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Original Research Article

Patient analysis and case-control investigation for high-output ileostomy control with glucagon (PACIFHIC-G) like peptide-1 analogues: a case control study

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ABSTRACT

Background: High ostomy losses (HOL) in the early postoperative (PO) period after an ileal resection are in an adaptation phase. After resection of the terminal ileum or proximal colon L cells are lost, this reduces the synthesis of glucagon-like peptide (GLP), its loss accelerates intestinal transit and gastric acid hypersecretion. An adequate adaptation phase is induced by enterotrophic hormones such as GLP. In this case control study, we performed an analysis of clinical outcomes with a conventional treatment compared with liraglutide intervention, a GLP-1 analogue.
Methods: A single center, case-control study, from January 2021 to April 2023, patients had an ileal resection >20 cm, >18 years old, previously treated with loperamide 12 mg and omeprazole 80 mg, continued >1500 ml output at 48 hours PO, 30 patients where collected, 15 patients followed with a watch and wait approach and 15 patients treated 0.6 mcg of liraglutide every day for 8 weeks.
Results: Clinical outcomes were followed for 6 months. Centimeters of resection had a statistically significant difference $p<0.001$ (control 20-180 cm vs. liraglutide 20-330 cm). Clinical outcomes with a significant difference where hospital length stay $p<0.01$ (control 4-133 days vs. 1-51 days) and hypovolemic shock $p<0.05$ (control 5 patients vs. 0 patients). Kaplan-Meier curve an 80% vs 100% 30 day survival rate in controls and liraglutide respectively.
Conclusions: This is the first study with patients with HOL using liraglutide as an adaptation therapy. Patients had better clinical outcomes in mortality, length stay and hypovolemic shock.

Keywords: Ileostomy, High-output stoma, GLP-1, Intestinal failure, Ileo-colonic break, Liraglutide

INTRODUCTION

The timeline of research on the use of GLP-1 analogs takes us to its origins in the first investigations where it was noticed that a smaller remnant of intestine required a greater parenteral contribution that was disproportionate to the loss of tissue. This was initially found in a case reported series of 17 patients, 12 with < 100 cm remnant required parenteral support and 21 with <50 m remnant required parenteral supply.[1] This led to the hypothesis that the plasma concentration of GLP-2 could influence the adaptation phase due to its enterotrophic effect.[2]

This theory was reinforced in 2000 in a study of 14 patients, 7 in a control group and 7 with a resection resulting in a remnant <140 cm, where they found a significant difference in plasma GLP-2, 23 pmol/l in the control group and 72 pmol/l in the studied group (more than 3 times the baseline value) with a significant difference $p<0.01$.[3] The administration of GLP analogues

increases its concentrations from 11 pmol/l to 3742 pmol/l.[4]

Subsequently, a trial was detailed to describe GLP supplementation in 2013. In a clinical trial of 9 patients, the use of an infusion of GLP-1 and GLP-2 was compared, where lower fecal output, lower fluid losses, greater weight gain and electrolytes were found.[5]

To describe the direct effect on the intestine, an *in vivo* study was carried out where GLP-1 and GLP-2 were used to stimulate L cells. When stimulated, these cells produce peptides derived from pro-glucagon, which have a direct effect on the intestine, causing hypertrophy of the microvilli. This growth was evident from the fourth day after starting the administration of GLP-2 in mice.[2]

GLP-1 has to date only been studied in patients with short bowel syndrome (SBS), a study details its effect on the performance of ileostomies in an non-randomized clinical trial of 8 patients where stoma output was reduced by 474±563 g/d (p=0.049), greater uresis by 765±759 ml/d, as well as energy absorption by 902±882 kJ/d (p=0.02).[6]

It is considered that the cause of HOL in patients with ileostomy in this context occurs due to a decrease in the absorption area, however, it is often forgotten that one of the causes may be the rupture of the ileocolonic break, since the half life of endogenous GLP is short, ileal resections can rapidly alter the ileal break feedback and lead to gastric hypersecretion, accelerated gastric and intestinal transit, and predispose to poor intestinal adaptation to recover its absorptive capacity.[16,17]

The L cells produce GLP-1 and generate physiological digestive changes such as: delayed gastric emptying, decreased gastric secretions, increases intestinal blood flow, improves the absorption of nutrients and fluids, prevents apoptosis of enterocytes, and, stimulates the growth of the large and small intestine through proliferation of crypt cells.[2,7-10,14,20] GLP-2 receptor analogs (GLP-2a) were the first hormones to be used to address ileocolonic brake, GLP-1 receptor analogs (GLP-1a) have equivalent effects.[5,6,15]

To date, there are generalized guidelines that recommend its use in intestinal failure of any cause; however, these recommendations are based on cohort interventions and clinical trials in chronic intestinal failure. To our knowledge, there is no evidence of its use in patients with acute intestinal failure in the postoperative period, which may be associated with the resection of the small intestine and the loss of GLP-producing tissue acutely disrupting the axis.

Objective

The objective was to compare how administration of liraglutide reduces complications, mortality, hospital stay and reinterventions in patients with ileostomies in the postoperative period of a small intestine resection when presenting a high-output ileostomy.

METHODS

This was a single center observational case-control study. The study was carried out from January 2021 to April 2023, in the Department of General Surgery of the Fernando Quiroz Gutiérrez Hospital, a second-level center in Mexico City, Mexico. Demographic, clinical and therapeutic data were taken from the electronic clinical record.

Participants

Inclusion criteria

Records of patients who were diagnosed in the period from January 2021 to April 2023, in the Department of General Surgery of the Fernando Quiroz Gutiérrez Hospital, a second-level center in Mexico City, Mexico; patient records with complete clinical records consisting of medical history, service note and follow-up notes, as well as surgical reports and histopathological reports; patients with acute intestinal failure in the postoperative period; patients older than 18 years of age; patients managed with loperamide regime; stomal output greater than 1500 milliliters daily; management with omeprazole regime; and patients in the immediate post-operative period with an intestinal resection of ileum greater than 20 centimeters were included.

Exclusion criteria

Patient records with incomplete information or clinical history and without follow-up during the period included; patients allergic to liraglutide, allergic to loperamide, allergic to omeprazole; patients who reject management with injected medications; patients with documented hypoglycemia prior to the intervention; patients with pancreatitis; patients with intestinal obstruction; time to start management greater than 2 days of optimal management without intervention with liraglutide; patients with adverse reaction to liraglutide were excluded.

Variables

Independent

Sex: Biological difference between male and female based on anatomical characteristics.

Age: Chronological measure unit based on years lived by the participant.

Lenght of resection: Amount of intestine removed during surgery measured in centimeters.

Height of resection: Distance from the Treitz flexure to the resection measured in centimeters.

Acute intestinal failure: Failure according to the ESPEN criteria of pathophysiology of loss of mucosa resulting in insufficient absorption, clinically expressed as ostomy output more than 1,500 ml; a type I functional failure of the postoperative period and FE1 clinical criteria requiring more than 1,000 ml of parenteral fluid.

Loperamide regime: Treatment of loperamide with the traditional maximum dose of 12 mg.

Liraglutide regime: According to the usual dose used by the American Diabetes Association of 0.6 mcg daily for 2 weeks, 1.2 mcg daily for 2 weeks and 1.8 mcg daily for 4 weeks after 48 hours of previous medical loperamide and omeprazole regime was used.

Omeprazole regime: Dose used for secretory intestinal failure as 80 mg of omeprazole daily.

Dependent

Stomal output: Wet weight of stoma output measured in milliliters.

In-hospital stay: Length of hospital stay measured in days before safe discharge.

Safe discharge: Patient discharge meeting criteria of: output <1,000 ml, hemoglobine >8 mg/dl, parenteral fluid or parenteral nutrition therapy (PNT) requirement <1000 ml.

Re-admission: Event where a patient who was previously discharged from the healthcare facility is admitted again within 6 months, measured in times the event was present.

Dehiscence: Separation of the junction where the mucous membrane of the ileostomy meets the surrounding skin.

Surgical reinterventions: Need for an additional surgical procedure after an initial surgery.

Days to control: Days taken to achieve ileostomy output lower than 1,000 fluid.

Intensive fluid therapy reanimation (IFTR): Aggressive administration of fluids to restore circulation after, severe dehydration, hypovolemic or septic shock.

Severe dehydration: advanced and potentially life-threatening loss of fluid and electrolytes with classical clinical manifestations as: oliguria, lethargy, extreme tiredness with dry and cool skin, with cognitive and neurological effect as dizziness, confusion and fainting.

Hypovolemic shock: Loss of circulating volume with clinical manifestations of tachycardia, hypotension (mean arterial pressure less than 65 mmHg, oliguria with cool and clammy skin.

Septic shock: Definition of sepsis-3 criteria.

Death: Permanent and irreversible cessation of all vital functions.

Patients were followed-up for 6 months after diagnosis of acute intestinal failure was stablished. After 48 hours of loperamide and omeprazole regime with dietary changes liraglutide regime was started in 15 patients. Clinical data was obtained and compared between groups.

Bias

We conducted a multiple data source, we did a transparent reporting of comorbidities, there were no difference in age and comorbidities between groups and the intervention group had a statistical significance difference in length of resection favoring a longer intestine remanent in the control group.

Study size

Incidence rate of the disease inherently limits the number of available cases, making it impractical to use more rigorous sampling methods. As such, a convenience sample was chosen to ensure that we could gather enough data to make meaningful analyses. As with all studies using this sampling method, we recognize its potential limitations and advocate for a cautious interpretation of the findings. While this sample size provided valuable insights, the findings should be interpreted with caution, and replication in studies with larger samples is recommended to confirm our observations.

Statistical method

In our analysis, we employed a range of statistical tailored to the nature of our data. For categorical variables, the chi-squared test was utilized to discern associations between groups. For comparing continuous, non-normally distributed data between groups, the Mann-Whitney U test was chosen. When dealing with normally distributed data, the student's t test was applied. Additionally, given the need to assess the mortality without the intervention in our study, the Kaplan-Meier survival curve was plotted to visualize the differences in survival periods between group.

RESULTS

A sample of 30 patients were studied, in the control group there were 53% men and 47% women, in the reated group there were 60% men and 40% women. In the control group the average age was 61 years with a range of 49 to 90 years, in the intervention group it was 53 years with a range of 38 to 85 years.

In the liraglutide group the average number of centimeters resected was 40 cm with a range of 20 to 180 cm, in the liraglutide group an average of 60 cm was

resected with a range of 20 to 330 centimeters. The height at the Treitz angle at which the stoma was located on average was 350 cm in the control group with a range of 120 to 390 cm and 280 cm in the liraglutide group with a range of 90 to 390 cm.

Table 1: Baseline population characteristics.

Characteristics	Control	Liraglutide	P
Sex (%)			
Men	53	60	0.703
Woman	46	40	0.703
Age	61 (4-90)	53 (38-85)	0.079
Length of resection	40 (20-180)	60 (20-330)	0.001
Hypertension (%)	20	30.80	0.512
Obesity (%)	6.70	0	0.342
Diabetes (%)	20	38.50	0.281
Cancer (%)	0	15.40	0.115
Height of resection	350 (120 - 390)	280 (90-390)	0.275

Table 2: Clinical outcomes, ranks and p values.

Parameters	Control	Liraglutide	P
Reintervention	1 (0-14)	0 (0-6)	0.196
In-hospital stay	11 (4-133)	5 (1-51)	0.007
Intensive fluid therapy reanimation	5	0	0.049
Length of resection	40 (15-180)	60 (20-330)	0.001
Re-admission	7	3	0.426
Deaths	3	0	0.088
Days to control	6 (0 - 35)	3 (1-8)	0.058

Table 3: Percentage results between groups.

Result	Control (%)	Liraglutide (%)
Reintervention	64	35.70
Intensive fluid therapy	33.3	0
Re-admission	46.60	20
Deaths	20	0

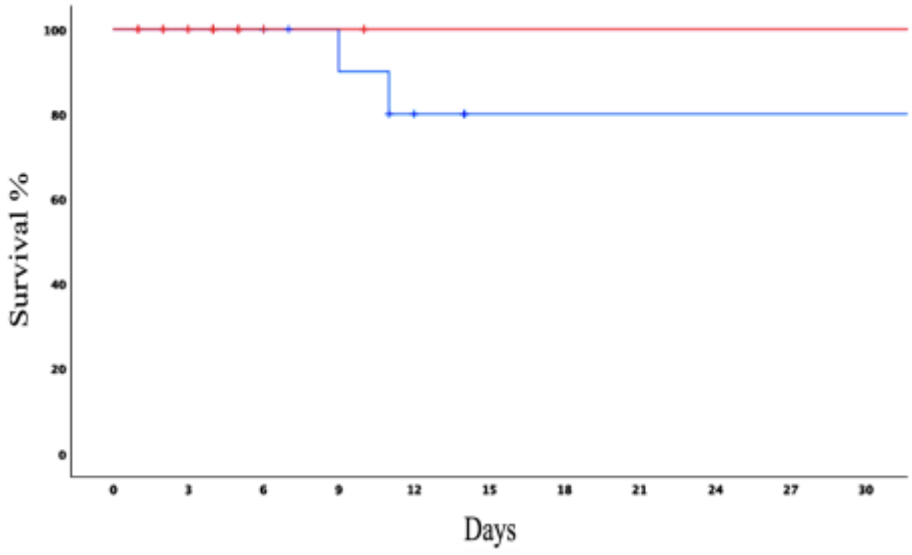

Figure 1: Kaplan-Meier survival curve.

About comorbidities, 20% of hypertensive patients were found in the control group and 38.5% in the liraglutide group, 20% with diabetes mellitus in the control group and 30.8% in the liraglutide group. Regarding patients with a history of a cancer diagnosis, 0% were found in the control group and 15.4% in the liraglutide group.

We only found a significant difference in terms of centimeters of intestine resected, with less resection in the control group than in the liraglutide group. Baseline characteristics and resection length are illustrated in Table 1.

Regarding the detailed variables, we found reinterventions with a mean of 1 with a range of 0 to 14 and a mean of 0 with a range of 0 to 6 in the operated group, finding a p=0.196. Regarding the in-hospital stay, we found in the control group 11 days on average with a range of 4 to 133 days compared to the operated group with 5 days on average with 1 to 51 days in range, a non-normal distribution was found that comparing the ranges a p of 0.007 is found (p<0.01).

There were 5 patients who required IFTR in the control group and 0 in the intervention group with a p of 0.049. Regarding readmissions, there were 7 patients with readmissions in the control group and 3 in the operated group with a p of 0.426. Differences in clinical outcomes expressed in percentage are detailed in Table 2.

The number of days to achieve control was found to be 6 days on average in the control group with a range of 0 to 35 days and 3 days in the intervention group with a range of 1 to 8, resulting in a p value of 0.058.

The survival trend at 30 days without intervention is 80% compared to 100% in the intervention group as shown in Figure 1.

DISCUSSION

This was the first analysis of the use of GLP-1a in postoperative intestinal failure associated with ileum resection. There were no published experience on interventions in patients with type I and II intestinal failure theoretically caused by the reduction of GLP-2-producing enteroendocrine tissue. In this study we analyzed an intervention in the ileocolonic axis as it could be a crucial target therapy for a rapid and improved recovery.

Patients with SBS or chronic intestinal failure treated with GLP analogues have lower frequency of adverse events, urgent major surgical interventions, complications and deaths.[5,6,15,18-20] The available literature focused on chronic intestinal failure and the surgical effect to the ileal brake axis have not been explored. Prospective, randomized clinical trials and cohorts have not currently explored this mechanism. Therefore, this would be the first case-control study focused on acute intestinal failure.

Complications frequently occurred with a longer adaptation period that can be avoided by shortening it with GLP-1a, (21,22) in our study we found a significant difference in the days of hospital stay, 4 to 133 days in the control group and 1 to 133 days in the control group. 51 days in the operated group with a p 0.007 (p<0.01), theoretically this would reduce the hospital stay and could also reduce complications inherent to it, as well as health cost" delete "such as infections associated with health care, in addition to reducing the health cost to the hospital stay.

Since success is achieved through a multimodal approach to the control of intestinal failure, GLP1a provides the opportunity for better recovery by avoiding rescue strategies.[21,23] Despite our prediction, no significant difference was found in the number of reinterventions or requirement for stoma remodeling with p=0.196 and p=0.465. However, patients treated with GLP-1a in this study did not have a requirement for IFTR compared to the control group, resulting in a p 0.049 (p<0.05).

There were limitations to our study. Denmark had the highest incidence of patients with inflammatory disease in the world with 500 patients per 5 million inhabitants, approximately half of them suffer from intestinal failure, therefore, there are few patients living with IF. A bigger sample in our environment was a challenge.

CONCLUSION

Patients treated with liraglutide have a shorter in-hospital length stay, fewer requirement for IFTR, when analyzing the Kaplan Meier curve we found alarming data regarding conventional management, with a low survival trend of 80% at 30 days, when survival with GLP1-a remains at 100%. Currently, the complications of patients with intestinal failure have been normalized in an era with several therapeutic options to guide our management and avoid these consequences. It continues to be a research opportunity to detail in a larger study the effect of this and other agents to offer an improved recovery. Sample size and a statistical significance difference in length of resection could have harmed results disfavoring de liraglutide group, nonetheless results favored our intervention.

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