Clinics in Surgery

Research Article
Published: 05 Jul, 2022

What to do with Gastroparetic Patients? A Systematic Review of Treatment Options

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Abstract

Introduction: Gastroparesis is a chronic functional disorder including nausea, vomiting, bloating, abdominal pain, early satiety and postprandial fullness [1–4]. Several treatments have been reported, e.g. G-POEM, gastric electrical stimulation or pyloroplasty. There exist some metaanalysis of one of these treatments each, yet they do not compare all of them [5,6].

Methods: We extracted data from studies on intrapyloric Botox injection, G-POEM and gastric electric stimulation and calculated significance of mean differences according to Random-effects-Model including DerSimonian-Laird test ($p<0.05$).

Results: Nutrition, pharmacotherapy and surgical treatments couldn`t be analyzed due to missing data or minor quality of data. We stated a significant reduction of 4.9 ± 0.48 in total GCSI in pre/post Botox injection comparison, so did G-POEM`s mean GCSI (1.651 ± 0.144). 4 h -scintigraphies of G-POEM participants illustrated a significant decrease in gastric emptying scintigraphy (26.932% ± 2.442%). The most impressive effect occurred after implantation of a gastric electric stimulator: TSS scores decreased significantly in short and long term, as well as by comparing ON and OFF mode.

Discussion: Comparing all these therapies, gastric electric stimulation seems to be the most successful option according to our findings. Our recommendation is, due to heterogeneity of data, moderate [6]. G-POEM and intrapyloric Botox injections are evidence based treatments according to our and others' findings [5]. Further studies, especially on the impact of combined therapies as well as on step up approaches are necessary.

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Received Date: *20 May 2022*
Accepted Date: *28 Jun 2022*
Published Date: *05 Jul 2022*

Citation:
Eckhardt D, Elshafei M. What to do with Gastroparetic Patients? A Systematic Review of Treatment Options. Clin Surg. 2022; 7: 3540.

Abbreviations

GP: Gastroparesis; GE: Gastric Emptying; GCSI: Gastroparesis Cardinal Symptom Index; TSS: Total Symptom Score; G-POEM: Gastric Peroral Endoscopic (pyloro-)Myotomy; GES: Gastric Electric Stimulation

Introduction

Gastroparesis (GP) refers to a chronic functional disorder of the stomach caused by retention (of solid food) without mechanical obstruction, the most frequent symptoms are nausea, vomiting, bloating, abdominal pain, early satiety and postprandial fullness [1–4,7-9]. Additionally, delayed Gastric Emptying (GE), usually measured scintigraphically, is often used as second part of objectivation [7]. The most common causes are diabetes mellitus, both in type one and two [10], as well as surgery: Surgical GP is defined as gastroparesis after prior upper GI surgery like Nissen fundoplication, Billroth's gastrectomy type I or II, vagotomy or cardiac cryoablation [11–18]. Preoperative gastric outlet obstruction as well as its treatment, Billroth's resection type II especially seen on tumor in the distal stomach, isoperistaltic reconstruction and elevated BMI are risk factors of GP [17,19]. Fistulas, sepsis and reoperation after pancreatectomy are risk factors of GP, too [17]. GP caused by neurological disorders like Parkinson`s disease, cerebrovascular disease, Multiple Sclerosis or autonomic and peripheral neuropathies, e.g. diabetic polyneuropathy, depression, anxiety, chronic pancreatitis, end stage renal syndrome, irritable bowel syndrome, systematic lupus erythematosus, fibromyalgia, scleroderma, hypothyroidism, obstructive sleep apnea, cardiac arrhythmia or venous thromboembolism are referred to as "idiopathic gastroparesis" [17,20].

In contrast, gastroparesis-like syndrome refers to patients with typical GP symptoms without delayed gastric emptying [21].

Diagnostics contains of questionnaires and imaging technics: PAGI-SYM, for example, is a twenty-items questionnaire, designed for evaluation of reflux disease, dyspepsia and gastroparesis by Rentz et al. 2004, referring to regurgitation/heartburn, fullness, early satiety, nausea/vomiting, bloating, upper and lower abdominal pain [22,23]. Gastroparesis Cardinal Symptom Index (GCSI) is a nine-items questionnaire containing items for nausea/vomiting, postprandial fullness/early satiety and bloating [24]. Total Symptom Score (TSS) sums up items of bloating, early satiety, abdominal pain, nausea and vomiting to a maximum of 20 points [25]. Standardized scintigraphic retention two und four hours after eating a low-fat meal consisting of eggs, bread, nuclear tracer and water is gold standard [8,26-29]. It has to be mentioned that fatty meals increase GP symptoms and the clinical relevance of retention of scintigraphic enhanced meals remains unclear [2,29]. C14-octanoic acid and C13-glycin breath tests work similarly [1,28].

Esophagogastroduodenoscopy is often performed to exclude mechanical or morphological causes [26,30].

Common therapies

Concerning nutrition as therapy option, it is described that liquid/low-fat/small-particle aggravate symptoms less than solid/high-fat meals [2,31].

Pharmacological treatment, like D2-antagonists, Domperidone and Metoclopramide for example, are prokinetic drugs. Short term usage of domperidone improves GP symptoms, yet chronic intake accelerates symptom intensity [32-34]. Makrolide antibiotics, namely azithromycin and erythromycin, initiate migrating motor complexes in stomach and intestine. Although studies were of minor quality, desensitization after short duration of intake is well documented [35-38]. For the 5-HT3 antagonist granisetron, it has been shown that transdermal application reduces overall symptom severity significantly and nausea, vomiting, loss of appetite and postprandial fullness particularly [39,40]. 5-HT4 receptor agonists like cisapride, tegaserod or prucalopride are withdrawn from market or leak evidence as gastroparesis treatment [35]. 5 mg Haloperidol significantly reduced abdominal pain and nausea in gastroparetic patients, while placebo came close to significance as well in a single trial [41]. Dronabinol, a nonselective cannabinoid agonist, is used as analgetic drug as well as stimulator for appetiteless patients or chemotherapy induced nausea, but the efficiency of painkilling and reducing nausea is on a minor level [42]. Pregabalin, a co-analgetic, can be used within a dose range of 450 mg to 1800 mg per day to accelerate analgetic effect of diabetic neuropathy after a minimum of four days to decrease opiate usage [43]. Several antidepressants reduced score of functional dyspepsia after two (Mirtazapine) or four weeks (Paroxetine) compared to control group [44]. Optimizing glucose level using a glucose controlled, continuous insulin substitution, especially for type 1 DM, lead to a decrease in GP symptoms [45,46]. The neurokinin-1 receptor antagonist pre-patent reduces nausea intensity significantly, as well as nausea-/vomiting- and overall GP symptom-free time [47]. Rifaximin, approved for irritable bowel syndrome therapy, reliefs symptoms like bloating or abdominal pain at least two of four weeks of treatment, the anti-bloating effect lasts for up to three months [48].

Salvage therapies target on opening the stomach exit permanently: Percutaneous endoscopical gastrostomy causes a reduction in GP symptoms, but gastric emptying is unaffected [49]. Percutaneous endoscopic jejunostomy in comparison is a more complex procedure, including a higher range of complications (e.g. volvulus, bleeding, bowel perforation) and disadvantage [50].

In a few case reports transpyloric or in gastrectomized patients stenting has successfully be performed to allow oral feeding, but randomized controlled trials are missing [51-53]. Early stent migration and therefore recurrence of symptoms limit the potential of this method [49,51]. Dilatation of pylorus *via* "through-the scope" balloon, at least in combination with intrapyloric Botulinum Toxin injections, improved symptoms in 72% to 88% of the patients after one or more treatments [54]. The effect seems to sustain for several months, although the authors used free interviews about symptom development [54].

Injecting different amounts of Botulinum Toxin A (abbreviated Botox) endoscopically into different parts of the pyloric muscle is another well-known option.

Pyloroplasty according to Heineke and Mikulicz can be performed open, laparoscopical or robot assisted, consists of a transversal closure of a longitudinal incision of the pylorus in one- or two-layer manor (Weinberg modification) [55-58]. Further pyloroplastic options, for example Finney or Jaboulay pyloroplasty, follow the same principal of widening the pylorus.

Gastric Per-Oral Endoscopic (pyloro-)Myotomy (G-POEM) starts with endoscopic disclosure of morphological pathologies, followed by incision along the greater curvature/posterior wall with a hook or hybrid I-type needle knife [59–62], while some prefer the lesser curvature reaching the ring muscle on a shorter tunnel [63–66]. Preparing a submucosal tunnel to the pyloric ring muscle fibers enables the myotomy, which is sometimes not performed as full-thickness incision [60,62,64,65,67]. The mucosal incision is closed via clips or endoscopical suture [60,61,63].

Defining Gastric Electric Stimulation (GES), it tries to improve gastric motility and coordinated contractions of antral wall muscle fibers via laparoscopic or laparotomic implantation of electrodes on the antral serosa near the greater curvature and a stimulator in a subcutaneous pocket [56,68–72]. Endoscopic placement of (wireless) electrodes exist as well as percutaneous electrodes to check temporarily for clinical improvement before implanting permanent devices [70,73–79]. The main effect of electrical stimulation is considered the pacemaker function of gastric slow waves in order to maintain phase-locked entrainment of gastric wall contractions. Nowadays stimulation can be altered in intensity and frequency of electric pulsation [79,80–83].

Our aim of this study has been figuring out, which treatment options are appropriate to GP patients, which are evidence based. Is there a hierarchy of therapies?

Materials and Methods

In a first step, we identified suitable literature via scanning for "gastoparesis", "gastric emptying", "G-POEM", "Botox", "pyloromyotomy" and "gastric electric stimulation" in databases like www.cochranelibrary.com or www.ncbi.nlm.nih.gov. The following review contains all the available literature published online before August 1st, 2020.

In a second step, publications were assessed according to the following criteria: Data must be based on treatment of human individuals; key data (questionnaire and scintigraphic data) must be available before and after treatment; if a research group published

more than one study probably containing data from the same participants, we would choose the larger study to be included. All Data within one treatment option group needs to be collected within one test type (e.g. GCSI or TSS) to be comparable to those of other authors. Each exclusion or inclusion has been approved by both authors independently.

Comparing the items, we used Random-effects-Model including DerSimonian-Laird test ($p<0.05$) by performing OpenMeta [Analyst], a free software tool invented by Brown University, USA and accessible *via* http://www.cebm.brown.edu/openmeta/download.htm comparing the means of two groups per study. We chose "mean difference" as metric and performed DerSimonian-Laird Random-Effects mode with a confidence level of 95%. Number of participants, mean total scores as well as scores of each symptom were stated as variable. Heterogeneity was measured via heterogeneity p-value and Tau^2.

Result

After scanning a total of 284 publications and exclusion of reviews and duplications, we focused on those 231 offering information on the treatments (Figure 1). In second step, we excluded studies offering insufficient data, from critically ill patients, etc. Detailed information about the included studies can be found at Appendix 1.

Examining nutrition as treatment option first, we could not identify a single study including questionnaire and imaging data. Switching to pharmacotherapy, data from intensive care units´ patients were excluded as transferability to chronically ill persons from intubated and ventilated individuals remains unclear. There were some reports of positive effects of domperidone, metoclopramide, macrolide antibiotics, 5-HT3 antagonist and haloperidol, yet all of them leak clinical and scintigraphic test standards. Salvage therapies were excluded for the same reason. Acupuncture didn´t show any hint for a sustainable effect, as a cochrane review revealed [84].

Intrapyloric injection of Botulinum Toxin A

Three studies were isolated offering data after injections of 100 IU to 200 IU [85-87]: Performing DerSimonian-Laird test on the studies, we detected a significant improvement of 4.9 ± 0.48 in total GCSI in pre/post Botox injection, heterogeneity wasn`t significant (Figure 2). But testing Botox intervention versus saline injection, we found no significant difference, although only two studies were included.

Several other studies showed significant benefits from intrapyloric

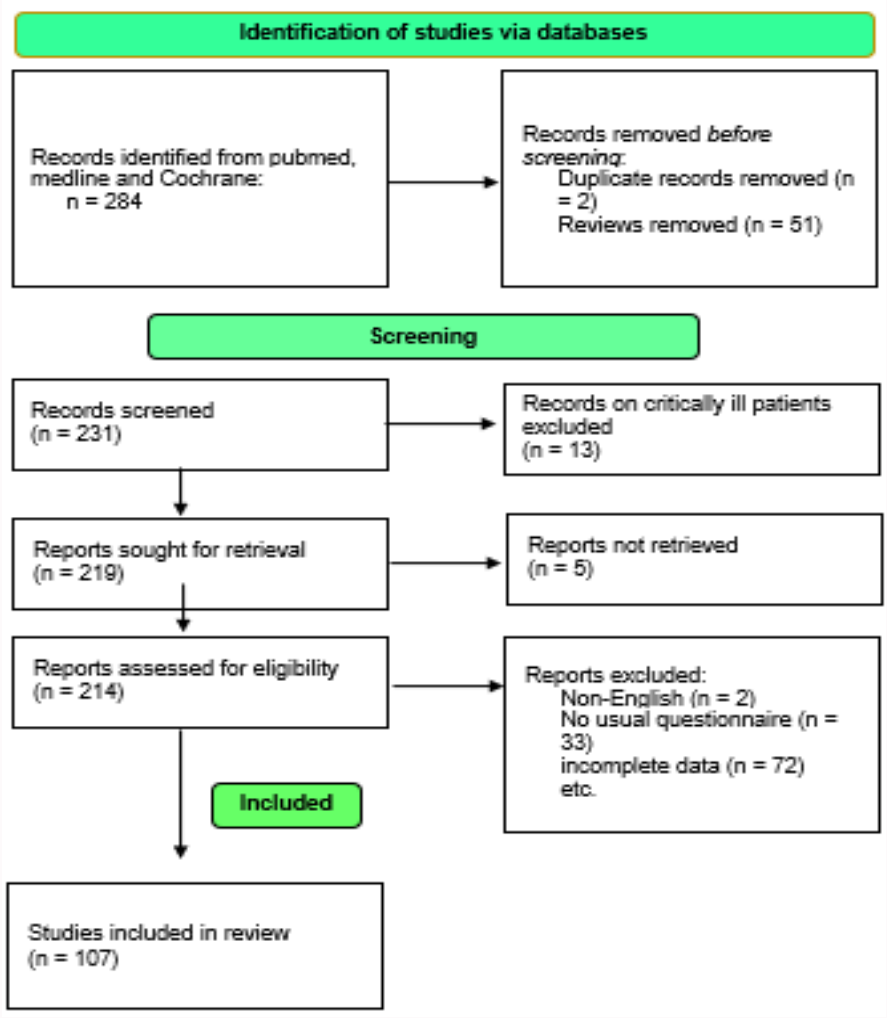

Figure 1: Flow diagram of study analysis according to PRISMA scheme. The initially found 284 publications were first screened for duplications and reviews (both excluded). Afterwards half of the publications were excluded due to our criteria described earlier. Finally, 107 studies were included to further investigations. This procedure and the flow chart have been adopted from Page et al. 2021 [146].

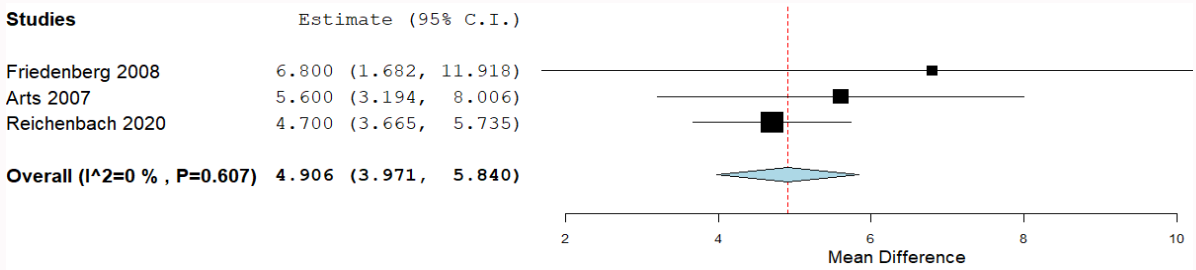

Figure 2: Forest Plot pre- versus postinterventional on Botox treatment. Two of three studies reported of significant benefits with Botox treatment. In total, Botox injections reduce total GCSI for about 4.9 significantly.

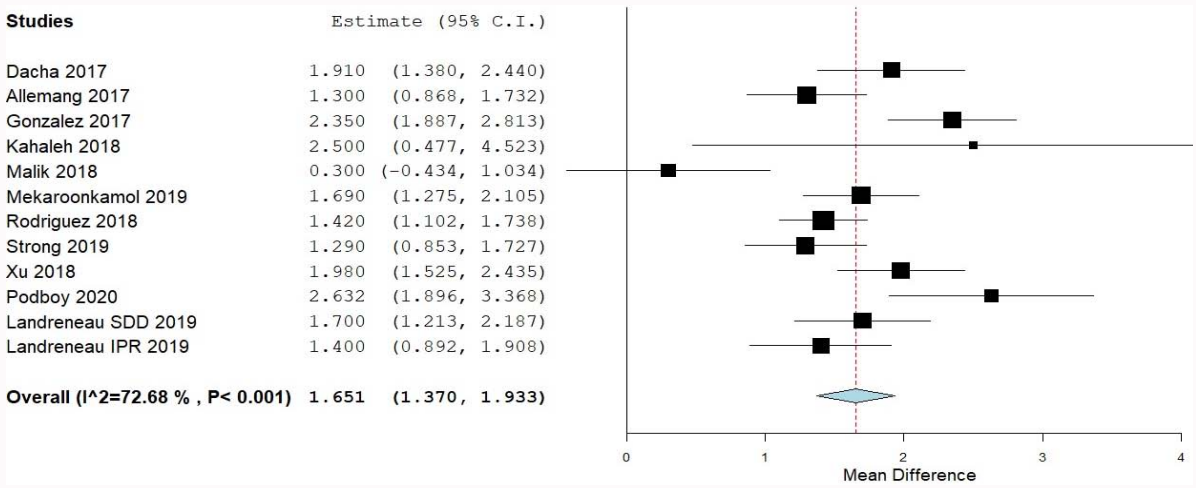

Figure 3: Forest Plot initial mean GCSI. Including eleven studies, the initial postinterventional mean GCSI decreased significantly for 1.651 ± 0.144. Heterogeneity among the included data was significant (I^2=72.683).

Botox injections, yet clinical tests were unsuitable [88–90].

Surgical options

Landreneau et al. were the only ones offering proper data concerning pyloroplasty, indicating significant reduction in gastric emptying scintigraphy and mean GCSI (4.0 ± 1.1 → 2.3 ± 1.5; 21 participants completed 90-day-follow-up [91]). That is why we refused to perform any statistics on a single suitable study.

Gastric Peroral Endoscopic (pyloro-) Myotomy (G-POEM)

Scanning the available literature, we found 27 publications describing effects of G-POEM on gastroparetic patients, eleven of them had to be excluded from further analysis due to a lack of standardized tests [92–95], sufficient categorization, missing data, combination of therapies or only responders were included to analysis [96-99].

Fifteen studies, including 601 participants, could be included for further investigations: To establish comparability, we calculated mean GCSI by dividing GCSI sum by 9 if necessary. Initial postoperative examination took place one to three months after intervention; midterm efficacy had been documented after 6 and 12 months.

As illustrated on the Forest plot above (Figure 3), mean GCSI decreased significantly after G-POEM for about 1.651 ± 0.144 at the initial post-interventional examination. Heterogeneity turned significant as well, illustrating relevant differences among the included data (I^2=72.683). Six months after G-POEM results from three studies were available [100–102], including 75 participants: Mean GCSI remained significantly reduced (1.945 ± 0.189; I^2=38.965), while heterogeneity didn`t turn significant. 12 months after intervention four studies [101–104] with 159 participants could be used for calculation: Mean GCSI had been reduced significantly (1.484 ± 0.235) and heterogeneity remained not significant (Tau^2=0.073). Subscores for Nausea (1.404 ± 0.159), Vomiting (1.455 ± 0.115), early satiety (1.544 ± 0.273) and postprandial fullness (1.380 ± 0.173) were significantly reduced, yet the data from early satiety were of significant heterogeneity (Tau^2=0.389; I^2=82.422).

Focusing on gastric emptying scintigraphy, results from five studies [67,100,104–106] could be evaluated for 2 h -scintigraphy: Signals reduced significantly for 27.017% ± 3.636% (Tau^2=19.467; I^2=30.689). Yet it has to be mentioned, that standard deviation of the data by Kahaleh et al. 2018 [105] is quite large compared to those by other authors. Eight studies [100,102,104–109] were available including data from 417 4h-scintigraphies, showing homogeneous results with significant reduction in gastric emptying scintigraphy (26.932% ± 2.442%; Tau^2=16.471; I^2=33.388; Figure 4).

Gastric electric stimulation (GES)

Several studies, as in G-POEM paragraph, had to be excluded from metaanalysis due to missing or inconclusive data, non-standard questionnaires or leak of preoperative data [32,56,70,75,79,110–123]. As there is only one trial using mean GCSI as clinical test and transformation to TSS was not possible, clinical data from Zoll et al. 2019 [124] couldn`t be included.

Seventeen studies with a total amount of 960 could be included to metaanalysis of differences between preoperative and postoperative

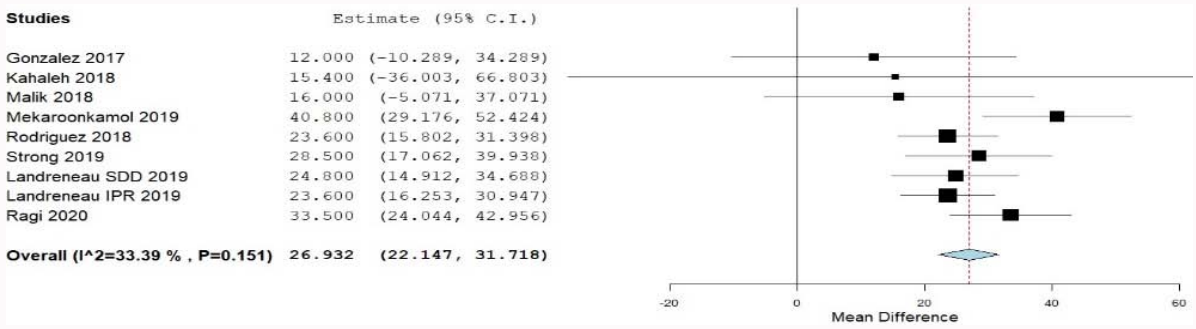

Figure 4: Forest Plot 4 h-gastric emptying scintigraphy. As shown on the left side, the eight included studies documented a significant reduction in scintigraphy for 26.932% ± 2.442% (blue diamond). Heterogeneity was not significant, although the data by Kahaleh were of wide range.

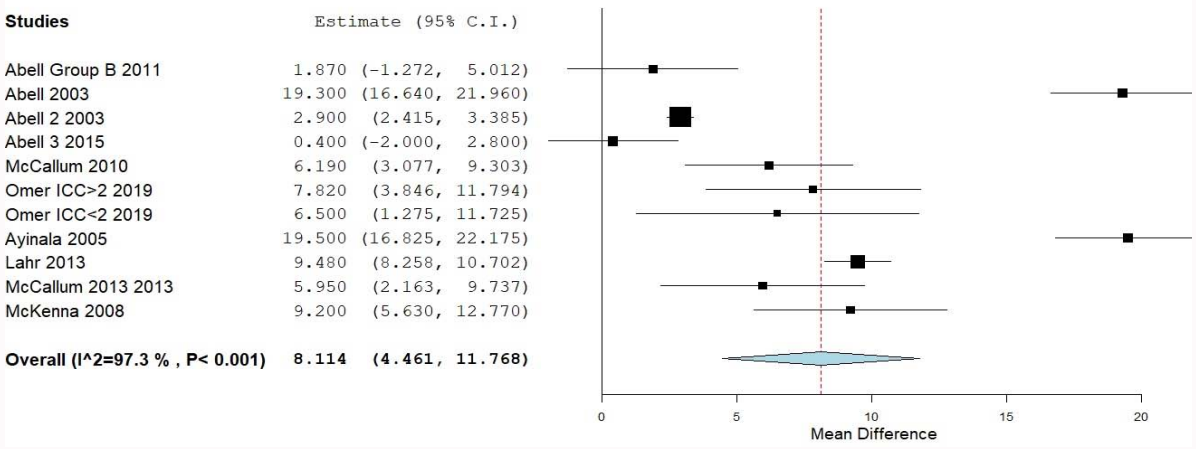

Figure 5: Forest plot of initial TSS after implantation of gastric electric stimulator. As shown on the right hand side of the graph, two studies reported of huge mean differences between pre- and postoperative TSS, therefore heterogeneity turned significant. The mean effect, reduction of TSS for about 8.1 in TSS, is significant.

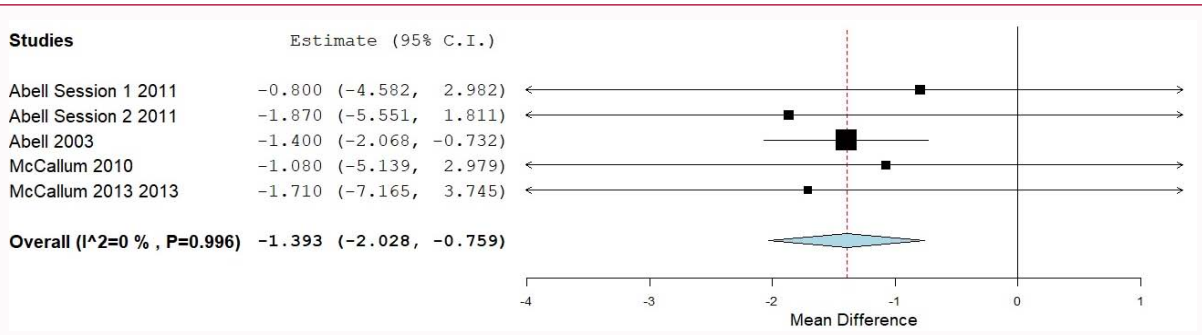

Figure 6: Forest plot of mean differences between device being turned ON and OFF. The cross-over study design by Abell et al. 2011 led to difficulties in reorganizing them in just two groups. We therefore decided to refer to them as part 1 and 2 (ON → OFF and OFF → ON). The graphs illustrate the huge variances within each study, but all but one was of small sample size (small black squares).

clinical and scintigraphical status. The works by Omer et al. 2019 [125] and Abell et al. 2011 [77].

Focusing on p-values, we calculated significant improvements after implantation in TSS in short, medium and long-term follow up. The benefit varies between 7.98 ± 1.721 and 10.95 ± 1.921 (Table 1). Below that, subscores turned significant as well showing best score decreases in nausea (1.33 ± 0.099) and vomiting (1.332 ± 0.085). Early satiety and postprandial fullness were decreased in a range between 0.94 and 0.99, while abdominal pain and bloating were reduced the less (0.82 each). Noteworthy, heterogeneity was significant in all scores showing systematic differences between the included trials, illustrated by forest plot (Figure 5) showing initial TSS:

10.7% ± 2.1% in 2h-GES (included studies: [129,138,149,155–158]) and 5.9 ± 2.4% in 4h-GES (studies: [129,138,149,156–158] were significant reductions, the heterogeneity was not significant.

In a second step we compared 4 studies offering data of devices turned OFF with ON state adjusted to baseline (148 participants in total). Abell et al. 2011 performed a cross-over design, as no mixed data were available we included both sessions separately. The same study was the only one offering gastric emptying scintigraphy data, therefore we didn`t performs further statistics on scintigraphy results (Table 2):

Homogeneity of the studies was sufficient in TSS and all

Table 1: Results GES using continuous Random-effects method with DerSimoneon-Laird. Each of the TSS subscores, as well as TSS scores at all documented time points decrease significantly. Best effects were obtained after six or twelve months (10.95 ± 1.92 and 8.23 ± 1.21, respectively). As heterogeneity among the included data turned significant at all tests as well, interpretation should be handled with care.

Mean reduction	Lower bound	Upper bound	Standard error	p-value	Tau2	Heterogeneity p-value	I2	authors
Comparing pre- and postinterventional TSS (1-3 months after implantation)								
7.984	4.61	11.358	1.721	<0.001	33.072	<0.001	97.048	(68,69,77,78,115,115,125–129)
Comparing pre- and postinterventional TSS (6 months after implantation)								
10.948	7.182	14.713	1.921	<0.001	17.137	<0.001	98.772	-6,86,97,81,30,131
Comparing pre- and postinterventional TSS (12 months after implantation)								
8.225	5.862	10.587	1.205	<0.001	13.186	<0.001	99.017	(68,69,78,127–134)
Comparing pre- and postinterventional TSS vomiting subscore								
1.332	1.164	1.499	0.085	<0.001	0.03	0.011	56.599	(68,77,125,128,129,131,131,132,135)
Comparing pre- and postinterventional TSS bloating subscore								
0.824	0.424	1.224	0.204	<0.001	0.283	<0.001	93.092	(68,77,125,127–129,131,132,135)
Comparing pre- and postinterventional TSS early satiety subscore								
0.936	0.571	1.302	0.187	<0.001	0.158	<0.001	85.554	(68,127–129,131,132)
Comparing pre- and postinterventional TSS nausea subscore								
1.33	1.137	1.524	0.099	<0.001	0.054	<0.001	73.717	(68,77,125,127–129,131,132,135)
Comparing pre- and postinterventional TSS abdominal pain subscore								
0.824	0.301	1.348	0.267	0.002	0.534	<0.001	96.893	(68,125,127–129,131,132,135)
Comparing pre- and postinterventional TSS postprandial fullness subscore								
0.992	0.597	1.388	0.202	<0.001	0.198	<0.001	93.316	(68,12,81,29,13,11,32,100)

Table 2: Comparing TSS differences when devices were turned OFF and ON.
Comparing the effects of shame procedure (OFF mode) to treatment procedure (ON mode) p-value at initial postoperative measurement turned significant (-1.393 ± 0.324). No subscore did so, too.

Mean reduction	Lower bound	Upper bound	Standard error	p-value	Tau^2	Heterogeneity p-value	I^2	authors
Comparing OFF versus ON mode TSS (1-3 months after implantation)								
-1.393	-2.028	-0.759	0.324	<0.001	0	0.996	0	(68,77,128,129)
Comparing OFF versus ON mode TSS vomiting subscore								
-0.423	-0.89	0.044	0.238	0.076	0	0.908	0	(77,128,129)
Comparing OFF versus ON mode TSS bloating subscore								
0.035	-0.624	0.695	0.336	0.917	0	0.679	0	(128,129)
Comparing OFF versus ON mode TSS early satiety subscore								
-0.168	-0.767	0.43	0.305	0.582	0	0.654	0	(128,129)
Comparing OFF versus ON mode TSS nausea subscore								
-0.336	-0.755	0.082	0.214	0.115	0	0.992	0	(77,128,129)
Comparing OFF versus ON mode TSS abdominal pain subscore								
-0.124	-0.84	0.593	0.366	0.735	0	0.704	0	(128,129)
Comparing OFF versus ON mode TSS postprandial fullness subscore								
-0.202	-0.805	0.402	0.308	0.512	0	0.478	0	(128,129)

subscores. Only the reduction of 1.39 ± 0.32 in TSS was significant (see forest plot below), yet subscores for nausea or vomiting were close to significance. Additionally, it should be mentioned that due to variations in sample size, the work by Abell et al. 2003 is of superior weight (90%) (Figure 6).

Discussion

As gastroparesis is a functional disease of stomach motility primarily diagnosed on the one hand by symptoms (nausea, vomiting, bloating and stomach fullness [4–7,40]) and delayed gastric emptying on the other hand [26,29,136,137], it remains under diagnosed and therefore undertreated [137].

Analyzing the treatment options, we were astonished by the small amount of publications on the evidence of nutrition, medication and Botox treatment as we expected these options to be the first in line: Nutrition advice seems to be difficult: On the one hand it seems to be helpful for those who stick to the (eminence based) advices, on the other hand those patients were minorities which leads to the suspicion of in practicable advisory [138,139]. In a small randomized trial different types of meals were compared demonstrating that all of them caused aggravation of GP symptoms [2]. Solid, fatty food significantly worsened symptoms, while liquid, low fat, small particle

diets increase symptoms the least [2,31]. The impact of nutrition and acupuncture, the last especially in long term modification of gastroparesis remains unclear [84], that is why we don`t recommend neither. Most studies pharmacotherapy focuses on symptom control and is not a causal therapy. Due to the small amount of studies and a lack of questionnaire and scintigraphic data, we stay suspicious of their effects. Only the usage of domperidone as short-term treatment, transdermal granisetron and aprepitant are based on single study outcomes.

The intrapyloric application of Botulinum Toxin A is an endoscopic treatment option with low frequency of side effects: Only three randomized controlled trials with different amounts of Botox could be found in literature databases [85–87]. On the one hand, comparing symptom severity before and after Botox injection, we have to confess a significant improvement in GCSI score of 4.906 ± 0.477. On the other hand, comparing clinics of Botox and saline injections, there is a non-significant difference of 0.538 ± 1.403 in GCSI score.

As the amount of studies is small and the improvement after injection significant, we recommend the usage. As injection of saline as placebo is a relatively safe and easily accessible procedure, we were surprised that no further research on pylorus manipulation itself is available. Additionally, it is assumed that the effect decreases over time but data to confirm this is missing.

Publications of salvage therapies, often quite invasive, were of minor quality and therefore the benefit remains unclear.

G-POEM is a new and feasible technique. GCSI<30 and 2-h-GES <78% are predictive factors of clinical success [67,140,141]. Comparing the study designs to the critics we discussed on intrapyloric Botox injections, we must confess: There is exactly no randomized controlled trial, meaning we could not find a single study comparing G-POEM outcome to shame procedure. We therefore had to compare pre- and post-operative measurements including 14 studies. Focusing on postoperative outcome, our statistics illustrates significant improvements of mean GCSI at initial, six months and one year follow-up. We have to confess that heterogeneity of the data at initial and twelve months follow-up is significant, therefore data must be interpreted with special care. A possible explanation could be the wide range in mean difference. Mean GCSI decreased up to 1.945 ± 0.189 at six months follow up. As no shame procedure had been performed it is unclear whether the effect is caused by G-POEM itself or by manipulation on the pylorus itself. Gastric emptying improves significantly as well by 27.017% ± 3.636% (2h-GES) and 26.932% ± 2.442% (4h-GES), respectively. This may explain the value of high gastric retention in 2h-GES as predictive factor [67], as higher values lead to higher decreases.

G-POEM needs to be evaluated by new, randomized-controlled trials to eliminate placebo effect and explain the significant heterogeneity of the available data. The heterogeneity of study effects combined with missing effect of control group may cause an overestimation of G-POEM effects. As pre interventional *vs.* post-interventional data shows significant improvements, we recommend this technique as did others performing metaanalysis on that topic on eight studies [5].

Using electric stimulation to improve the motility of the stomach [68,70,71,128] by modulating intensity and frequency of stimulation [79,81–83] is the latest option in treatment. Gastric emptying scintigraphy was 10.7% ± 2.1% significantly lower in 2h-GES postoperatively than prior to intervention and two hours later significantly 5.9% ± 2.4% lower. TSS decreased significantly for up to 8 points at initial, 10.9 at six months and 8.2 points at latest follow-up. The effect size in nausea and vomiting subscores with 1.3 points reduction is higher the those in bloating/early satiety sub score (0.8 and 0.9, respectively). Interpretation of the TSS development is quite complicate, because at all time point and in every sub score heterogeneity reaches significance with I^2>90%. That means that more than 90% of the variance between studies is caused by systematic differences.

In a second step we extracted data from four studies, who used to create a control group with device turned off (one study was a cross-over trial): TSS decreased significantly by 1.4 points, but no difference in subscores reached significance. There is a tendency towards reduction in nausea (-0.3) and vomiting (-0.4), yet not significant. Heterogeneity in every analysis was not significant with low I^2.

If we compare both steps, it is astonishing that stimulation itself seems to have a minor impact on TSS reduction. The 7-fold higher estimated difference in pre/postoperative evaluation must have multiple causes. As pre/post data need to be carefully interpreted due to significant heterogeneity, further research is needed. That is why we are careful in recommending this procedure in discordance to others [6].

Pyloroplasty according to Heineke-Mikulicz is one of the earliest therapies in gastroparesis, that is why several approaches (open, laparoscopic, robotic-assisted) are now available [56–58,142]. The two available studies on postoperative outcome describe clinical improvement, yet quantification using one of standard gastroparesis scores is missing [56,58]. As pyloroplasty is a quite invasive technique it is often used late in treatment pathways. Therefore, most patients undergoing pyloroplasty are simultaneously treated with several other options, e.g. gastric electrical stimulation [91,142,143]. The authors reported of significant improvements in clinical outcomes, yet only in one study GCSI data is available (4.0 ± 1.1 to 2.3 ± 1.5; [91]). The simultaneous usage of electric stimulators does not seem to improve outcome [91,143].

An alternative surgical option is the gastric bypass with Roux-en-Y-reconstruction as Papasavas et al. documented significant clinical benefits (M severity =13.8 to 7.6; M frequency =15.4 to 8.4; [140]).

As we were not able to perform DerSimonian-Laird, we cannot confirm the impact of pyloroplasty to gastroparesis treatment. It may be a salvage strategy, at least.

Extracting some suggestions for clinicians treating patients with gastroparesis, we strongly recommend an appropriate diagnostic including not only questionnaires and scintigraphy but also endoscopy, Endo Flip [144]) and blood parameters.

Treatment options remain unclear: The intervention itself could have a strong impact on symptom severity. For example, injecting Botox in the pylorus doesn`t improve GP symptoms compared to saline but it does compared to pre interventional baseline. Therefore, we disagree with former reviewers (e.g. (1)) on using Botox injections: Injecting saline could be a midterm treatment. G-POEM is a safe and feasible alternative, but no randomized-controlled trials were available. But pre/post-analysis show significant improvement on a higher level than Pylorus injections. Garg et al. confirmed this in a metaanalysis based on three studies (GCSI decreased from 8.2 to 2.7;

[145]). Gastric electric stimulation is the only randomized-controlled procedure leading to significant reduction in symptom severity (control/intervention).

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