A duodenal sleeve bypass device added to intensive medical therapy for obesity with type 2 diabetes: a RCT

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Scientific summary

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Scientific summary

Background

The EndoBarrier® is an endoluminal duodenal–jejunal bypass liner developed by GI Dynamics Inc. (Boston, MA, USA) for the treatment of obese patients with type 2 diabetes mellitus. It consists of a single-use endoscopic implant with a removable nitinol stent anchor to affix to the wall of the duodenum to which an impermeable fluoropolymer sleeve is attached that extends 60 cm into the small bowel. As a result, gastric contents bypass the proximal intestinal tract by travelling inside the sleeve, coming into contact with pancreatic juices and bile only when they exit the sleeve in the jejunum. This device is currently licensed for up to 12 months of treatment.

A systematic review and meta-analysis of five randomised controlled trials and 10 observational studies on the effects of the endoluminal duodenal–jejunal bypass liner versus medical care demonstrated that patients in the endoluminal duodenal–jejunal bypass liner group lost 5.1 kg more weight than patients who underwent medical care, and, although glycated haemoglobin reduced substantially in both groups, there was no significant difference in glycated haemoglobin between the groups. The safety profile of the endoluminal duodenal–jejunal bypass liner was considered acceptable and predominantly considered abdominal pain, nausea and vomiting. The meta-analysis demonstrated significant risk of bias and called for larger randomised controlled trials with longer follow-up.

The aim of this randomised controlled trial was to compare the efficacy of intensive medical therapy with and without the endoluminal duodenal–jejunal bypass liner on glycaemic control in patients with type 2 diabetes mellitus and obesity in both the short and medium terms. In addition, we wanted to evaluate the cost-effectiveness of the interventions and elucidate the physiological mechanisms through which the endoluminal duodenal–jejunal bypass liner exerts its clinical effects.

Methods

This was an open-label randomised controlled trial conducted in two academic clinical centres in the UK: Imperial College London and University Hospital Southampton NHS Foundation Trust. Male and female patients aged 18–65 years with a body mass index of 30–50 kg/m^2 and a confirmed diagnosis of type 2 diabetes mellitus for at least 1 year, and who had inadequate glycaemic control and were on oral glucose-lowering medications, were eligible for the trial. Randomisation was conducted via the InForm system (InForm version 4.6, database version Oracle 10g release 10.2.0.4.0, Oracle Corporation, Redwood City, CA, USA) and stratified by site and body mass index group.

The study captured and processed data using the InForm electronic case report form. The trial was sponsored by Imperial College London and managed by the Imperial Clinical Trials Unit in accordance with the National Institute for Health Research guidance. The trial was approved by the Research Ethics Committee (14/LO/0871) and conducted in accordance with the Declaration of Helsinki (trial registration: ISRCTN30845205).

Patients in both treatment arms were invited to participate in the following mechanistic study subgroups:

- subgroup 1 – functional magnetic resonance imaging of food reward
- subgroup 2 – insulin sensitivity
- subgroup 3 – eating behaviour.

Trial interventions

Intensive medical therapy without the EndoBarrier

Participants in both arms of the trial had their type 2 diabetes mellitus managed in accordance with the guidelines of the American Diabetes Association. Patients received dietary and physical activity counselling in accordance with local standards with the intention of providing each patient with lifestyle/behavioural modification information and good eating practices.

Intensive medical therapy with the EndoBarrier

After an 8-hour fast, patients had the endoluminal duodenal–jejunal bypass liner implanted as a day-case procedure under a general anaesthetic and as previously described. The device was removed after 12 months under sedation or general anaesthetic. Following explantation, patients were followed up for a further 12 months.

Mechanistic subgroups

Subgroup 1

Patients from both groups underwent functional neuroimaging of the brain reward response to food using a validated food evaluation functional magnetic resonance imaging protocol before and 6 months after the intervention.

Subgroup 2

Patients from both groups underwent measurements of hepatic and peripheral insulin sensitivity using the gold standard technique of hyperinsulinaemic–euglycaemic clamps with the addition of stable isotopes at baseline within 2 weeks of the intervention and at 6 months after the intervention.

Subgroup 3

Patients from both groups underwent measurements of their eating behaviour using a 24-hour recall, food preferences questionnaires, tests of the sensory and reward function of sweet/fat taste, and a mixed-meal tolerance test that included measurements of glucagon-like peptide 1, peptide tyrosine–tyrosine and fibroblast growth factor-19.

Plasma, urine and faecal samples for metabolic profiling analysis were collected from all participants who were able to provide samples at baseline and at 10 days, 6 months, 12 months and 24 months after the intervention. All samples were run through nuclear magnetic resonance spectroscopy using a validated protocol.

Cost-effectiveness

The cost-effectiveness of the endoluminal duodenal–jejunal bypass liner intervention was estimated in comparison with a combination of conventional medical therapy, diet and exercise alone. The analysis was conducted with data on the use of health and social care resources and health-related quality of life (EuroQol-5 Dimensions, five-level version) collected over the 2-year study period. Quality-adjusted life-years were estimated for members of the intervention and control groups based on EuroQol-5 Dimensions utility scores. The cost of explant procedures was also included in the cost-effectiveness analysis.

Primary objective

To compare intensive medical therapy with and without the endoluminal duodenal–jejunal bypass liner for obesity-related type 2 diabetes mellitus on its effectiveness as defined by the International Diabetes Federation as a glycated haemoglobin level reduction of $\geq$ 20%.

Secondary objectives

- To compare intensive medical therapy with and without the endoluminal duodenal–jejunal bypass liner for obesity-related type 2 diabetes mellitus for their effect on:
  - metabolic state as defined by the International Diabetes Federation with a glycated haemoglobin level of < 6% (or < 42 mmol/mol)
  - blood pressure of < 135/85 mmHg
  - absolute weight loss.
- To investigate the mechanism of the effect of the endoluminal duodenal–jejunal bypass liner via changes in:
  - brain reward response to food
  - insulin sensitivity
  - eating behaviour
  - plasma, urine and faecal metabonomics.
- To estimate the cost-effectiveness of the endoluminal duodenal–jejunal bypass liner compared with conventional treatment over the trial period (within-trial analysis).

Sample size calculations

The primary end point of a 20% reduction in glycated haemoglobin was chosen because the International Diabetes Federation produced new guidelines in June 2011 for the conduct of studies in diabetes using bariatric surgery or devices, with the aim of producing standardisation to allow comparison between studies. It was estimated that 15% of patients in the control arm would achieve the target of a 20% reduction in glycated haemoglobin. It was estimated that up to 30% of patients in the treatment group may have the device removed early. We diluted the treatment effect from 40% versus 15% to 35% versus 15%, achieving the target of a 20% reduction in glycated haemoglobin for the treatment arm versus the standard arm. A total of 73 patients per group would give 80% power to detect a significant effect. Adding 10% as the loss to follow-up increased the sample size to 80 per group.

Statistical analyses

The difference between the two study groups in the proportion of patients achieving the primary and secondary outcomes was analysed using logistic regression adjusting for the stratification variables (body mass index groups and sites). All statistical tests were two-tailed with a 5% significance level. Primary and secondary analysis were undertaken under the intention-to-treat principle such that all patients who provided data were included in the analysis. A sensitivity analysis to take missing data into account was carried out. Analyses for the mechanistic subgroups were assessed using a mixed model including fixed effects for treatment and time point (and their subsequent interaction) and an additional random effect for time point. Post hoc testing via least square means was also performed on any model parameters with a p-value of < 0.05.

Results

Primary and secondary clinical outcomes

There was no difference between groups in the percentage of patients achieving the primary outcome of a reduction in glycated haemoglobin level of 20% at 12 months [endoluminal duodenal–jejunal

bypass liner 54.5% vs. control 55.2% (odds ratio 0.93, 95% confidence interval 0.44 to 1.98; $p = 0.85$)] or at 24 months. A total of 16 out of 66 (24.2%) patients achieved 15% weight loss in the endoluminal duodenal–jejunal bypass liner group compared with 2 out of 56 (3.7%) patients in the control group at 12 months (odds ratio 8.33, 95% confidence interval 1.78 to 39.0; $p < 0.001$) but no difference was observed at 24 months (odds ratio 2.80, 95% confidence interval 0.27 to 28.54; $p = 0.39$). Participants in the endoluminal duodenal–jejunal bypass liner group experienced superior reductions in systolic blood pressure [−6.8 ± 17.8 mmHg vs. −1.0 ± 15.2 mmHg, respectively (adjusted mean difference −7.5 mmHg, confidence interval −12.5 to −2.4 mmHg; $p = 0.004$], total cholesterol concentrations [−0.49 ± 0.80 mmol/l vs. −0.01 ± 0.98 mmol/l, respectively (adjusted mean difference −0.41 mmol/l, 95% confidence interval −0.72 to −0.11 mmol/l; $p = 0.009$)] and alanine aminotransferase [−20.0 ± 22.0 U/l vs. −11.8 ± 15.7 U/l, respectively (adjusted mean difference −7.9 U/l, 95% confidence interval −11.90 to −4.03 U/l; $p < 0.001$)] at 12 months but not at 24 months.

Safety

A total of 856 adverse events were reported in 151 (89%) of the randomised patients; 47 of these were determined to be serious adverse events and occurred in 39 (23%) patients. Of the 47 serious adverse events, 42 (89%) were reported in the endoluminal duodenal–jejunal bypass liner arm; 26 out of the 42 serious adverse events (62%) were deemed to be definitely related to the study treatment. Of the five serious adverse events in the standard therapy arm, one was reported as life-threatening; all five events were unrelated to the study treatment. There was one confirmed liver abscess that was treated with computerised tomography-guided drainage and explantation of the device; the patient made a full recovery. In this study, a total of eight torn devices were noted on explant.

Mechanistic studies

Subgroup 1: brain reward responses to food

The appeal of food pictures decreased at week 26 in both groups. Although the decrease over time in the endoluminal duodenal–jejunal bypass liner group was larger than it was in the standard treatment group, and the decrease over time for high-energy food was greater than that found for low-energy food across both groups, neither result proved significant. Neither endoluminal duodenal–jejunal bypass liner insertion nor standard therapy changed blood oxygen level-dependent signal in a priori reward system functional regions of interest during the evaluation of any food pictures at week 26.

Subgroup 2: insulin sensitivity

There were significant reductions in endogenous glucose appearance in both groups at 10 days compared with baseline, but no differences between groups. Glucose disappearance was significantly higher in the endoluminal duodenal–jejunal bypass liner group than in the control group at 6 months.

Subgroup 3: eating behaviour

Total energy intake per day obtained from both the 24-hour recall and the 3-day food diaries was significantly reduced from baseline in both groups at all time points except for 24 months, but there were no significant differences between the groups. There were no consistent food preference differences between the groups.

There were no significant changes in plasma total glucagon-like peptide 1 and peptide tyrosine–tyrosine concentrations in either group. There were no consistent differences in plasma total glucagon-like peptide 1 and peptide tyrosine–tyrosine concentrations between the groups. There were no significant changes in fibroblast growth factor-19 concentrations either within the groups or between the groups.

Metabonomics

Plasma levels of the metabolites, including trimethylamine *N*-oxide and ascorbate, were found to be lower in the endoluminal duodenal–jejunal bypass liner group at 6 months than in the control group. In the endoluminal duodenal–jejunal bypass liner arm, there were significant changes in plasma metabolic profiles of patients at 6 or 12 months post EndoBarrier implantation in comparison with the baseline profiles. In the control arm, a significant orthogonal partial least-squares discriminant analysis model based on samples from baseline and 12 months was also observed.

Higher concentrations of faecal metabolites including lactate, 5-aminopentanoate and tyramine were observed in the endoluminal duodenal–jejunal bypass liner group than in the control group at 6 months, whereas glucose levels were lower. At 12 months, in addition to an increase in the metabolites lactate and tyramine seen at 6 months in the endoluminal duodenal–jejunal bypass liner group, there was also an increase in 2-aminoisobutyrate. At 12 months, there was also a decrease in tyrosine, malate, fumarate, glucose and oligosaccharides in the endoluminal duodenal–jejunal bypass liner group compared with the control group. Analysis of the endoluminal duodenal–jejunal bypass liner cohort of patients at 6 months and 12 months showed increased levels of lactate and tyramine in the stool samples compared with baseline, but a decrease in glucose levels. Another metabolite, trigonelline, was found to be lower in the endoluminal duodenal–jejunal bypass liner patients at both 6 months and 12 months compared with their baseline samples. In the endoluminal duodenal–jejunal bypass liner group, there were significant changes in the faeces metabolic profiles of patients at 6 months or 12 months post endoluminal duodenal–jejunal bypass liner implantation in comparison with the baseline profiles. In the control arm, there were no significant differences in faecal samples from baseline and 12 months.

Cost-effectiveness

Mean quality-adjusted life-years were similar between both treatment groups with overlapping confidence intervals: 1.660 (95% confidence interval 1.596 to 1.723) compared with 1.643 (95% confidence interval 1.581 to 1.705). Controlling for baseline utility and with imputation, the between-group difference in quality-adjusted life-years was estimated at 0.022 (95% confidence interval −0.047 to 0.090) over 2 years.

Base-case mean costs were higher in the treatment arm than in the control arm: £5445 (95% confidence interval £4921 to £5968) compared with £2225 (95% confidence interval £1853 to £2596). The difference was due to the direct cost of the intervention and higher medication costs in the treatment arm than in the control arm. The incremental cost-effectiveness ratio was £147,408 per quality-adjusted life-year gained. The incremental cost-effectiveness ratio was not sensitive to uncertainty over costs remaining > £100,000 per quality-adjusted life-year gained at the lower confidence limit for incremental costs and when a zero price was assumed for the endoluminal duodenal–jejunal bypass liner and consumables. Although more sensitive to incremental effects, the incremental cost-effectiveness ratio was still £35,700 per quality-adjusted life-year gained at the upper confidence limit for the mean quality-adjusted life-year difference.

Discussion

In this trial, we have demonstrated that the addition of the endoluminal duodenal–jejunal bypass liner to an intensive medical therapy was not associated with higher rates of participants achieving a ≥ 20% reduction in glycated haemoglobin. Participants in the endoluminal duodenal–jejunal bypass liner group lost significantly more weight than patients in the control group at 12 months, but this benefit was not observed at 24 months. The percentage of 'excellent responders' (i.e. participants achieving a clinically meaningful reduction in weight of 15%) was eight times higher in the endoluminal duodenal–jejunal

bypass liner group than in the control group at 12 months but was not statistically different between groups at 24 months. Participants in the endoluminal duodenal–jejunal bypass liner group experienced superior reductions in blood pressure, total cholesterol, alanine aminotransferase and aspartate aminotransferase at 12 months. The beneficial effects of the endoluminal duodenal–jejunal bypass liner on weight and cardiometabolic markers dissipated following explantation, with only marginal and non-significant differences between the groups at 24 months. We were nevertheless encouraged by the observation that both groups sustained part of their achievements in terms of glycated haemoglobin and weight loss reductions at 24 months, thus demonstrating the effectiveness of a truly intensive behavioural modification programme.

Overall, the side-effect profile from this study was similar to those in previously published studies of the endoluminal duodenal–jejunal bypass liner, with the major complications being liver abscess and migration of the device, with bleeding less likely if the patient is prescribed a high dose of proton pump inhibitor. In nearly all cases in which serious adverse events occurred, there were no permanent sequelae.

Despite the deep phenotyping of patients in terms of eating behaviour, we were unable to identify the mechanisms through which the endoluminal duodenal–jejunal bypass liner reduces energy intake. Even though we did not measure energy expenditure, the available literature does not provide any indication that this may be altered after implantation of the endoluminal duodenal–jejunal bypass liner.

The strengths of the trial include the randomised design; long-term follow-up period of 2 years; multidisciplinary care and delivery of a truly intensive medical therapy programme; use of two trial sites; study management by the Imperial Clinical Trials Unit; comprehensive profiling of patients in terms of their eating behaviour, glucose regulation and metabolic responses; and detailed health economic analysis. The main limitation of the trial is its open-label design, which could be a source of bias.

Following the closure of the ENDO trial (ClinicalTrials.gov. *Safety and Efficacy of EndoBarrier in Subjects With Type 2 Diabetes Who Are Obese (ENDO) Trial*. NCT01728116. URL: https://clinicaltrials.gov/ct2/show/NCT01728116; accessed 18 August 2020.) in the USA by the Food and Drug Administration in 2015, the EndoBarrier device was withdrawn from the US market. Furthermore, the recent increase in the number of reported device tears and the non-compliance related to quality control issues culminated in the endoluminal duodenal–jejunal bypass liner losing its Conformité Européenne (CE) mark in November 2017.

The evidence suggests that the EndoBarrier is not superior to intensive medical therapy for glycaemic control but is associated with significantly greater weight loss and improvements in cardiometabolic parameters at 12 months but not at 24 months.

Trial registration

This trial is registered as ISRCTN30845205.

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