

Background: Gastroparesis (GP) is a disorder characterized by delayed gastric emptying in the absence of a symptomatic mechanical obstruction of the stomach with cardinal symptoms. Two principal pathophysiological mechanisms are believed to be responsible for development of GP: global gastric hypomotility and pylorospasm. As pylorospasm may play an important role in GP, the efficacy of treatment modalities targeting the pylorus, such as gastric peroral endoscopic pyloromyotomy (G-POEM), is currently being intensively studied, as these methods have the potential to help especially patients with severe symptoms for whom other treatment measures are ineffective. The aims of our studies were: **(1)** to evaluate clinical efficacy of G-POEM in the treatment of patients with severe GP; **(2)** to evaluate the changes in objective periprocedural parameters measured by gastric emptying study (GES) and functional planimetry; **(3)** to evaluate safety of G-POEM and **(4)** to compare the efficacy of two closure methods used to close the mucosal incision in G-POEM: clips and endoscopic suturing (ES).

Patients and methods: Patients older > 18y, with gastroparesis cardinal symptoms index (GCSI) > 2.3 and abnormal GES were eligible for inclusion. All projects had been performed between 2015 and 2021. Project **(1)**: Clinical efficacy of G-POEM was assessed in a randomized, sham controlled (cross-over) trial. The primary outcome was the proportion of patients with treatment success at 6 months (M) after the procedure. Treatment success was defined as a decrease of at least 50% in the total GCSI from baseline. Project **(2)**: All consecutive patients were evaluated using GES prior to procedure and at 3M after G-POEM (either primary or cross-over G-POEM). Dynamic changes in pyloric function have been assessed using functional planimetry prior and after G-POEM and at 3M follow-up visit and we identified predictive parameters of treatment success. Project **(3)**: The primary objective was to evaluate the rate of serious and non-serious AEs associated with G-POEM. Project **(4)**: The closure method (clips vs ES) was assigned at the discretion of an endoscopist prior to the procedure and the main outcome was the proportion of subjects with successful closure. Unsuccessful closure was defined as a need for a rescue method, or a need for an additional intervention or incomplete closure related adverse events. Secondary objectives were to assess easiness of incision closure [scored by visual analogue scale (VAS)] and time to incision closure.

Results: Project **(1)**: Total of 41 patients were included, GP etiologies were diabetic (41%), postsurgical (32%) and idiopathic (27%). Treatment success at 6M was observed in 14 of 20

patients (70%, 95% CI: 48% – 85%) in G-POEM group vs 4 of 19 patients (21%, 95% CI: 9% – 43%) in sham group. Nine out of twelve patients (75%, 95% CI: 47% – 91%) achieved treatment success after cross-over G-POEM at 6M. Overall mean GCSI improved from mean of 3.5 (95% CI: 3.2 – 3.7) to 1.1 (0.5 – 1.5) after G-POEM vs. 3.2 (2.8 – 3.4) to 2.5 (1.9 – 3.2) after sham. After cross-over G-POEM, mean GCSI significantly decreased from 2.8 (2.5 – 3.7) to 1.0 (0.6 – 1.7). Project (2): Among the patients with available postoperative GES, 85% had objectively improved GES with 55% having normalized GES post G-POEM. There was no correlation between GCSI and GES at 3 months after G-POEM [$r= 0.15$ (95% CI: -0.18 to 0.42)]. Distensibility index (DI) at 40 mL (mm^2/mmHg) increased from a baseline value of 7.6 (6.0 – 9.3) to 12.7 (11.4 – 14.3) after G-POEM and in the logistic regression model a DI value > 13 mm^2/mmHg after G-POEM was able to predict the treatment effect. Project (3): Among 63 patients, twelve adverse events (AEs) occurred and only 4 (6.4%) were serious according to an accepted classification; no AE was fatal and no patients needed surgery. All serious AEs were related to G-POEM procedure. Project (4): Out of 40 patients; 20 received ES and 20 clips [mean 6 (4 – 19)]. All 20 patients with ES (100%, CI: 84% – 100%) and 18 with clips (89%, CI: 70% – 97%) had successful closure ($p= 0.49$). One patient needed a rescue method and another patient an additional clipping on first postoperative day. Closure with clips was quicker [9.8 (4 – 20) vs 14.1 (5 – 21) min; $p= 0.007$]. Endoscopist assessed the easiness of ES and clips as comparable [mean VAS, range: 7.5 (3 – 10) (ES) vs. 6.9 (3 – 10) (clips); $p= 0.3$].

Conclusions: We have shown, that: (1). G-POEM is superior to placebo in unselected patients with GP. These results confirm the hypothesis that pylorospasm may play a major pathophysiologic role in patients with severe GP. (2). G-POEM improved and/or normalized GES in majority of patients. $\text{DI} > 13$ mm^2/mmHg after G-POEM could predict of clinical success. (3). G-POEM appears is a safe procedure, although serious complications may rarely occur. (4). Both ES and clips are effective methods for mucosal closure in patients undergoing G-POEM. However, clipping, in contrast to ES, does not guarantee the “100%” success rate.