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Published in:
Neurogastroenterology and Motility

DOI (link to publication from Publisher):
[10.5056/jnm16179](https://doi.org/10.5056/jnm16179)

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Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Klinge, M., Rask, P., Ejksjaer, N., Krogh, K., Lassen, K., & Ehlers, L. H. (2017). Early assessment of cost-effectiveness of gastric electrical stimulation for diabetic nausea and vomiting. *Neurogastroenterology and Motility*, 23(4), 541-549. <https://doi.org/10.5056/jnm16179>

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Early Assessment of Cost-effectiveness of Gastric Electrical Stimulation for Diabetic Nausea and Vomiting

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Background/Aims

Recurrent nausea and/or vomiting are common complications of diabetes mellitus. The conditions severely impact the quality of life of patients and often cause repeated admissions to hospital incurring significant healthcare costs. If standard treatment fails, gastric electrical stimulation (GES) may be offered in selected cases, as a minimally invasive, but expensive, therapeutic option. Our aims are to evaluate the clinical effect and the cost-utility of GES as a treatment for severe diabetic recurrent nausea and/or vomiting.

Methods

Among 33 diabetes patients implanted with GES because of recurrent nausea and/or vomiting, 30 were available for evaluation. The effect of treatment was assessed prospectively using symptom-diaries and the SF-36 questionnaires at baseline, after 6 and 12 months, and thereafter yearly. The number of days in hospital due to symptoms related to gastrointestinal dysfunction was calculated using hospital records 12 months prior to and 12 months after implantation.

Results

The surgical procedures were performed without mortality or major complications. Six months after surgery 78% of the respondents had at least 50% reduction in time with nausea and 48% had at least 50% reduction in days with vomiting. Symptom relief persisted at follow-up after at least 4 years. Quality adjusted life years improved after GES, which was cost-effective after 24 months.

Conclusions

GES reduces symptoms and improves quality of life in diabetes patients with recurrent nausea and/or vomiting. The procedure is supposed as cost-effective over a 2-year time horizon.

(*J Neurogastroenterol Motil* 2017;23:541-549)

Key Words

Diabetes mellitus; Electrical stimulation; Health care costs; Nausea; Vomiting

Received: October 15, 2016 Revised: January 4, 2017 Accepted: February 27, 2017

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Introduction

Gastroparesis (GP) is defined as a chronic gastric emptying disorder with absence of mechanical obstruction.¹ The 3 main groups of GP are diabetic, postsurgical, and idiopathic. The clinical characteristics of diabetes related GP include recurrent nausea and/or vomiting, early satiety, bloating, and abdominal pain. Symptoms of GP typically occur at least 10 years after diagnosis of diabetes mellitus (DM).² The estimated 10-year cumulative incidence of symptomatic GP is 5% in type 1 DM and 1% in type 2 DM.³ The condition is associated with significantly reduced quality of life and frequent admissions to hospital because of recurrent vomiting leading to dehydration and poor glycaemic control.⁴ The pathophysiology of diabetic GP is not fully established, but it is associated with neuropathy of extrinsic and intrinsic neurons, abnormal function of smooth muscle cells, and neuropathy of glia cells and the interstitial cells of Cajal.⁵ The majority of diabetes patients with delayed gastric emptying remain asymptomatic, and severe symptoms can be present even if gastric emptying tests are normal.⁶ Thus, treatment is usually initiated based on recurrent episodes of nausea and/or vomiting rather than a diagnosis of GP based on gastric emptying tests.

Dietary modifications are the first line of intervention for recurrent nausea and/or vomiting in diabetes patients. This is often insufficient and treatment is supplemented with prokinetics and antiemetics. If medical therapy fails, gastric electrical stimulation (GES) is a minimally invasive option. More extensive surgical procedures are only rarely performed as their rate of success is low and complications are common.⁷ Previous studies have shown that GES reduces nausea and/or vomiting and improves quality of life in patients with DM.⁸⁻¹¹ GES is performed by a laparoscopic procedure and usually only requires a few days in the hospital. The stimulator is, however, relatively expensive and previous analysis of cost-utility was based on very few patients who mainly had idiopathic GP.¹² Results from patients with idiopathic GP may not be directly applicable to patients with symptoms due to DM, as this group demonstrates progression in their condition, and often other diabetes related complications might be present. Although definitive assessment of cost-effectiveness may require long-term evidence from randomized trials, it is important early in the life-cycle of new technologies to begin to estimate likely cost-effectiveness.¹³ Such estimates can help prioritize new research and inform early adopters of the technology.^{13,14} Thus, the aims of the present study were to assess the clinical effects of GES and to perform an early cost-utility analysis of GES for severe recurrent nausea and/or vomiting in patients with DM.

Materials and Methods

Patients

Between August 2005 and August 2013, 33 diabetes patients (16 men, median age 41 [range 23-75] years) with severe recurrent nausea and/or vomiting had a gastric electrical stimulator (Enterra Therapy; Medtronic Inc, Minneapolis, MN, USA) implanted at the Department of Abdominal Surgery, Aarhus University Hospital, Aarhus, Denmark. The department is currently the only one in Denmark performing this procedure.

All patients had a history of recurrent episodes of severe nausea and/or vomiting for more than 12 months and none had sufficient relief of symptoms after dietary instructions and medical treatment for a minimum of 6 months. None of the patients had a history of major abdominal surgery and all had undergone standard evaluation including upper endoscopy.

Pre-operative Gastric Emptying Tests

Since the first GES was implanted at our department in 2005, the gastric emptying tests used had been refined from the radiopaque meal, to the paracetamol absorption test, and finally gastric emptying scintigraphy. Thus, gastric emptying was assessed using a radiopaque meal in 7 (4 prolonged), paracetamol absorption test in 18 (7 prolonged), or gastric emptying scintigraphy in 5 patients (1 prolonged). The paracetamol absorption test and gastric emptying scintigraphy were performed according to previously published protocols.^{15,16} The radiopaque meal consisted of a veal steak, potatoes, sauce, and a glass of X-ray contrast. It was performed after at least 3 hours fasting with radiolucency performed for 2-3 minutes at baseline and again after 6 hours.

Surgical Procedure

The GES was implanted under laparoscopic guidance under general anaesthesia. Access was through the umbilicus followed by a 5-mm port in the right flank and a 12-mm port in the lower left quadrant. Two intramuscular electrodes (Medtronic model 4351; Medtronic, Inc) were placed 1 cm apart along the major curvature approximately 10 cm from the pylorus. Upper endoscopy was performed to ensure that the electrodes had not penetrated the gastric mucosa. The leads from the electrodes were extracted through the port in the lower left quadrant and connected to the pulse-stimulator (Medtronic model 3116; Medtronic, Inc). The pulse-stimulator was placed subcutaneously and sutured to the abdominal

fascia to the left of the umbilicus. A standard program was set for the stimulator (standard: Medtronic N^ovision 8840; Medtronic, Inc; intensity 5 mA, frequency 14 Hz, pulse width 330 microseconds, cycle on 0.1 seconds, cycle off 5 seconds).

Pre-operatively 1500 mg of cephalosporin was given intravenously and gentamicin sulphate was placed locally over the stimulator. Post-operatively, the patients were restricted to a liquid diet for 24 hours until discharged on their usual diet. If the patients did not have symptom relief the intensity of the current was increased from 5 mA to 10 mA during follow-up at our outpatients' hospital after 1, 3, 6, and 12 months and hereafter yearly.

Assessment of Symptoms and Quality of Life

The symptoms were evaluated by having patients fill in a diary for 2 weeks before GES-surgery (baseline), 6 and 12 months post-surgery, and hereafter every year. The diaries were sent to the patients by mail or issued at scheduled visits in the outpatient's hospital. The diaries included: episodes of vomiting (episodes/day), number of hours with nausea (hours/day), satiety (graded on a scale from 0 to 4, where 0 represents no satiety and 4 represents severe satiety), bloating (0 represents no bloating and 3 represents severe bloating), and general well-being (0 represents a state where the patient is able to do whatever she/he likes and 4 represents a miserable state where the patient is confined to bed). Vomiting was defined as a forceful expulsion of the contents of the stomach through the mouth. Reiterate expulsions at the same time only counted as one episode of vomiting.

Alongside the diaries patients filled in the Short Form 36 health survey (SF-36). SF-36 is divided into 8 domains, which were added into the 2 summary scores: a physical component summary score and a mental component summary score. In each, 0 represents worst and 100 the best function (SF-36 version 1; RAND Corporation, Santa Monica, CA, USA; <http://www.rand.org/health/>

surveys_tools/mos/mos_core_36item.html).

In the present paper, all data are given at baseline, 6, and 12 months after surgery, and at long-term which is the longest follow-up for each individual with a follow-up of at least 4 years. Our pre-defined main criteria for success were: (1) at least 50 % reduction in time with nausea and (2) at least 50% reduction in the number of episodes with vomiting.

The study fulfilled the criteria within the Helsinki II declaration and was approved by the Danish Data Protection Agency (Ref. No. 2007-58-0010).

Cost-utility Analysis

In order to generate quality adjusted life years (QALYs), SF-36 data were converted to SF-6D using the algorithm by Brazier et al.¹⁷ Single imputation was used on missing data points. The total cost for the GES procedure was composed of the device cost, surgical procedure, 3 days of hospital admission in relation to surgery, 5 out-patient visits before or after surgery, and costs for pre-operative endoscopy (Table 1). As 1 re-operation was performed in 1 of our 30 patients, 1/30 of the surgical costs for that were added to all.

One of the authors (L.S.M.) read hospital records of all the patients in this study and counted the number of days in hospital due to symptoms related to gastrointestinal dysfunction for 12 months prior to surgery and for 12 months after. Costs of hospital contacts were calculated from Danish diagnose related group (DRG) rates as given by the Danish healthcare authorities for the year of 2016.¹⁸ According to these, the average cost of one day in hospital for a patient with the diagnosis DE108 (Type 1 diabetes with complication unspecified) or DE118 (Type 2 diabetes with complication unspecified) is 742 Euros (€). The DRG has a set trim point at 11 days, meaning that if patients are continuously in hospital for more than 11 days, a lower extensive-stay rate of €265 is used. All costs were reported in Euros (1 € = 7.45 Danish kroner).

Table 1. Cost of Gastric Electrical Stimulation for Diabetes Patients With Recurrent Symptoms of Nausea and/or Vomiting.

Service	Cost (€)	No.	Total cost (€)
Pre-operative outpatients hospital visit	76	1	76
Upper endoscopy	410	1	410
GES device	13.423	1	13.423
Laparoscopy	2.416	1	2.416
Post-operative follow-up visit in outpatients hospital	217	4	868
Re-operation for electrode adjustment	2.416	1/30	81
In hospital days related to surgery	742	3	2.226
Total cost per patient			19.500

GES, gastric electrical stimulation.
Costs are given in Euros (€).

To test for uncertainties in the sample population, bootstrap re-sampling was performed on both costs and effects at baseline, at 12 months, and for an estimated 24-month's sample. For each parameter the sample was re-sampled 500 times and confidence intervals for the mean were calculated. An incremental cost-effectiveness ratio (ICER) scatterplot was made to visualize the data in relation to an assumed Danish willingness to pay of €40.268 per QALY gained (corresponding to British pound (£) 30.000/QALY). Since there is no exact threshold value for the Danish decision-makers' willingness to pay per QALY, we applied the £30.000/QALY proposed by the British National Institute for Health and Care Excellence to indicate a limit for what may be considered cost-effective.¹⁹

The "control group" used in the calculations were the patients' own baseline data during the 12 months prior to surgery.

Statistical Methods

All statistical calculations on patients' symptoms were performed using Stata Statistical Computer Program 2013 (STATA; StataCorp LP, College Station, TX, USA) with only descriptive statistics performed. Quartile-quartile plots showed that data were not following normal distribution. Thus, results are given as median and full range and comparisons made with the Wilcoxon signed rank test and Mann-Whitney test. *P*-values < 0.05 were considered statistically significant. Calculations on cost-effectiveness were made in Microsoft Excel (Microsoft, Corp, Redmond, WA, USA).

Results

Study Population

Baseline data on symptoms were available for 30 of 33 patients (Fig. 1). These included 20 patients with type 1 DM and 10 with

Table 2. Summary Table Showing Descriptive Data in the Included Diabetes Patients in Numbers and Percent

	n (%)
Gender	
Women	15 (50)
Men	15 (50)
Diabetes	
Diabetes type 1	20 (67)
Diabetes type 2	10 (33)
Death in follow-up period	
Cause of death: purulent meningitis (1), heart arrest (1), unknown (1), disseminated lung cancer (1)	4 (13)
Diabetes complications before operation	
Retinopathy	9 (30)
Nephropathy	9 (30)
HbA1C	74.5 mmol/mol
Late onset diabetes complications	6 (20)
Diabetic foot ulcer	6 (20)
Kidney transplantation	0
Dialysis	0
Weight before operation (median 25 [range 15.6-33.1])	
Underweight	2 (7)
Normal	12 (41)
Overweight	9 (31)
Obese	6 (21)
Stomach emptying test	
Gastric emptying scintigraphy	5 (17)
Paracetamol absorption test	18 (60)
Radiopaque meal test	13 (43)
Post-operative complications	
Feeding tube (permanent)	1 (3)
Death	0 (0)
Re-operation to adjust the position of the Stimulator	1 (3)
Pain in the subcutaneous pocket	3 (10)
Diffuse abdominal pain	2 (7)
Small seromas	2 (7)
Small hematomas	1 (3)

HbA1C, glycated hemoglobin A1C.

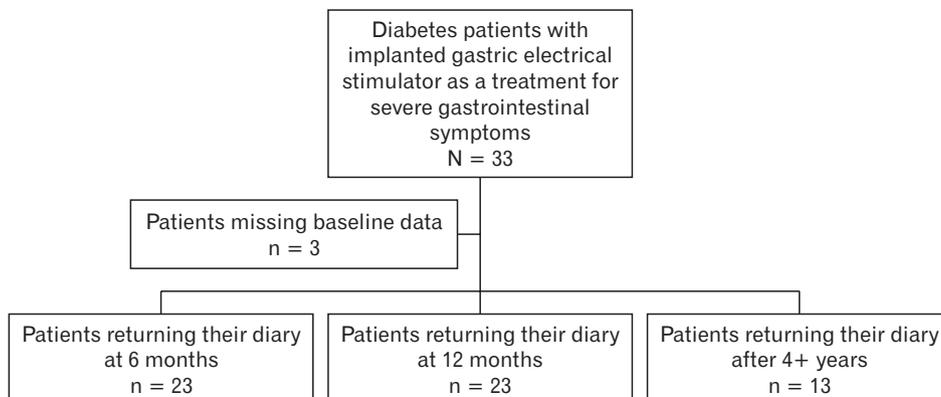


Figure 1. Flow diagram of the study cohort of diabetes patients with recurrent nausea and vomiting. Four patients died after 3, 3, 5, and 7 years of follow-up respectively. Data were not complete. Thus, 12 months follow-up included 4 patients who had not returned their diary at 3-6 months whereas 4 years+ also included some patients who had not returned their diary at either 3-6 or 12 months.

type 2 DM (Table 2). Median duration of diabetes was 21 (range 3-37) years. Median time from debut of recurrent nausea and/or vomiting until GES implantation was 4 (range 1-10) years.

Late complications to diabetes included retinopathy in 22 (73%), nephropathy in 9 (30%), macrovascular disease in 6 (20%), and diabetic foot ulcer in 6 (20%) patients. None had received a kidney transplant or were in dialysis treatment before the GES operation. The median follow-up was 35 (range 1-120) months. During the follow-up period; 8 (27%) developed a diabetic foot ulcer, 5 (17%) started dialysis treatment, and 1 (3%) received kidney transplantation.

None of the batteries for the GES had exceeded its lifetime during the follow-up period.

Complications to Surgery

The surgical procedure was without mortality or major complications. The following minor complications were reported within 30 days. Pain near the subcutaneous pocket for the stimulator ($n = 3$), diffuse abdominal pain ($n = 2$), small seroma ($n = 2$), and small hematoma ($n = 1$). None of the complications required surgical intervention. One patient required re-operation to adjust the position of the stimulator and another had a permanent jejunostomy feeding tube because of chronic malnutrition. Twenty-one of the patients had the current of the stimulator raised to 10 mA because of lack of effect. During the follow-up period four patients died of causes not related to the procedure (purulent meningitis [$n = 1$], unexpected cardiac arrest [$n = 1$], unknown [$n = 1$], disseminated lung cancer [$n = 1$]). Death of the above occurred after 3, 3, 5, and 7 years respectively.

Clinical Effects

At least 50% reduction in time with nausea was achieved in 78% of the diabetes patients after 6 months, in 30% after 12

months, and in 75% at follow-up after at least 48 (median 96 [range 48-120]) months. At least 50% reduction in episodes with vomiting was achieved in 48% of the diabetes patients after 6 months, in 43% after 12 months, and in 69% at follow-up after at least 48 (median 96 [range 48-120]) months.

Changes in individual symptoms are shown in Table 3. At 6 months follow-up there was a statistically significant improvement in vomiting, nausea, satiety, bloating, and general well-being. Most patients still reported improvement at long-term follow-up even though improvement of some symptoms did not reach statistical significance as the number of subjects became fewer (Table 3). The effect on symptoms did not differ between patients with normal or prolonged gastric emptying tests before implantation and GES. The median number of days in hospital was 4.5 (range 0-172) in

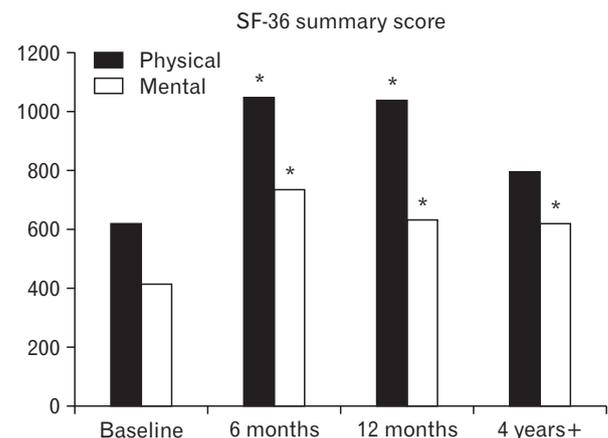


Figure 2. Short form 36 health survey (SF-36) summary scores for physical and mental health at baseline and after gastric electrical stimulation. The highest possible scores in healthy individuals are respectively 2100 for physical and 1500 for mental health. Asterisk (*) shows significant changes compared to baseline.

Table 3. Symptoms of Included Patients With Diabetes at Baseline and After Gastric Electrical Stimulation

Symptoms	Baseline (median [range])	6 months (median [range])	12 months (median [range])	At least 4 years (median [range])
Vomiting (episodes/wk)	4.5 [0-110]	1 [0-15] $P = 0.009$	0.6 [0-21] $P = 0.207$	0 [0-3.5] $P = 0.004$
Nausea (hr/wk)	31.2 [0-112]	5 [0-31] $P < 0.001$	11.5 [0-71] $P = 0.003$	0.3 [0-26] $P = 0.002$
Satiety (scale 0-4)	2.2 [0-4]	1.4 [0-3.8] $P = 0.003$	1.9 [0-4] $P = 0.091$	1.8 [0-4] $P = 0.077$
Bloating (scale 0-3)	2.1 [0-3]	1.8 [0-3] $P = 0.032$	1.8 [0-3] $P = 0.292$	1.2 [0-3] $P = 0.077$
Well-being (scale 0 [best]-4 [worst])	2.4 [0.9-4]	1 [0-2.9] $P < 0.001$	1.7 [0-7] $P = 0.032$	1.9 [0.1-3.3] $P = 0.583$

Table 4. Incremental Cost and Effects 12 Months and 24 Months After Surgery

	Incremental cost (€)		Incremental effect (QALY)	
	12 months	24 months	12 months	24 months
Mean	10 031	104	0.076	0.154
95% CI	9630-10431	-723-932	0.075-0.078	0.151-0.157
SD	4567	9454	0.019	0.038
Minimum-maximum	-10 117-19 810	-35 059-19 599	0.018-0.131	0.057-0.279
ICER (€/QALY)			132.161	676

€, Euro; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

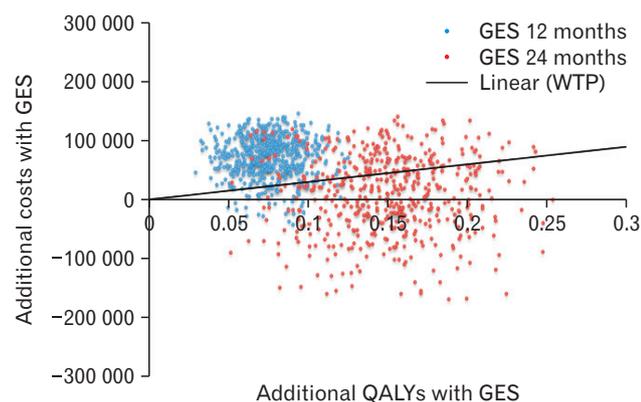


Figure 3. Bootstrap analysis showing incremental cost-effectiveness ratios at 12 months (blue) and estimated at 24 months (red) after gastric electrical stimulation (GES). Data from the 28 patients included in the analysis were re-sampled 500 times for each patient. As seen in the figure, more samples are located under the line for willingness to pay (WTP) after 24 months (red) than after 12 months (blue). Based on the analysis GES was cost-effective after 24 months. QALY, quality adjusted life year.

the 12 months before surgery, and 0 (range 0-74) during the 12 months after ($P = 0.005$).

The SF-36 summary scores for physical health and for mental health both improved significantly after 6 months, 12 months, and at long-term follow-up (Fig. 2). Before GES the median hemoglobin A1C was 75 mmol/mol (9%) (range 45-128 mmol/mol), and following GES it was 76 mmol/mol (9,1%) (range 45-121 mmol/mol) ($P = 0.358$).

Cost-utility

Mean health economic costs were €16.611 per year at baseline and €26.549 at 12 months after GES implantation, giving an incremental cost of €10.031. The incremental cost after 24 months was €104. The mean utility value was 0.5204 at baseline and 0.5963 at 12 months follow-up, giving an incremental QALY of 0.0759 after

one year with GES. The incremental QALY after 24 months was 0.1539. This gives an estimated ICER after 24 months of €676 per QALY (Table 4). The computed bootstrap analysis of the ICER after 12 months follow-up and estimated 24-months follow-up (28 patients) is shown in Figure 3.

Discussion

The present study confirms previous studies demonstrating GES to be a safe and clinically effective procedure^{8,9,20,21} which improves quality of life²² in a substantial proportion of highly selected patients with diabetes and severe recurrent nausea or vomiting. Our study is, however, the first to provide health economic-evaluation, and the data indicate that the procedure is cost-effective after 2 years. As the lifetime of the GES-battery is at least 10 years and the clinical effects seem to persist during follow-up, the procedure must be considered to be very cost-effective over a longer range of years.

GES has proven to be superior to placebo in 4 placebo-controlled trials in patients with diabetic, post-surgical, or idiopathic recurrent nausea and/or vomiting.^{11,23-26} In a double-blinded, randomized, crossover study, symptoms and quality of life improved significantly more while the stimulator was on than when off.¹¹ However, in another study from the same group, vomiting and nausea improved both during on and off periods.²⁵ In a double-blinded, randomized crossover study among 32 patients with idiopathic GP, nausea and vomiting improved non-significantly both with the stimulator on and off, but with a trend towards more improvement with the stimulator on. However, the lack of a wash-out period between the on and off phases may have compromised the data in the study.²³ Interpretation of the previously mentioned studies is hampered by a large variation in time between implantation of GES and inclusion into the randomized trials. Furthermore, the crossover design may not be appropriate for GES as the carry-over effect and the necessary washout period are unknown.

In spite of severe symptoms, only 12 of 30 of our patients had prolonged gastric emptying-time before GES. The poor correlation between symptoms and objective measures of gastric emptying is well known.^{6,27,28} Thus, the decision to offer the individual diabetes patient GES was based on a history of recurrent nausea and/or vomiting and not on a strict diagnosis of GP.

GES is a relatively expensive procedure, mainly because of the price of the electrode and battery, which is approximately €13.000. The immediate cost is probably the major limitation to a more common use of the procedure. A previous study comparing the use of healthcare resources among patients with idiopathic GP having either GES or medical treatment concluded that GES was the most cost-effective. This study had 3 years follow-up, but it was unfortunately not randomized.¹² An open study among 37 patients, of whom 24 had diabetic GP, followed for 12 months found that days in hospital were significantly reduced after GES, but no cost-effectiveness analysis was performed.²⁹ Our study is the first to focus on the early cost-effectiveness of GES in a population with diabetic recurrent nausea and/or vomiting. The data strongly indicate that GES is cost-effective after approximately 2 years and demonstrate that the clinical effect is maintained for a longer period of time. In a study on 188 patients, McCallum et al.⁹ found that the clinical improvement persisted up to 10 years.

The mechanism of action of GES remains unclear. The current intensity is too low to cause contractions of the antrum or initiate a peristaltic wave.¹¹ No associations between changes in symptoms and gastric emptying have been found.¹¹ Changes in central control of nausea and vomiting mediated through the vagal nerve have been suggested. Thus, vagal activity increases during GES, which may increase the threshold for discomfort during gastric distension. Data indicate increased thalamic and caudate nuclei activity during chronic high-frequency GES therapy.³⁰ In a canine model, gastric emptying during GES correlated well with plasma motilin levels. The authors concluded that motilin levels could be important to alter gastric motility during GES.³¹

The main limitations in the present study are the low number of patients and that the reduced cost from days in hospital between 12 and 24 months was assumed to be the same as during the first year after GES. The “control group” used in the calculations was patients own baseline data during the 12 months prior to surgery. It is assumed that an actual control group would have the same amount of in-hospital days the following years as the patients had before surgery. A randomized placebo-controlled design has obvious advantages. However, such a design would have restricted the study period to weeks or a few months. All patients had severe

symptoms and poor quality of life without sufficient relief from any other treatment attempted. The effect of GES on symptoms has been shown in previous studies, and for ethical reasons patients could only have been randomized to placebo/standard treatment for a relatively short period of time. Symptoms of gastroparesis are very variable and a much longer time is probably needed to estimate the cost/effect, especially in terms of number of days in hospital. Thus, we had to choose between a control group without GES that was followed for a relatively short period of time, or an appropriate follow-up period, which was compared to patients’ baseline data.

Compared to the 2 previous studies on cost-effectiveness of GES, our study included approximately the same number of patients. As the clinical effects were maintained after more than 2 years, we find the assumption that the cost would be reduced too is valid.

First line intervention against GP is dietary modification. Patients are asked to minimize the meal-content of fat and fibers and consume frequent but smaller meals. Liquid meals are recommended because they require a minimum of mechanical processing.^{7,32} In addition to that, hyperglycemia *per se* can cause delayed gastric emptying and it is important that patients control their blood glucose levels.³³

Medical treatment including antiemetics and prokinetics should be attempted. If medical therapy fails, GES or a jejunostomy feeding tube are alternatives to more extensive surgical procedures. Surgical interventions; as pyloric injection with botulin toxin,³⁴ pyloroplasty,³⁵ and total or subtotal gastrectomy³⁶ have been described but their effect is poorly documented.

In conclusion, our data support previous reports that GES is a safe procedure, which markedly reduces symptoms and improves quality of life in diabetes patients with recurrent nausea and/or vomiting. Our study is the first to perform an early regular cost-effective analysis of GES in diabetes patients with symptoms of GP. We found that GES reduced the days in hospital by 61% during the first year and that treatment seems to be cost-effective after a 2-year horizon.

Financial support: The study was supported by the Novo Nordisk Foundation, Denmark (Grant No. 13159).

Conflicts of interest: None.

Author contributions: Mette W Klinge: analysing data from SF-36 and diaries, and writing article; Peter Rask: collecting data and study-design; Lene S Mortensen: collecting data and reading

hospital records; Kathrine Lassen: calculations in the cost-utility analysis included Fig C; Niels Ejlskjær: initiating the project, collecting data, and proofreading article; Lars H Ehlers: calculations in cost-utility analysis and proofreading article; and Klaus Krogh: study-design, writing article, and proofreading the final version of the article.

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