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ORIGINAL CONTRIBUTIONS

Liraglutide Augments Weight Loss After Laparoscopic Sleeve Gastrectomy: a Randomised, Double-Blind, Placebo-Control Study

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Abstract

Purpose Both laparoscopic sleeve gastrectomy (LSG) and liraglutide cause a significant weight loss. We evaluated the effect of liraglutide in comparison with placebo on total weight loss (TWL) and excess body weight loss (EWL) and when added in initial weight loss period after LSG in obese individuals.

Material and Methods Participants with BMI > 30 kg/m^2 undergoing LSG were randomised to receive either liraglutide (subcutaneous) in increasing does of 0.6 mg/day until maximum tolerated dose of 3.0 mg (L-L group) or placebo (L-P group) from 6 weeks post-operative until 6 months. Weight, BMI, %TWL, %EWL, HbA1c, fasting plasma glucose, HOMA-IR, resolution of type 2 diabetes mellitus, hypertension, dyslipidaemia, sleep apnea and quality of life were evaluated. Primary end point was %TWL and % EWL at post-operative 6 months.

Results Thirty participants underwent LSG, and 23 were randomised to receive liraglutide ($n = 12$) or placebo ($n = 11$).The mean dose of liraglutide in L-L group was 1.41 ± 0.49 mg/day. Patients in L-L group had %TWL of 28.2 ± 5.7 and %EWL of 58.7 ± 14.3 as compared with 23.2 ± 6.2 ($p = 0.116$) and 44.5 ± 8.6 ($p = 0.043$) in L-P group at 24 weeks, respectively. BMI decreased by 11.7 ± 3.5 in L-L group compared with 9.5 ± 4.0 in L-P group ($p = 0.287$). All patients with diabetes or pre-diabetes had resolution of dysglycemia in the L-L group as compared with 50% in L-P group. However, there was no significant difference in resolution of other obesity-related comorbidities between two groups at 24-week follow-up.

Conclusion Liraglutide added early after LSG significantly augments weight loss from LSG in obese individuals.

Trial Registration The study protocol was registered at clinical trials.gov.in with NCT: 04325581.

Keywords Laparoscopic sleeve gastrectomy · Liraglutide · Excess body weight loss · Obesity · Bariatric surgery

Introduction

Obesity is an increasingly important health problem worldwide which also affects low- and middle-income countries. According to recent estimates, almost 30–65% of urban Indians are either overweight or obese or have abdominal obesity [1] that contributes to obesity-related comorbidities of type 2 diabetes mellitus (T2DM), hypertension, hyperlipidaemia, degenerative joint disease, obstructive sleep apnea (OSA) and gastroesophageal reflux disease (GERD) [2]. Bariatric surgery is considered as the most durable treatment for weight loss and becoming an increasingly common therapeutic option for morbid obesity and obesity-related comorbidities [2].

The gold standard for weight loss bariatric surgery remains laparoscopic Roux-en-Y gastric bypass (LRYGB), as an excess body weight loss (EBWL) of 55.9% and 72.3% is observed at 6 and 12 months with concurrent significant improvement in obesity-related comorbidities and the quality of life [3]. Laparoscopic sleeve gastrectomy (LSG) was initially advocated as the first stage of a two-stage procedure of RYGB for the high-risk, super-obese patients. Of late, LSG is performed as a single-stage procedure for weight loss in the obese individuals

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being less cumbersome and technically easy. It is observed that EBWL is greater with LYRGB compared with LSG [3–5], though a recent study suggested a similar excessive body mass index loss between LSG and LRYGB at 1 and 3 years [4]. Also, comorbidities were significantly reduced and comparable after both procedures except for GERD and dyslipidaemia, which were more successfully treated by LRYGB. In a recent meta-analysis, authors noted insignificant difference between LRYGB and LSG in midterm weight loss; however, LRYGB produced better weight loss in the long term [5]. The mechanism for weight loss after LSG being gastric restriction and possible neurohormonal changes resulting from a higher level of glucagon-like peptide-1 (GLP-1) due to faster gastric emptying and lower levels of ghrelin, as a consequence of removal of the gastric fundus [6, 7].

Amongst pharmacotherapy, liraglutide, a long-acting analogue of the human incretin GLP-1, is approved by the FDA [8] for the treatment of type 2 diabetes and for chronic weight management in adults as it was shown to cause 8% weight loss in a dose of 3.0 mg per day [9]. The mechanism of weight loss with liraglutide includes slowing gastric emptying and instilling a feeling of satiety [9]. However, the EBWL with liraglutide is significantly less in comparison with LSG alone in our prior experience [10]. Therefore, we hypothesise that combining LSG with liraglutide early after sleeve gastrectomy may augment the initial weight loss effect of LSG, thus contributing to additional EBWL than either of them used individually in obese individuals. Retrospective studies have used topiramate and liraglutide as weight loss pharmacotherapy 4–6 years after RYBG or LSG and found them to be useful in additional weight loss in patients having inadequate weight loss or weight regain after bariatric surgery [11, 12]. To the best of our knowledge, there is no prior study that has prospectively analysed the effect of early addition of liraglutide to LSG as compared with placebo on obesity-related weight loss and other comorbidities in first 6 months.

Patients and Methods

This was a prospective double-blind, randomised, placebo control, single-centre study in North India. Consecutive patients presenting with morbid obesity or obesity with comorbidities willing for LSG were enrolled in the study. The study was approved by the Institute Ethics Committee and all participants provided written informed consent for participation in the study. The study protocol was registered at clinical trials.gov.in with NCT: 04325581.

Eligibility Criteria Participants of age between 18 and 65 years with BMI ≥ 30 kg/m^2, with or without obesity-related comorbidities attending the obesity clinic, were included. Diabetes and pre-diabetes was defined as per prevailing American Diabetes Association criteria. Participants with the prior use of GLP-1 agonist therapy or past history of pancreatitis, personal/family history of medullary thyroid cancer or Multiple Endocrine Neoplasia-type 1, presence of secondary cause of obesity or any eating disorder, pregnancy/lactation, acute coronary syndrome (CAD) or stroke in previous 6 months, hepatic dysfunction (AST/ALT >3 times ULN), renal dysfunction (eGFR$<$ 45 ml/min/1.73 m^2), active malignancy and previous bariatric surgery, gastric surgery or complex abdominal surgery were excluded from the protocol.

Study Protocol Participants fulfilling the inclusion criteria were assessed by a multidisciplinary team consisting of bariatric surgeon, endocrinologist, cardiologist, gastroenterologist, pulmonologist, radiologist, psychiatrist and a dietician to assess their general condition and for obesity-associated comorbidities such as diabetes, dyslipidaemia, hypertension or cardiovascular diseases. Weight (kg) and height (cm) were measured and their body mass index (BMI), ideal body weight (IBW) as that equivalent of BMI >25 kg/m^2 and excess body weight (EBW) calculated. The pre-operative workup included hemogram, liver and renal function tests, chest radiography, upper gastrointestinal endoscopy, electrocardiogram, abdominal ultrasound, thyroid function test and nutritional evaluation. The prevalence of GERD symptoms was assessed through GERD questionnaire. The prevalence of sleep apnea symptoms was assessed through sleep apnea questionnaire (STOP-BANG model, SAS score). Cardiovascular risk of the participants was assessed by calculating the Framingham risk score. Quality of life was assessed using bariatric analysis and reporting outcome system (BAROS).

Patients in both the groups underwent a 2-week run-in period during which low calorie liquid diet (600 cal) was provided prior to surgery and patients were encouraged to do chest physiotherapy and incentive spirometry. Elastic stockings along with intermittent pneumatic compression device was used pre- and post-operatively to prevent deep vein thrombosis (DVT). All the procedures were performed by the RG and UT who were blinded to group allocation according to standard surgical protocol discussed earlier [10]. Gastrectomy was performed laparoscopically and the sleeve size was calibrated using 36-F bougie and gastric transection was done using endoscopic staplers. Patients were allowed oral sips of clear liquid post-operatively and ambulated on the same day with emphasis on chest physiotherapy. All participants in addition also received fractionated heparin for 14 days post-operatively. They were monitored for any complications like wound infection, basal atelectasis, deep vein thrombosis, staple line leak or bleeding. Oral sips were gradually progressed to oral liquid diet over the next 2 days. Patients were discharged on a liquid diet in consultation with a dietician, with advice to take liquid diet for the first 3 weeks,

pureed diet for the next 3 weeks and solid diet after 6 weeks post-operatively following discharge from hospital.

Participants were randomised using block randomisation table 2 weeks prior to surgery by an unblinded investigator (AR) into two groups to receive 0.6 mg (= 0.1 ml) liraglutide (L-L group) or placebo (0.1 ml) (L-P group) daily subcutaneous injection after the laparoscopic sleeve gastrectomy (LSG) from post-operative sixth week. Liraglutide dose was increased weekly by 0.6 mg (= 0.1 ml) up to the maximum tolerable dose (ceiling dose of 3 mg/day (0.5 ml/day) and continued unto 24 weeks. Similarly, placebo dose was increased 0.1 ml every week up to maximum of 0.5 ml/day and continued until 24 weeks. Six-week lag time for the administration of study drug following LSG was planned so that participant may regain their usual diet regimen and ensuring compliance to liraglutide as is known to induce nausea and vomiting. Both liraglutide and placebo injection were packaged and distributed by the unblinded investigator in a prefilled disposable pen syringe as a 3 ml solution containing 18 mg liraglutide or placebo (glycerol, metacresol, sodium hydroxide, hydrochloric acid and water for injection) to be administered subcutaneously in the abdomen, at fixed time (8 pm) each day independent of meals. Participants were asked to return the unutilised study pen syringe at each study visits to monitor adherence to the study medication protocol.

Outcome Measure Primary outcome measure was percentage total weight loss (%TWL) and excess body weight loss (%EWL) at the end of 6 months following bariatric surgery. Secondary outcomes included change in glucose (fasting and post prandial blood glucose), HbA1c, insulin resistance (HOMA-IR), lipid parameters, sleep apnea score, GERD score and change in quality of life (BAROS).

Statistical Analysis Modified intention-to-treat analysis was performed. Normality of the data for each of the studies variables was assessed by Kolmogorov-Smirnov test. Mean ± SD was used to depict data following normal Gaussian pattern and skewed data was represented by median and interquartile range as a measure of central tendency. Student's t test was used to compare the means of two groups for parametric data and Mann-Whitney U test for non-parametric data. The Spearman test was used to compute non-parametric correlation and the Pearson test was used to compute parametric correlation. SPSS version 22 was used for data analysis and a p value < 0.05 was considered significant.

Results

A total of 32 patients underwent LSG during the study period, out of which 23 patients were randomised to receive liraglutide (L-L group; 12 participants) or placebo (L-P group; 11 participants). Five patients were excluded for various reasons and 4 other patients denied consent as shown in Fig. 1. In the placebo group, one patient died due to massive pulmonary thromboembolism during week 10 post-operative. Baseline characteristics of the participants including height, weight, ideal body weight, BMI and co-existing comorbidities were comparable between two groups as shown in Table 1. Type 2 diabetes was present in 4 patients each in either group with a mean duration of 7.5 ± 4.9 years and other 4 patients were

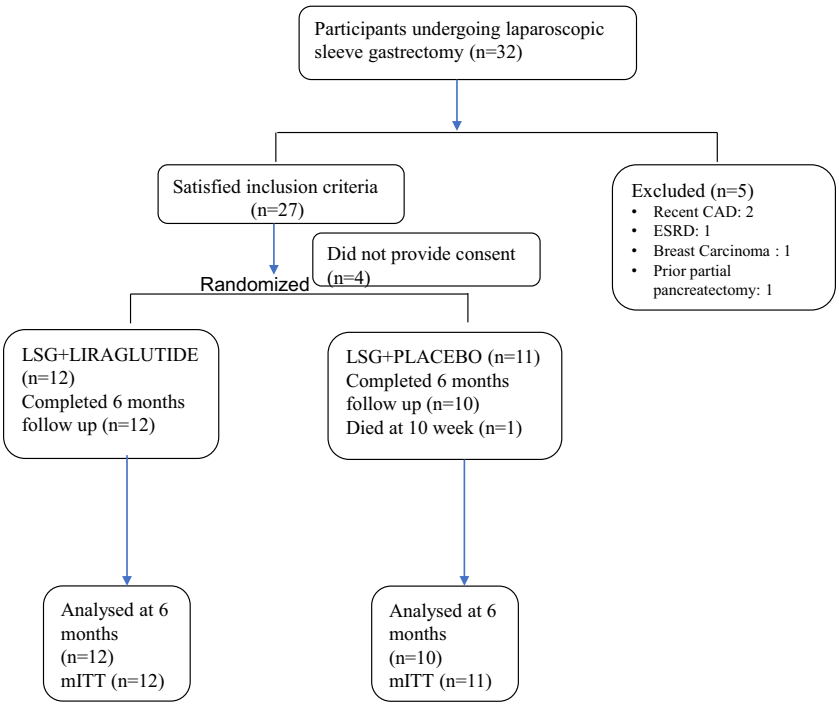

Fig. 1 Schematic representation showing inclusion and exclusion of participants in the study

Table 1 Baseline characteristics of the participants in two groups

Parameters	Total ($n = 23$)	Group L-L ($n = 12$)	Group L-P ($n = 11$)	p value
Gender (M:F)	11:12	6:6	5:6	0.330
Age (years)	42.9 ± 10.9	40.2 ± 11.8	44.7 ± 11.7	0.339
Height(cm)	160.5 ± 9.4	165.4 ± 12.7	156.7 ± 4.6	0.043
Weight(kg)	109.7 ± 18.5	117.6 ± 20.8	103.1 ± 15.1	0.071
BMI(kg/m^2)	42.5 ± 5.6	42.6 ± 6.3	41.6 ± 5.1	0.734
IBW(kg)	53.9 ± 10.0	60.1 ± 11.6	50.2 ± 6.4	0.069
EBW(kg)	55.7 ± 14.0	58.5 ± 18.3	52.9 ± 12.5	0.520
Dysglycemia, *n* (%)	12 (52.2)	6 (50)	6 (54.5)	0.901
Hypertension, *n*(%)	11 (47.5)	6 (50)	5 (45.5)	0.795
Dyslipidemia, *n* (%)	28 (87.5)	11 (91.7)	9 (81.8)	0.484
Sleep apnea, *n* (%)	28 (87.5)	11 (91.7)	9 (81.8)	0.484
GERD, *n* (%)	16 (50)	6 (50)	4 (36.4)	0.510
Arthritis, *n* (%)	14 (43.8)	4 (33.3)	5 (45.5)	0.552
Hypothyroidism, *n* (%)	8 (25)	3 (25)	4 (36.4)	0.554
Gall stone disease, *n* (%)	6 (18.8)	1 (8.3)	2 (18.18)	0.484

*$p < 0.05$ was considered significant

L-L, LSG +liraglutide; *L-P*, LSG + placebo

BMI, body mass index

IBW, ideal body weight; *EBW*, excess body weight

found to have pre-diabetes (2 each in either group) on oral glucose tolerance test at baseline.

Effect of Intervention on EBWL (Primary Outcome Measure)

The mean dose of liraglutide received in L-L group was 1.41 ± 0.49 mg per day. The %TWL at 6 months was 28.2 ± 5.7 and 23.2 ± 6.2 ($p = 0.116$); and %EWL was 58.7 ± 14.3 and 44.5 ± 8.6 ($p = 0.043$) (intergroup difference of 14.2 ± 5.4) in L-L group and L-P group, respectively (Table 2). The BMI decreased by 11.7 ± 3.5 in L-L group and 9.5 ± 4.0 ($p = 0.287$) in the L-P group from the pre-operative BMI (Table 2).

Effect of Intervention on Comorbidities (Secondary Outcome)

There was a significant decrease in FBG (11.7%), PPBG (15%) and HbA1c (13.2%) in either group with no intergroup difference in glycemic parameters at 24 weeks as shown in Table 3. Five (62.5%) out of 8 patients with diabetes and all participants with pre-diabetes were normoglycemic at the end of follow-up. Overall, 11 (47.8%) patients had hypertension before surgery with a mean duration of 5.7 ± 4.9 years, which resolved in10 (81.8%) participants at 24 weeks of follow-up. Hypertension resolved in all patients in L-L group and 4 out of 5 (80%) patients in the placebo group ($p = 0.08$).There was a significant increase in HDL-c, decrease in LDL-c and TG in either group with no intergroup difference at the end of the study (Fig. 2).

Nineteen (86.36%) patients had symptoms of sleep apnea at baseline with SAS of 4.00 ± 1.57 (symptom questionnaire) and none had OSA after 24 weeks of intervention (SAS 0.73 ± 0.83) in either group with no intergroup difference. Symptoms of GERD resolved in 4 (44.44%) out of 11 participants (50%) who had symptoms of GERD pre-operatively while 7 (63.64%) continued to be symptomatic. Out of the rest 12 asymptomatic patients pre-operatively, new onset GERD symptoms developed in 4 (44.44%) (3 in L-L group and 1 in L-P group) participants at 6 months post-surgery. The quality of life as assessed by BAROS score of entire cohort was 5.05 ± 1.55 at 6 months with an excellent outcome in 5, very good in 7, good in 9 and fair in 2 patients. The mean BAROS score at 6 months was 6.1 ± 1.21 and 4.07 ± 1.11 ($p = 0.01$) in L-L and L-P group, respectively. Excellent, very good, good and fair outcome were observed in 2, 6, 3 and 1 participants in liraglutide group and 1, 2, 6 and 2 participants in the placebo group, respectively.

The mean Framingham ASCVD risk score before surgery was 0.27 ± 0.15 and 0.20 ± 0.04 ($p = 0.662$) before surgery which reduced to − 0.73 ± 0.46 and − 0.75 ± 0.57 (0.879) in L-L and L-P group, respectively. The corresponding estimated 10-year coronary heart disease risk before and after surgery was 10.15 ± 11.82 and 6.19 ± 4.20 ($p = 0.464$) before surgery that reduced to 2.64 ± 1.72 and 2.95 ± 1.36 ($p = 0.757$) after 6 months in L-L and L-P group, respectively. There was a

Table 2 Impact of interventions on weight parameter in the two groups

Parameters	Follow-up	L-L group ($n = 12$)	L-P group ($n = 11$)	p value
IBW (kg)		60.1 ± 11.6	50.2 ± 6.4	0.069
Weight (kg)	Baseline	118.6 ± 24.6	103.1 ± 16.4	0.190
	6 weeks	103.5 ± 20.3	92.0 ± 32.4	0.237
	12 weeks	94.2 ± 17.6	84.8 ± 11.4	0.258
	24 weeks	85.1 ± 13.5	79.2 ± 10.6	0.381
BMI (kg/m^2)	Baseline	42.6 ± 6.3	41.6 ± 5.1	0.734
	6 weeks	36.5 ± 5.2	37.0 ± 3.9	0.848
	12 weeks	34.0 ± 4.4	34.5 ± 3.5	0.833
	24 weeks	30.9 ± 4.0	32.1 ± 3.0	0.554
EBW (kg)	Baseline	58.5 ± 18.3	52.9 ± 12.5	0.520
TWL (%)	6 weeks	12.7 ± 4.1	10.7 ± 3.9	0.198
	12 weeks	20.6 ± 6.3	17.7 ± 6.1	0.188
	24 weeks	28.2 ± 5.7	23.2 ± 6.2	0.116
BMI loss (kg/m^2)	6 weeks	6.2 ± 2.4	4.6 ± 2.6	0.267
	12 weeks	8.6 ± 3.0	7.1 ± 3.3	0.381
	24 weeks	11.7 ± 3.5	9.5 ± 4.0	0.287
EWL (%)	6 weeks	27.2 ± 10.1	20.4 ± 6.8	0.168
	12 weeks	42.6 ± 10.3	34.1 ± 8.1	0.112
	24 weeks	58.7 ± 14.3	44.5 ± 8.6	0.043*

*$p < 0.05$ was considered significant

L-L, LSG +liraglutide; *L-P*, LSG + placebo

BMI, body mass index

IBW, ideal body weight; *TWL*, total weight loss; *EWL*, excess body weight loss

decrease in 10-year CHD risk of 8.16% at 6 months. However, the decrease in FRS score and 10-year CHD risk was similar in the two groups after 6 months of respective interventions.

Adverse Events

There was no mortality or major complications in the immediate post-operative period. One patient required non-invasive ventilation on post-operative day 0 which subsequently improved. Ten (45.5%) patients complained of transient scalp hair loss at 6-week follow-up, which resolved at 6 months. The incidence of symptoms of nausea (41.7% and 36.4%, $p = 0.765$), vomiting (33.3% and 27.3%, $p = 0.655$) and headache (16.7% and 9.1%, $p = 0.866$) was similar in L-L and L-P group, respectively.

Discussion

In the present study, we investigated whether adding liraglutide after LSG may augment the weight loss in obese individuals. We found that liraglutide when added after LSG was associated with 14% additional weight loss in comparison with placebo. Liraglutide was tolerated by the participants after LSG and incidence of gastro-intestinal symptoms was no more different in comparison with prior reports of liraglutide administration alone. We also observed a significant resolution/improvement of obesity-related comorbidities including dysglycemia, hypertension, dyslipidaemia, CAD risk, sleep apnea, GERD and quality of life.

We observed a 51.7% EWL after 6 months of intervention in either group. EWL in obese individuals receiving liraglutide after surgery was significantly higher (58.7%) compared with surgery alone (44.5%) ($p = 0.043$) at 6 months. There was an additional 14.2% EWL over and above that of placebo suggesting the benefit of liraglutide. The EWL in the present study after addition of liraglutide following LSG was higher than our prior experience with LSG alone (47.9%) [10]. Similarly, various other studies from different continents including participants of varied ethnicities have documented EWL of 35–50% in the first 24 weeks of LSG [13–18] which is lesser as compared with the weight loss observed following early addition of liraglutide to LSG in the present study. The mean BMI decrease of 10.4 kg/m^2 at 24 weeks from a baseline BMI of 41.7 kg/m^2 in the present study is comparable with a prior published report of 11.3% following bariatric surgery [10].

Table 3 Glycemic parameters in the two groups after intervention

Parameters	Follow-up	L-L group ($N = 12$)	L-P group ($N = 11$)	p value
FBG (mg/dl)	Baseline	106.5 ± 38.4	127.1 ± 69.2	0.504
	6 weeks	96.5 ± 24.1	99.6 ± 12.0	0.771
	24 weeks	98.4 ± 35.0	95.6 ± 14.9	0.741
PPBG (mg/dl)	Baseline	161.9 ± 51.3	192.5 ± 57.6	0.314
	6 weeks	144.3 ± 26.5	159.6 ± 20.5	0.251
	24 weeks	127.9 ± 19.5	159.9 ± 25.0	0.020*
HbA1C (%)	Baseline	6.0 ± 1.5	6.5 ± 1.4	0.554
	6 weeks	5.6 ± 0.7	5.9 ± 0.5	0.868
	12 weeks	5.1 ± 1.5	5.4 ± 0.6	0.736
	24 weeks	5.1 ± 0.5	5.3 ± 0.1	0.516
C-peptide (IU/l)	Baseline	2.6 ± 1.2	3.6 ± 0.1	0.136
	6 weeks	4.9 ± 3.6	3.2 ± 1.8	0.273
	12 weeks	3.6 ± 1.4	3.3 ± 1.7	0.721
	24 weeks	3.2 ± 2.8	2.2 ± 1.2	0.411
Insulin (pg/ml)	Baseline	9.7 ± 5.5	9.8 ± 10.3	0.979
	6 weeks	10.6 ± 13.7	8.3 ± 7.5	0.201
	12 weeks	9.9 ± 4.9	7.0 ± 4.2±	0.267
	24 weeks	6.4 ± 3.2	4.4 ± 2.7	0.245
HOMA-IR	Baseline	4.2.0 ± 4.0	7.0 ± 4.2	0.262
	6 weeks	3.9 ± 3.1	4.2 ± 3.2	0.160
	24 weeks	1.8 ± 0.9	2.9 ± 2.2	0.233

*$p < 0.05$ was considered significant

L-L, LSG +liraglutide; *L-P*, LSG + placebo

FBG, fasting blood glucose

PPBG, post-prandial blood glucose

HOMA-IR, homeostatic model assessment of insulin resistance

LSG is known to increase GLP-1 levels by four times from basal levels (supra-physiological) [19]. A further augmentation of GLP-1 levels by the addition of liraglutide may be the reason for significantly higher excess body weight loss with the addition of liraglutide to LSG in the present study was possibly. Secondly, liraglutide users had more incidence of nausea and vomiting in the present study which might have contributed to additional weight loss in L-L arm. However, EBWL in initial few weeks was not found to be statistically different in the two groups. It is known that EBWL increases over longer duration of follow-up following bariatric surgery and may further increase with the continuation of liraglutide, as it has been observed that participants undergoing LSG continue to experience weight loss so as to reach nadir around 24 months before plateauing [18]. Body weight loss in early few months following restrictive bariatric procedures is attributed to initial calorie restriction, an increase in GLP-1 levels that starts as early as 2 days post-surgery and may persist up to 24 months (mainly so with RYGB), increase peptide YY (PYY), decrease in ghrelin or a change in gut microflora [6, 7, 19]. The individual contributions of these mechanisms to weight loss following bariatric surgery is not known but enhanced augmentation of GLP-1 levels may be associated with significant weight loss in patients receiving liraglutide early after LSG in the present study [9, 20, 21].

Overall, 52.2% (12 of the 23) patients had dysglycemia at baseline in the present study that included 8 participants with diabetes and 4 with pre-diabetes. There was a significant improvement in glucose parameters including fasting (11.7% decline), post-prandial glucose (15%) and HbA1c (13.2%) during follow-up. The decrease in blood glucose values was observed as early as day one following sleeve gastrectomy. Overall, "resolution" of type 2 diabetes was observed in 62.5% participants (4 out of 4 in liraglutide arm and 1 out of 4 in placebo arm), and glucose improved in remaining 37.5% of patients with diabetes; however, none had pre-diabetes at the end of 6 months after surgery. The resolution or improvement in glucose parameters in the present study is comparatively less in comparison with 1-year resolution of diabetes data by Agarwal et al. [22](77.8%), but similar to PCORNet study (55.9%) [23]. However, the improvement in dysglycemia in the present study is more than our prior experience in that we noted 58.6% resolution at 6 months

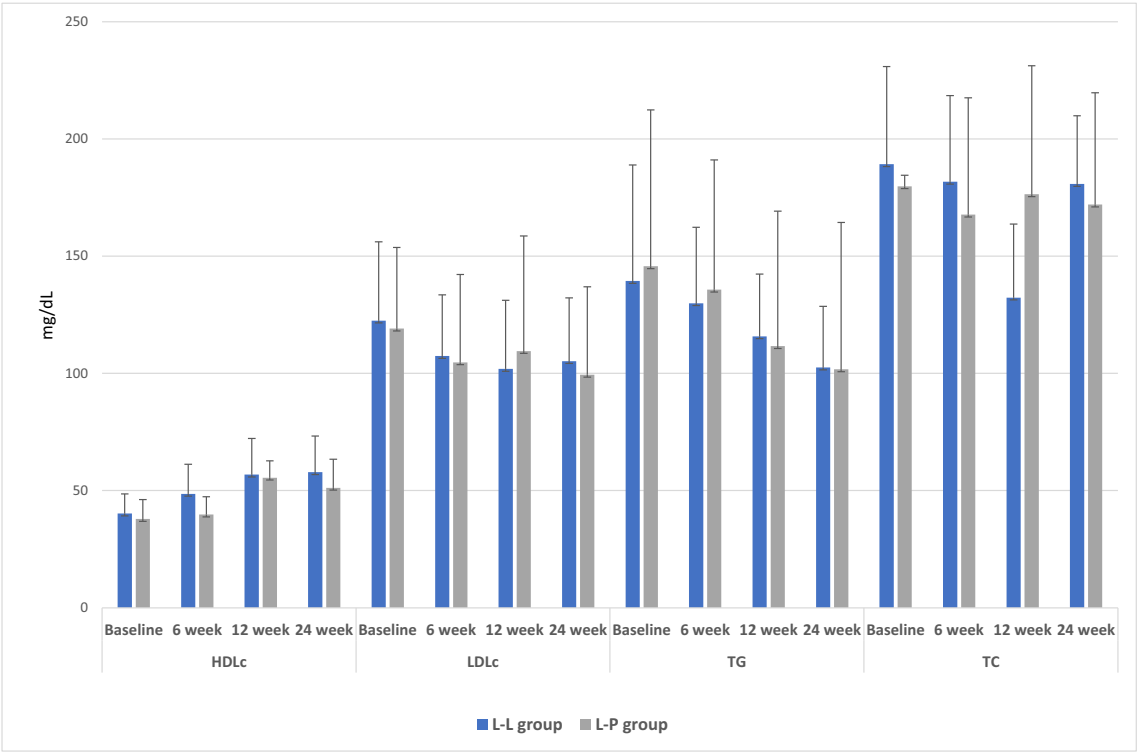

Fig. 2 Change in lipid parameters after intervention in the two groups. HDLc, high-density lipoprotein cholesterol; LDLc, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; L-L group, laparoscopic sleeve gastrectomy + liraglutide; L-P group, laparoscopic sleeve gastrectomy + placebo

and 36% at 1 year [10]. Better glycemic outcomes of LSG within a short follow-up of 24 weeks in the present study are attributable to liraglutide, as all patients with diabetes in liraglutide arm had resolution. However, "resolution" of diabetes may not be strictly applied in the present study as diabetes resolution is defined by the discontinuation of all the pharmacotherapeutic agents for glucose management unlike the patients in our study who were on liraglutide until the end of follow-up [24]. We also observed a direct correlation between the decrease in BMI and fall in insulin by 36.8% in the present study. The observed improvement in insulin response was mainly because of decrease in weight, low caloric intake, decreased inflammatory mediators and decreased ghrelin production which has diabetogenic effects and increased GLP-1 production which has anti-diabetic effects leading to improved glucose metabolism [20, 24].

LSG has also been shown to cause decrease in blood pressure and resolution of hypertension in significant number of participants [25]. Overall, 80.8% of participants in the present study were off all anti-hypertensives at the end of 24 weeks of follow-up, in spite of 7-year duration of hypertension before the bariatric surgery. Our results (80.8% resolution) are in agreement with prior published meta-analysis [26] and a large study by Alvarenge et al. [27] reporting 91% resolution or improvement of hypertension in patients undergoing LSG. Hypertension resolved in 100% patients in liraglutide group and 80% patients in placebo group in the present study. A higher and earlier resolution of hypertension in the present study could be attributed to liraglutide as it has been shown to effect dose-dependent decrease in systolic blood pressure by 3.18 mmHg (95% CI: 4.32–2.05) but no significant effect on diastolic blood pressure [28]. The decrease in blood pressure is noticed as early as 2 weeks after initiation of liraglutide and only partly explained by weight loss effect [28]. Similarly, dyslipidaemia resolved in overall 70% patient in our study which is comparable with a single-centre study of 1020 patients by Alvarenge et al. suggesting 79% dyslipidaemia resolution [27]. Dyslipidaemia resolved in 71.4% patients in liraglutide group and 50% patients in the placebo group, a difference that was not statistically significant probably because of small sample size and short duration of follow-up. We noticed 33% increase in HDLc and a 28.3% decrease in TG, with lesser effect on LDLc and total cholesterol as also observed by Zhang et al. [29]. A decrease in insulin levels and insulin resistance was the possible reason for the predominant effect of LSG on HDLc and TG. However, liraglutide administration for short duration has not been shown to alter the HDLc or VLDL [9]. The improvement in lipids and decrease in insulin after LSG was associated with a decrease in Framingham risk score in both arms of the present study in spite of more weight loss in the liraglutide arm. No additional benefit of liraglutide on ASCVD risk score in the present

study could be because unlike the SGLT2 inhibitors [30], liraglutide does not decrease CHD risk in patient without previous history of CAD, as was the participant profile in the present study [21].

We noticed a significant decrease in sleep apnea score in both the groups attributed to a significant decrease in weight. GERD symptom though improved after LSG in the two groups but significant number of participants experienced new-onset GERD symptoms with liraglutide usage. There was a resolution of GERD symptoms after LSG in 33% patients in our prior experience [10] and 50% resolution by Agarwal et al. [22]. Many studies have previously showed improved quality of life after LSG like Bobowicz et al. reported excellent global BAROS outcome in 13% of patients, very good in 30%, good in 34%, fair in 9.5% and failure in 13% [31]. We also observed excellent outcome in 5, very good in 7, good in 9 and fair in 2 patients on BAROS score after LSG. The mean BAROS score in liraglutide group was better than placebo at 6 months (6.11 ± 1.21 and 4.07 ± 1.11, $p = 0.01$), which could be attributed to more weight loss in the liraglutide group.

The main strength of the study is the novel concept of assessing the impact of a combination of laparoscopic sleeve gastrectomy with liraglutide on additional weight loss over and above that of laparoscopic sleeve gastrectomy alone. A placebo-drug-controlled design, uniform pre- and post-operative dietary regimen with good adherence to study medication and rigorous follow-up lends the data robustness. An additional weight loss by early introduction of liraglutide to patients undergoing LSG lends credit to the proof-of-concept of benefits of weight loss pharmacotherapy to bariatric surgery. However, limitations of present study include a small sample size and a short follow-up period of 6 months. The weight loss with bariatric surgery usually peaks by 24 months; hence, the addition of pharmacotherapy in poor responders to LSG after 2 years could be considered in future studies. We assessed by SAS questionnaire and sleep polysomnography considered as the gold standard could not be performed.

In conclusion, the addition of liraglutide in early weight loss phase after LSG is more effective than LSG alone for weight loss in morbidly obese patients during the initial 6 months. However, the addition of liraglutide after LSG may not provide additional benefit for the glycaemic parameters, insulin resistance, lipids and other obesity-related comorbidities over a short period of 6 months. A longer continuation of liraglutide would be desirable in future studies for additional cardiovascular benefits.

Author's Contribution LSG was performed by RG and UT. UT and AR were involved in pre-operative and post-operative clinical care of the patient and writing initial draft of the manuscript. RG, AR and AB proposed the concept, designed the protocol of the study and edited the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all participants included in the study.

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