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DOI: 10.17235/reed.2020.6559/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:

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Gastric per-oral endoscopic myotomy (G-POEM) is a promising treatment for refractory gastroparesis: a systematic review and meta-analysis

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Received: 26/8/2019
Accepted: 27/11/2019
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ABSTRACT

Aim: to evaluate the efficacy and safety of gastric per-oral endoscopic myotomy (G-POEM) for the treatment of refractory gastroparesis.

Methods: PubMed, Embase and Cochrane databases were searched and used for study inclusion. Clinical studies since January 2013 to October 2019 were identified as suitable for inclusion. Conference papers, review articles, case reports, animal studies, letters, studies with repetitive data, studies that did not mention the Gastroparesis Cardinal Symptom Index (GCSI) score/gastric emptying scintigraphy (GES) hours or were not indicated in the standard form were excluded. GCSI score, GCSI reduction, gastric emptying scintigraphy at four hours (GES-4h) and GES time (GET) reduction were considered as major indexes and the meta-analysis was achieved using Review Manager 5.3. Research bias was measured according to Cochrane handbook.

Results: nine studies were included with a total of 235 patients that underwent G-POEM, and the technical success rate was 100%. After G-POEM, patients reported
changes in GCSI score (6/9 studies, mean difference 1.41 [CI: 0.93, 1.88], p < 0.0001), GCSI reduction (8/9 studies, odds ratio 3.00 [CI: 2.24, 4.03], p < 0.0001), GES-4h (8/9 studies, mean difference 23.78 [CI: 19.88, 27.68], p < 0.00001) and GET reduction (6/9 studies, odds ratio 3.50 [CI: 2.12, 5.78], p < 0.00001). The intra-procedure complication rate was 5.1% (12/235), including capnoperitoneum (seven cases) and accidental mucotomy (five cases). The post-procedure complication rate was 6.8% (16/235), including abdominal pain (three cases), bleeding (three cases), ulcer (one case), difficulty swallowing (one case) and others (eight cases). Both per- and post-procedure complications were easily managed by conservative or endoscopic treatments.

**Conclusion:** the results show that gastroparesis patients can benefit from G-POEM, the success rate was impressive and the complication rate was relatively low. However, caution is necessary when interpreting the results, primarily due to the limitations of uncontrolled studies. Randomized control studies are still needed for further evaluations.

**Keywords:** Gastric per-oral endoscopic myotomy (G-POEM). Gastroparesis. Gastroparesis cardinal symptom index (GCSI). Gastric emptying scintigraphy (GES). Meta-analysis.

**INTRODUCTION**
Gastroparesis is defined as a syndrome of objectively delayed gastric emptying with no mechanical obstruction (1). Cardinal symptoms include early satiety, postprandial fullness, nausea, vomiting, bloating and upper abdominal pain. There are several etiologies, such as diabetic, post-infectious, postsurgical contexts, infiltrative and neurological disorders such as amyloidosis and parkinsonism. However, the pathophysiology of gastroparesis is complicated and is still not fully understood. Pylorus dysfunction is believed to be the main reason for gastroparesis. Studies have suggested that a lack of the interstitial cell of Cajal may impair fundic accommodation, antral hypomotility, gastric dysrhythmias and pyloric compliance (2). Full thickness gastric biopsies in diabetic and idiopathic gastroparesis also
support this hypothesis (3). Similar to achalasia, the deficiency and decrease of nitric oxide synthesis and release is another possible reason for impaired relaxation of the smooth muscle from the digestive tract (4). Besides, parasympathetic dysfunction and vagus nerve injury are also considered as the underlying factors in gastroparesis pathogeneses (5).

Traditionally, conservative treatments such as oral nutrition, glycemic control of diabetic gastroparesis, pharmacologic therapy and symptomatic treatment were used to relieve symptoms. For those who do not respond to conservative treatments, so called refractory gastroparesis, instrumental treatments such as intra-pyloric botulinum toxin injection (BI), gastric electrical stimulation (GES) and laparoscopic pyloromyotomy (LP) are alternative treatments. Although they are either invasive or less effective.

Gastric per-oral endoscopic myotomy, also called G-POEM, is a technique derived from the per-oral endoscopic myotomy (POEM) procedure. It is comprised of four similar steps of POEM (Fig. 1). First, the mucosal incision is created, second, the submucosal tunnel is developed and extended, third, pyloromyotomy is performed and finally, the mucosal incision is closed. In 2012, Kawai et al. first applied this treatment in a pig pyloric stenosis model (6). Subsequently, Khashab performed the first human endoscopic pyloromyotomy in 2013 (7). Henceforth, the applications of G-POEM have been reported worldwide.

A literature review and meta-analysis was performed of current studies to summarize the current evidence of the efficacy and safety of G-POEM as an alternative approach in the treatment of refractory gastroparesis.

MATERIALS AND METHODS

Study selection

A systematic search was performed in PubMed, Embase and the Cochrane Central Register using specific keywords such as “G-POEM”, “gastric per-oral endoscopic myotomy”, “gastric peroral endoscopic myotomy”, “per-oral endoscopic pyloromyotomy” and “peroral endoscopic pyloromyotomy”, by two independent authors. Since the first application of G-POEM was in 2013, a literature review was
performed from January 2013 to October 2019. Inclusion criteria were: studies on G-POEM for the treatment of refractory gastroparesis. Exclusion criteria were: a) studies on G-POEM not in human groups; b) studies not published in English; c) articles that lacked GCSI and GET data or not in a mean ± SD form; and d) studies not published as a full article (such as conference papers). When multiple publications from the same cohort and/or overlapping cohorts were found, data from the most recent and/or most appropriate comprehensive report were retained.

Data extraction
Two authors scanned all the identified citations and abstract data independently, according to a standard form. Parameters included: first author and year of publication, study duration, country of origin, research design, sample size and follow-up rate, age, gender, subtype, prior-treatment, start of tunnel, myotomy length and depth, procedure time, hospital stay, follow-up duration, complications, Gastroparesis Cardinal Symptom Index (GCSI) score, GCSI reduction, gastric emptying scintigraphy at four hours (GES-4h) and GET reduction. The third reviewer was responsible for resolving all the disagreements. The data extraction form was pilot-tested and agreed by all authors.

Outcomes measurement
In these studies, some indexes were used to estimate the curative effects of G-POEM treatment. The GCSI was designed to evaluate symptom severity of gastroparesis patients (8). Symptoms such as nausea, retching, vomiting, stomach fullness, not being able to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating and the stomach or belly visibly larger were divided into three main aspects and graded from 0 to 5. Gastric emptying scintigraphy, also called GES, is a method to assess gastric emptying (1). Although there are no diagnostic criteria, GES at four hours remains the gold standard to diagnose gastroparesis.

Assessment of study quality
The Cochrane Collaboration’s tool was used to assess the risk of bias and confirmed
the appropriateness and correctness of pooling evidence across the studies. In addition, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias were recorded.

**Statistical analysis**
Statistical analyses were performed using Review Manager 5.3. A pre-post design was used to evaluate outcome after G-POEM in the same study. Effect sizes for numerical variables (GCSI score and GES-4h) were expressed as standardized difference in the mean with 95% confidence interval (CI), while effects sizes for categorical variables (GCSI reduction and GET reduction) were expressed as the odds ratio with 95% CI. The log OR method was used to analyze GCSI reduction and GET reduction. The $I^2$ statistic was used to examine and quantify statistical heterogeneity. Heterogeneity greater than 25% was considered as important. According to the Cochrane Handbook, the random effects model was chosen for all calculations. The original data of GCSI reduction and GET reduction did not form a normal distribution and their outcomes were adjusted.

**RESULTS**
**Study characteristics**
The initial search identified 235 studies, of which 173 were screened for eligibility criteria after removing duplications. Of 173 studies, 150 were excluded based on abstract review; 97 studies were not related to G-POEM or gastroparesis, seven were conference papers, 17 were review articles, 19 were case reports, three were animal studies and seven were letters. In total, 14 studies were excluded after full-text review as there was no mention of GCSI/GES hours. When articles only provided medians and range of data, authors were contacted and asked for the original data. However, no author replied and therefore, articles that did not express the data as the mean ± SD form were excluded. By the time the search was concluded, there was no published randomized control trials (RCT) of G-POEM. Thus, non-controlled observational studies were included and considered as before and after self-
controlled studies. Finally, nine studies were considered as suitable for quantitative
analysis (Fig. 2).
All nine studies were published in the past five years (Table 1). They originated from
single research center, except for one multi-center research article (9) (two in USA,
two in Asia and one in South America). Other studies were performed in North
America (six in USA), Asia (one in China) and Europe (one in France). There are seven
retrospective studies and two prospective studies. The total number of included
patients was 269 and the follow-up rate was 76.6% (269/206). There were almost
three times as many female patients compared to males (197/72). The main
subtypes of gastroparesis were idiopathic gastroparesis, post-surgery pyloric stenosis
and diabetic gastroparesis. Scleroderma and post-infection gastroparesis patients
were also included. Some of the patients underwent prior treatment such as
botulinum toxin injection, gastric electrical stimulation, balloon dilation, transpyloric
stenting and PEG with jejunal extension.

**Technical aspects of G-POEM**
The first case series of G-POEM procedure was performed by Shlomovitz et al. (10) in
2015. Among seven cases reported, six procedures were guided by laparoscopy and
one procedure was purely endoscopic. G-POEM was performed successfully in all
seven cases. In the remaining studies, the predominant method to establish a
submucosal tunnel was to start 5 cm from the pylorus along the greater curvature.
However, some studies also chose the lesser curvature, the anterior wall or the
posterior wall to approach the pylorus. There is a disagreement among different
institutions as to whether the greater or the lesser curvature is more straightforward. Full thickness myotomy or selective circular muscle myotomy were
also preferred in different centers. Not all studies mentioned the myotomy length,
but some believed that it is unnecessary to dissect beyond the pylorus into the
duodenal bulb (11). The risk of mucosal perforation is increased and the symptoms
will not be significantly relieved. The procedure time and length of stay are shown in
table 2. Only one study completed long-term follow-up until 12 months. The
technique success rate was 100%, if mentioned (Table 2).
Main outcomes and quality of studies

After G-POEM, patients reported changes in the GCSI score (Fig. 3A). There was a remarkable reduction in GCSI score with an overall effect size (Z) of 5.75 (p < 0.0001) and a mean difference of 1.41 (CI: 0.93, 1.88) in six of nine studies. However, significant heterogeneity among studies was observed in GCSI (Tau² = 0.28; Chi² = 25.40, df = 5 [p = 0.0001]; I² = 80%). Eight of nine studies reported the number of patients who achieved improvements in GCSI. The overall effect size (Z) was 7.34 (p < 0.0001), with an odds ratio of 3 (CI: 2.24, 4.03) (Fig. 3B).

Besides the subjective index to describe symptoms, GET was also analyzed to evaluate gastric retention improvement. GES-4h improved with an overall effect size (Z) of 11.96 (p < 0.00001) in eight of nine studies and a mean difference of 23.78 (CI: 19.88, 27.68) (Fig. 4A). Six of nine studies reported the number of patients who achieved improvements in GET. The overall effect size (Z) was 4.90 (p < 0.00001), with an odds ratio of 3.50 (CI: 2.12, 5.78) (Fig. 4B).

Complications

Among the included cases, the intra-procedure complication rate was 5.1% (12/235), including capnoperitoneum (seven cases) and accidental mucotomy (five cases). The post-procedure complication rate was 6.8% (16/235), including abdominal pain (three cases), bleeding (three cases), ulcer (one case), difficulty swallowing (one case) and others (eight cases) (Table 3). Both intra- and post-procedure complications were easily managed by conservative or endoscopic treatments. Capnoperitoneum and mucotomy can be dealt with by intra-procedural needle drainage or closed with clips. If patients complain about abdominal pain, their oral intake should be delayed until the pain disappears. Some acute bleeding stopped spontaneously. Moreover, proton pump inhibitor was effective in treating pre-pyloric ulcers. Previous surgical history of Nissen fundoplication was considered as a possible reason for difficult swallowing in one patient. Other complications such as hospital acquired nosocomial pneumonia, cardiac disease related death and pulmonary embolism were rare and not directly related to G-POEM procedure.
DISCUSSION

G-POEM has been considered as a promising therapy in the treatment of gastroparesis, even compared with traditional treatments such as GES, BI and LP. Our meta-analysis provides evidence-based results that G-POEM is both safe and effective in treating gastroparesis.

Previous interventional treatments such as GES, BI and LP have been discussed before G-POEM. A meta-analysis showed that the total symptom severity (TSS) score from 16 open label studies of GES was significantly decreased (mean difference 2.68 [CI: 2.04, 3.32]; Q = 39.0; p < 0.001) (12). Other treatments such as medical therapy (mean difference 1.97 [CI: 1.5, 2.44]), placebo arms (mean difference 1.52 [CI: 0.9, 2.15]) and BI (mean difference 2.32 [1.56, 3.06]) also improved TSS, although these results were significantly influenced by patients’ baseline condition according to meta-regression analysis. However, a recent RCT did not show any benefit when comparing BI to placebo (saline injection) and questioned its clinical efficacy (13). Miller et al. (14), nevertheless, reported a substantial decrease in GES-4h from 27% to 14%, as well as reliable symptom improvement six months after BI.

LP has been widely used for hypertrophic pyloric stenosis in infants and children (15), even the primary attempt of G-POEM was performed under the assistance of a laparoscope (10). Shada et al. (16) performed the largest published prospective study in 177 patients in a five-year follow-up. This study concluded that LP can effectively improve gastric retention and symptoms, and further recommend it as the first-line therapy for gastroparesis. However, the overall morbidity rate of LP was 6.8%, with four re-surgery, two confirmed leaks (1.1% leak rate) and 19 subsequent intervention. This suggested that LP is more invasive and will likely result in more complications. A recent study compared LP with G-POEM, retrospectively (17). Thirty patients who underwent G-POEM were propensity-matched with patients who underwent LP. Although the two methods resulted in a similar clinical efficacy, G-POEM had a better performance in the average length of stay, operative time, estimated blood loss and complication rate.

There is still no standard procedure recommended for G-POEM. Among all the
procedures of G-POEM, the identification of the pyloric muscular ring (PMR) remains the prior challenge which determines the treatment related prognosis. The traditional method to locate PMR is to take the scope out of the tunnel and advance the scope to find any blue color (created by the submucosal injection of a mixed solution of methylene blue and saline) at the pylorus or the duodenum near the pylorus. Xue H.B. et al. (18) identified PMR by placing an endoclip at the pylorus, which was a reliable marker when performing G-POEM under fluoroscopy. This was a reliable and safe method to orientate the submucosal tunnel, identify PMR and shorten the procedure time. In POEM, the double scope technique was reported to locate the gastroesophageal junction without withdrawing the endoscope (19), which indicated a potential method to locate PMR. Besides, the start of the tunnel, myotomy length and myotomy depth varies between different institutions. Therefore, these technique aspects need further research and evaluation.

In our study, significant clinical effects were reported following G-POEM. Among nine included studies, six reported a specific GCSI score and eight indicated the number of patients who achieved clinical success. A prominent decrease in GCSI indicated that symptoms were greatly relieved. Regarding gastric retention, eight of nine studies reported a decrease in GES-4h after G-POEM treatment. A recent pooled analysis underscored the clinical efficacy of GCSI (81.5%) and GES normalization in approximately 55% of the cases. This is in line with our results (20). Of note, all 235 patients achieved a technical success rate of 100%.

Meanwhile, the complication rate of G-POEM was also discussed. Similar to POEM, capnoperitoneum remains the most common complication during the procedure. Immediate needle puncture can effectively drain the gas and left no sequelae. Accidental mucotomy is not rare, especially at the duodenum, where the mucosa is relatively thin. Thus, further dissection into the duodenum will do more harm than good and it is not advised. After completing the procedure successfully, patients might still encounter some discomfort such as abdominal pain, bleeding, ulcer and difficult swallowing, etc. These symptoms can be managed by conservative treatments such as delayed oral intake or proton pump inhibitors. No severe consequences were observed in these studies. Therefore, the current data support
that G-POEM is a reliable treatment for gastroparesis.

In our study, there were almost three times as many female patients as male patients. Increasing evidence suggests that females are more susceptible to gastroparesis than age-matched males (21). There are several studies which concentrated on gender bias in gastroparesis. Tetrahydrobiopterin is a key regulator of neuronal nitric oxide (NO) synthase activity. In female diabetes mellitus (DM) patients, hyperglycemia affected the level of estrogen and its receptors, which can alter tetrahydrobiopterin biosynthesis. Consequently, the uncoupled neuronal NO synthase activity reduced NO levels in the stomach, which led to pylorus dysfunction and gastroparesis (22,23). Consistently, female gender (OR = 1.9 [95% CI: 1.2-2.9]) and diabetic gastroparesis (OR = 5.4 [95% CI: 1.3-23.4]) were considered as risk factors of the G-POEM procedure by González et al. (24), based on univariate analysis. Both correlated with clinical success after three and six months of follow-up. However, this result was not confirmed by multivariate analysis in the same study. Although G-POEM is less effective in female patients, its clinical application should not be restrained.

Before drawing an optimistic conclusion, several limitations still need to be mentioned. The quality of the included studies was relatively low. They had a high risk of selection bias, performance bias and detection bias (Fig. 5). All nine included studies were not RCT experiments and lacked controls. Only three were prospective studies (25,26). In addition, patient inclusion was based on personal clinical experience and the follow-up rate was only 76.6%. Meanwhile, the heterogeneity between studies was significant, probably due to the mismatching of baseline information such as subtypes, prior-treatments and endoscopists. Subgroup analysis or meta-regression is needed to deal with this problem. Even though the outcome of this meta-analysis is significant, caution is still needed to draw a conclusion as to whether G-POEM can be a complete treatment for the treatment of gastroparesis.

According to our study, further investigation based on additional reports is required. Even though G-POEM is considered as the prior treatment for gastroparesis in some institutions, RCT studies between G-POEM and LP or GES are required to evaluate whether G-POEM can be the first-line therapy for refractory gastroparesis. Besides,
disease duration, gender, glycemia level, predominant symptoms, myotomy depth and tunnel position may also affect the final outcome of G-POEM. Thus, we suggest that data for different subtypes should be presented separately in order to access the subtype which benefits most from G-POEM treatment.

In summary, G-POEM has shown its potential in treating gastroparesis, especially for its durable clinical effect and minimal invasion. For those patients who cannot undergo a surgical procedure or do not respond well to BI, G-POEM can be recommended as a salvage treatment. It can also be considered as equally effective as BI, GES and LP in untreated patients. Nevertheless, the clinical application of G-POEM is the short and long-term follow-up has not been shown.

CONCLUSION

Our results show that gastroparesis patients can significantly benefit from G-POEM and the complication rate is relatively low. Although caution is necessary when interpreting the results, primarily due to the limitations of uncontrolled studies. The possible predictive factor of the G-POEM procedure is still under discussion. Subtype analysis is needed to determine which subtype will benefit most from the G-POEM procedure.

REFERENCES


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<td>72 ± 42</td>
<td>3.3</td>
<td>6</td>
<td>1 capnoperitoneum/1 ulcer</td>
<td>100%</td>
</tr>
<tr>
<td>(19 greater curvature, 9 anterior wall, 2 posterior wall)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>Length (cm)</td>
<td>Type of Myotomy</td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Complications</td>
<td>Incidence</td>
<td></td>
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</tr>
<tr>
<td>--------------</td>
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<td>-----------</td>
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<td>---------------------------------------------------</td>
<td>-----------</td>
<td></td>
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<tr>
<td>Shlomovitz</td>
<td>N/A</td>
<td>Full thickness myotomy</td>
<td>N/A</td>
<td>2.3</td>
<td>1 bleeding ulcer/1 pancreatitis/1 difficult swallowing/1 nosocomial pneumonia</td>
<td>100%</td>
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<tr>
<td>Mekaroonkamol</td>
<td>2-3 cm</td>
<td>Circular muscle myotomy</td>
<td>48 ± 16.5</td>
<td>2.4</td>
<td>1 capnoperitoneum</td>
<td>100%</td>
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<tr>
<td>Landreneau</td>
<td>(lesser curvature)</td>
<td></td>
<td>33.9 ± 18.8</td>
<td>1.4</td>
<td>2 infection/2 post-operative pneumonia</td>
<td>100%</td>
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</tr>
<tr>
<td>Xu</td>
<td>5 cm from pylorus</td>
<td>Full thickness myotomy</td>
<td>45.25 ± 12.96</td>
<td>6</td>
<td>2 mucosal injury</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xue</td>
<td>(great curvature)</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xue</td>
<td>5 cm from pylorus</td>
<td></td>
<td>N/A</td>
<td>46 ± 16.2</td>
<td></td>
<td>100%</td>
<td></td>
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<tr>
<td>Total</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3 bleeding/2 ulcer/3 abdominal pain/1 difficult swallowing/7 capnoperitoneum/10</td>
<td>100%</td>
<td></td>
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N/A: not available.
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<td>Intra-procedure</td>
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<td>Capnoperitoneum</td>
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<td>Post-procedure</td>
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<tr>
<td>Abdominal pain</td>
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<td>Delayed oral intake</td>
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<td>Acute bleeding</td>
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<td>Prepyloric ulcer</td>
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<td>Proton pump inhibitor intake</td>
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<td>Difficulty swallowing</td>
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<td>Hospital-acquired nosocomial pneumonia, cardiac disease-related death, pancreatitis, pulmonary embolism</td>
<td>Not related to G-POEM</td>
<td>8</td>
<td>N/A</td>
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Fig. 2. PRISMA diagram showing study selection.
Fig. 3. Forrest plot showing the efficacy of G-POEM in GCSI score (A) and GCSI reduction (B) in patients with gastroparesis.
Fig. 4. Forrest plot showing the efficacy of G-POEM in GES-4h (A), and GET reduction (B) in patients with gastroparesis.
Fig. 5. Assessment of quality of individual studies.