB removal (mean kg±SD)	10.2±6.7	18.5±7.6	<0.0001
Mean Body Weight lost 6 months post removal (mean kg±SD)	2.7±4.1	4.7±6	0.019
Exercise (%)			
Yes	41 (55)	33 (46)	NS
No	23 (68)	11 (32)	
Division of meals (%)			
Yes	37 (49)	38 (51)	0.002
No	27 (82)	6 (18)	
Decreased caloric intake (%)			
Yes	42 (54)	36 (46)	NS
No	22 (73)	8 (27)	

IFG: Intragastric balloon, SD: Standard deviation, BMI: Body mass index, *NS: Non significant, P>0.05

Table 3: Simple and multiple linear regression analysis of predictors of mean body weight loss at the time of balloon removal

Variable	Univariate Coefficient (95% CI)	Multivariate Coefficient (95% CI)
Intervention (IGB vs. IGB/Liraglutide)	8.30 (5.54, 11.06)	7.71 (4.78, 10.63)
Gender	0.57 (−2.89, 4.04)	−0.10 (−3.17, 2.96)
Nationality	3.81 (−0.80, 8.42)	2.49 (−1.54, 6.53)
Age	−0.01 (−0.18, 0.16)	0.02 (−0.13, 0.17)
Baseline BMI	2.86 (1.28, 4.49)	0.40 (0.18, 0.62)
Exercise	0.63 (−2.74, 4.01)	−0.19 (−3.09, 2.71)
Meal division	2.74 (−0.63, 6.10)	0.44 (−2.64, 3.52)
Low calorie diet	3.21 (−0.23, 6.66)	0.77 (−2.25, 3.80)
Balloon tolerance	0.34 (−0.96, 1.64)	−0.50 (−1.71, 0.70)
Pain post insertion	−0.35 (−1.01, 0.94)	0.22 (−0.61, 1.04)
Nausea post insertion	0.49 (−0.31, 1.29)	0.63 (−0.05, 1.32)
GERD post insertion	−0.02 (−0.94, 0.90)	0.39 (−0.40, 1.18)
Early IGB removal	−13.32 (−24.66, −1.97)	−9.23 (−19.30, 0.85)

*CI: Confidence interval, GERD: Gastroesophageal reflux disease, IGB: Intra gastric balloon

Table 4: Simple and multiple linear regression analysis of predictors of mean body weight loss 6 months after balloon removal

Variable	Univariate Coefficient (95% CI)	Multivariate Coefficient (95% CI)
Intervention (IGB vs. IGB/Liraglutide)	2.02 (0.11, 3.95)	1.97 (−0.25, 4.18)
Gender	−1.13 (−3.44, 0.78)	−1.96 (−4.28, 0.36)
Nationality	0.20 (−2.67, 3.06)	0.02 (−3.04, 3.08)
Age	−0.03 (−0.13, 0.08)	0.01 (−0.11, 0.12)
Baseline BMI	0.15 (−0.004, 0.31)	0.15 (−0.02, 0.32)
Exercise	−0.11 (−2.18, 1.97)	−0.64 (−2.84, 1.56)
Meal division	0.38 (−1.71, 2.47)	−0.12 (−2.45, 2.21)
Low calorie diet	0.79 (−1.36, 2.92)	−0.06 (−2.35, 2.23)
Balloon tolerance period	0.26 (−0.53, 1.06)	0.30 (−0.61, 1.21)
Pain post insertion	−0.01 (−0.60, 0.59)	0.06 (−0.57, 0.69)
Nausea post insertion	−0.14 (−0.63, 0.36)	−0.15 (−0.66, 0.37)
GERD post insertion	0.06 (−0.51, 0.62)	0.10 (−0.50, 0.70)
Early IGB removal	−1.80 (−8.94, 5.33)	−0.37 (−7.99, 7.26)

*CI: Confidence interval, GERD: Gastroesophageal reflux disease, IGB: Intra gastric balloon

and posttreatment nausea ($P = 0.03$) as significant predictors of treatment response. Furthermore, a statistical trend was observed with gender ($P = 0.053$), exercise ($P = 0.054$), and meal division (0.078) [Supplementary Figure 1].

Multinomial regression

Multinomial regression analysis was used to examine the association between post IGB weight reduction category (no change in weight, lost 1–5 kg, lost 6–9 kg, lost 10–15 kg, lost 16–20 kg, lost 21–25 kg, lost 26–30 kg, lost 31–35 kg, lost 36–40 kg, against gaining of weight as a base category) and multiple confounders. Pre BMI and gender were associated with multiple categories of weight reduction [Supplementary Figure 2].

Adverse events

A higher proportion of patients were treated with IGB alone compared to those treated with IGB and Liraglutide tolerated therapy for 6 months (54% vs. 46%, $P = 0.038$). Otherwise, no significant differences were observed between the two groups with regards to pain, nausea, GERD, need for early IGB removal, IGB migration, or SBO [Table 6]. Two patients in the IGB group required early removal due to persistent nausea (vs. none in patients treated with IGB and Liraglutide, $P = 0.038$) and one patient developed IGB migration leading to SBO requiring surgical intervention.

DISCUSSION

In this era, IGB is considered a minimally invasive effective method that can be used to reduce weight in patients with obesity. In standard practices gastroenterologists perform such procedures for patients with BMIs exceeding 35 and generally remove the balloon endoscopically after 6 months.[14] The major limitation of IGB insertion remains weight regain after the balloon is removed, which is reported in up to 35% of patients.[13] Results from this first study to evaluate Liraglutide as an adjunctive therapy for IGB-induced weight reduction demonstrates that endoscopic IGB insertion on average reduces weight by 10.2 ± 6.7 kg at the time of balloon extraction and 2.7 ± 4.1 kg 6 months post extraction, indicating significant weight regain following removal. Although on simple comparisons, GLP-1 agonist Liraglutide appears to potentiate the weight reducing effect of IGB, multiple regression analysis not only ameliorates this effect but also in fact swings it in the opposite direction, suggesting that IGB monotherapy is sufficient. This observation might have some cost-effective implications given the cost of the drug. Patients treated with IGB alone appeared to have a 2.98 (95% CI = 1.3–6.8) higher odds of treatment success compared to IGB and Liraglutide [Table 7]. Upon adjusting for covariates, no advantage is seen with one approach over the other at the time of IGB extraction [Table 4], however, a 5.74 (95% CI = 1.79–188.42) higher odds is seen with IGB alone over IGB plus Liraglutide 6 months following IGB removal [Table 5] indicating superiority of IGB monotherapy over the addition of Liraglutide. IGB monotherapy and post-treatment nausea appeared to be statistically significant predictors of outcome based on model selection. The statistical trends observed with nationality, exercise, and meal division suggests that these might be clinically relevant factors. However, given that patients were not randomized to treatment arms, the potential for selection bias should be taken into account.

Table 5: Simple and multiple logistic regression analysis of predictors of successful weight lost 6 months after balloon removal

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Intervention (IGB vs. IGB/Liraglutide)	2.98 (1.29, 6.88)	5.74 (1.79, 188.42)
Gender	1.05 (0.43, 2.57)	1.03 (0.34, 3.10)
Nationality	0.40 (0.13, 1.26)	0.22 (0.05, 1.02)
Age	0.98 (0.94, 1.03)	1.00 (0.95, 1.06)
Baseline BMI	0.88 (0.57, 1.36)	0.79 (0.45, 1.38)
Exercise	0.44 (0.19, 1.03)	0.36 (0.13, 1.02)
Meal division	0.60 (0.25, 1.42)	0.34 (0.11, 1.13)
Low calorie diet	0.89 (0.36, 2.18)	0.78 (0.26, 2.39)
Balloon tolerance period	1.01 (0.72, 1.42)	1.13 (0.71, 1.82)
Pain post insertion	1.08 (0.83, 1.40)	1.10 (0.81, 1.50)
Nausea post insertion	0.80 (0.65, 0.98)	0.77 (0.61, 0.97)
GERD post insertion	0.99 (0.78, 1.26)	0.93 (0.70, 1.24)

*OR: Odds ratio, CI: Confidence interval, IGB: Intra gastric balloon, GERD: Gastroesophageal reflux disease

Table 6: Adverse events

	Balloon	Balloon plus Liraglutide	*P*
Balloon tolerance			
<1 week	2	0	0.038
2-8 weeks	5	0	
2-3 months	2 (33%)	4 (67%)	
3-6 months	12 (80%)	3 (20%)	
Reached 6 months	43 (54%)	37 (46%)	
Pain			
None	45 (66%)	23 (34%)	NS
<1 week	4 (29%)	10 (71%)	
1-2 weeks	12 (52%)	11 (48%)	
2-3 weeks	1	0	
4-8 weeks	2	0	
Nausea			
None	42 (62%)	26 (38%)	NS
<1 week	6 (55%)	5 (45%)	
1-2 weeks	9 (53%)	8 (47%)	
2-3 weeks	1 (50%)	1 (50%)	
4-8 weeks	2	0	
GERD			
None	54 (61%)	34 (39%)	NS
<1 week	1	0	
1-2 weeks	5 (42%)	7 (58%)	
2-3 weeks	1 (33%)	2 (67%)	
4-8 weeks	1	0	
Early removal	2	0	NS
SBO/migration	1	0	NS
Success			
Yes	50 (68%)	24 (32%)	
No	14 (41%)	20 (59%)	

*SBO: Small bowel obstruction, GERD: Gastroesophageal reflux disease

Table 7: Treatment outcome in patients treated with IGB alone and patients treated with IGB plus Liraglutide

Outcome	Exposure		
	IGB	IGB + Liraglutide	Total
Success	50	24	74
Failure	14	20	34
Total	64	44	108

*IGB: Intra gastric balloon

Despite cases of reports of rare AEs occurring following IGB insertion such as acute pancreatitis,[15,16] balloon migration leading to SBO, and acute cholecystitis, IGB is still considered a safe procedure. Common side effects such as epigastric pain, nausea, and GERD are typically managed with supportive care and rarely lead to early IGB removal. In this retrospective analysis, two patients treated with IGB alone underwent early removal, however, caution should be undertaken when interpreting this due to the small number observed, otherwise no differences in AE occurrence were seen between the two groups of patients. On regression analysis, none of the AEs were associated with the choice of intervention.

Although following a healthy lifestyle after IGB insertion is highly recommended to try to sustain weight reduction and improve overall health, our results suggest that exercise, meal division, and lowering daily caloric intake does not influence either early nor late outcome following IGB insertion, although an additive or multiplicative interaction cannot be ruled out.

This study has limitations inherent to the retrospective design such that there is potential for misclassification and confounding bias. An interaction between intervention and lifestyle modification (effect measure modification), although highly likely, could not be depicted through this analysis given that a population with neither interventions is needed. Furthermore, a larger study sample with predefined sample size calculation in a prospective randomized controlled design is needed.

CONCLUSION

In this retrospective study, our data failed to demonstrate any added benefit with the addition of Liraglutide therapy to IGB with regards to weight regain 6 months post IGB removal. Lifestyle modification might have a role in predicting the outcomes of endoscopic IGB insertion. Large prospective randomized trials are needed to validate these findings.

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Conflicts of interest

There are no conflicts of interest.

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