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Evaluation of the safety profile of endoscopic pyloromyotomy by G-POEM: a French multicenter study

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Florian Baret, Jeremie Jacques, Mathieu Pioche, Jeremie Albouys, Véronique Vitton, Geoffroy Vanbiervliet, Antoine Debourdeau, Marc Barthet and Jean-Michel Gonzalez

Abstract

Background: Gastric per oral endoscopic esophageal myotomy (G-POEM) is a promising procedure to treat refractory gastroparesis. The safety profile of G-POEM is an important topic because gastroparesis is a functional pathology, with a procedure whose effectiveness is between 50 and 65% depending on the studies.

Objectives: We present this retrospective multicenter study, with the aim of establishing a safety profile, focusing on serious adverse events (AEs).

Design: This was a multicenter observational cohort study conducted in five French expert centers.

Methods: All patients who underwent G-POEM for refractory gastroparesis between 2015 and 2021 were included for analysis. AEs were classified into per endoscopic, early postoperative, and late postoperative, up to 1 month. Their severity was assessed using Dindo–Clavien and American Society for Gastrointestinal Endoscopy classification. The primary objective was to evaluate the rate of G-POEM severe AEs. Secondary objectives were to document other postoperative AEs, and to identify predictive factors.

Results: In all, 217 patients were included: 81 men and 136 women, mean age 52 ± 17 years. The average procedural time was 44 ± 14 min (12–78). The average hospital stay was 3.7 ± 2.3 days. The AEs rate classified as Clavien–Dindo ⩾3 was 0.4% (one delayed bleeding requiring blood transfusion and endoscopic management). There were no deaths or patients admitted to intensive care unit. The rates of mucosotomy and capnoperitoneum were 3.7 and 1.8%, respectively, without clinical consequences. Most patients (81.5%) did not experience any AE. Three cases of dumping syndrome occurred, quickly managed by dietary measures.

Conclusion: Our study confirms the safety of G-POEM with less than 0.5% of serious AEs, medically managed. This outcome makes this a procedure to have a good benefit–risk ratio.

Keywords: gastroparesis, G-POEM, severe complications

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Correspondence to:
Florian Baret
Service d'Hépato-Gastro-Entérologie, CHU Nord, Chemin des Bourrely, Marseille 13015, France
florian.baret@ap-hm.fr

Véronique Vitton
Marc Barthet
Jean-Michel Gonzalez
Service de Gastroentérologie, CHU Nord, Marseille, France

Jeremie Jacques
Jeremie Albouys
Service de Gastroentérologie, CHU Dupuytren, Limoges, France

Mathieu Pioche
Service de Gastroentérologie, CHU Edouard Herriot, Lyon, France

Geoffroy Vanbiervliet
Service de Gastroentérologie, CHU Archet 2, Nice, France

Antoine Debourdeau
Service de Gastroentérologie, CHU Saint Eloi, Montpellier, France

Introduction

Gastroparesis is a functional digestive disorder defined by a delayed gastric emptying in the absence of mechanical obstacle.[1] Recently, an American population-based study estimated the prevalence of gastroparesis to be 0.16%,[2] previously estimated to be approximately 2–3% of the general population.[3] The possible etiologies are dominated by three main causes: diabetes, thoracoabdominal surgery[4] (vagus nerve injury), and idiopathic origin.[5]

The cardinal symptoms are nausea, vomiting, bloating, postprandial gastric fullness, early satiety, and abdominal pain.[6,7] These elements are grouped into a severity score called the Gastroparesis

Cardinal Symptoms Index (GCSI), with a score above 2.6 indicating moderate gastroparesis and above 3 indicating severe gastroparesis.[8] The pathophysiology of gastroparesis is complex and partially elucidated, including pyloric sphincter dysfunction,[9] in addition to hypomotility of the gastric antrum, insufficient fundic tone, desynchronization of the stomach with the antrum,[10] and probably visceral hypersensitivity.

The first-line treatment combines hygienic and dietary rules and is very often disappointing[11–15] and gastroparesis is considered refractory after a failure of 6 months of well-conducted medical treatment.[16] Various procedures targeting the pylorus have been attempted, including botulinum toxin injection, pyloric muscle dilatation, and transpyloric stenting showing no superior efficacy to placebo[17,18] or moderate, very transient efficacy, and a non-negligible risk of complications.[19–21]

The most recent procedure is the endoscopic pyloromyotomy, which has been developed in recent years,[22–24] derived from the per oral endoscopic esophageal myotomy (POEM) described by Inoue *et al.* in 2010 in Japan[25] which is very effective in the treatment of achalasia and thus proposed in the latest European Society of Gastrointestinal Endoscopy recommendations.[26] Moreover, POEM is a safe technique with studies dedicated to the analysis of intraoperative and postoperative complications showing very low early postoperative morbidity, with less than 1% of serious adverse events (AEs) in a study of more than 2000 patients (0.2% delayed bleeding and 0.5% hydrothorax), no need for revision surgery and zero mortality.[27] The first cases of treatment of gastroparesis by endoscopic pyloromyotomy [gastric POEM (G-POEM)] were therefore published, in 2013 in the United States and in 2015 in Europe, in France, in Marseille. Since then, several retrospective studies showed a technical success close to 100%, a short-term clinical efficacy rate around 80% and around 65% at 1 year.[28–37] More recently, a French retrospective multicenter study found a 1-year efficacy of 66%.[38] Finally, an international prospective study was performed by Vosoughi *et al.* showing an efficacy of 56% at 12 months, with a durable response.[39]

The safety profile of G-POEM is an important topic because gastroparesis is a functional pathology, with a procedure whose effectiveness is between 50% and 65% depending on the studies.[28–39] The safety profile, and in particular the risk of serious side effects, is a major issue in the context of the treatment of functional pathologies. Indeed, we cannot tolerate a significant risk of serious AEs in the treatment of a functional pathology.

The safety profile of G-POEM has been specifically evaluated in one study, as well as in secondary endpoints in other studies. In this study, Ichkanian *et al.*[40] reported severe complications in two patients out of 216 included.

The risk of serious adverse effects of G-POEM is therefore a major issue. In view of the scattered data in the literature concerning G-POEM, with mostly retrospective studies on a small number of patients, and a low rate of serious AEs reported until now, it was important to carry out a large multicenter study, with a significant number of operators, specifically evaluating this question.

Patients and methods

Study design and patient characteristics

This is a multicenter retrospective observational cohort study conducted at the CHU Nord of Marseille, the CHU Edouard Herriot of Lyon, the CHU l'Archet 2 of Nice, the CHU Dupuytren of Limoges, and the CHU Saint Eloi of Montpellier. All of them are recognized expert centers in submucosal endoscopy. All operators included in the study had performed at least 50 POEM or G-POEM. All patients who had a G-POEM for refractory gastroparesis between February 2015 and March 2021 were identified using a secure computerized database and were included in the study for analysis. About 50% of the patients in the study were published in previous studies about G-POEM.[28–30,38] According to the French law, no ethical committee approvement nor institutional review board is requested in the case of retrospective studies. However, our database was anonymized and declared and approved by the French National Commission for Information Technology and Civil Liberties (CNIL). As a retrospective study, according to the Declaration of Helsinki, informed consent was not required from patients. The characteristics collected from the patients were as follows: age, gender, etiology of gastroparesis, previous treatments, comorbidities presented by the patients, presence of anticoagulants or

antiplatelet agents, and recent involuntary weight loss of more than 10% secondary to gastroparesis. This article was published following the STROBE guidelines and the checklist is available as Supplemental Material.

Endoscopic procedure and follow-up

All procedures were performed by interventional endoscopists with a high level of expertise in submucosal dissection and in performing POEM and G-POEM. They were performed under general anesthesia with oro-tracheal intubation, with the patient in supine position. An intravenous antibiotic prophylaxis with amoxicillin/clavulanic acid or dalacin in case of allergy was performed before starting the procedure. All procedures were performed with a CO_2 insufflator. The type of knife used varied according to the teams: Triangle Tip Knife, Dual Knife, and Hook Knife (Olympus, Tokyo, Japan). The realization of the G-POEM followed the following steps, perfectly standardized, described below:

1) Submucosal injection of a mixture of saline and indigo carmine (0.25%)
2) Mucosal incision, 5 cm proximal to the pylorus at the posterior part of the antrum
3) Tunneling by submucosal dissection with Q endocut current (with preventive electrocoagulation of submucosal vessels) to the pyloric area, marked by the 'white arch' sign
4) Verification of the length of the tunnel, its position, and the absence of mucosal breach
5) Pylorotomy (of the internal circular and oblique layers) over 3 cm
6) Removal of the endoscope and closure of the mucosal access by endoclip

Regarding the procedure, the per-endoscopic data collected were the presence of significant gastric stasis, and the presence of significant submucosal vascularization and/or fibrosis and the occurrence of intraoperative complications as described below. In the immediate postoperative period, the patients were clinically monitored daily for pain and septic signs (fever) for 1–4 days before going home, to ensure that no immediate postoperative complications occurred. Re-feeding was carried out progressively with a specific dedicated protocol, with resumption of a liquid diet, then mixed, then normal. The duration of hospitalization was recorded for each patient. Single-dose proton pump inhibitor (PPI) treatment was started at discharge for a period of 3 months.

The patients were then seen in a follow-up consultation or contacted by telephone if they could not come to the clinic, between 3 and 6 months and at 1 year. They were subjected to a standardized questionnaire to evaluate the GCSI score, as well as an exhaustive interrogation to verify the absence of side effects during the endoscopic procedure.

Evaluation of complications

Complications were classified into three categories based on the time of occurrence: per endoscopic, early postoperative, during hospitalization, and late postoperative, up to 1 month postoperatively.

Per endoscopic complications could include significant bleeding defined as hemodynamic impact, loss of more than 2 hemoglobin points or the need for transfusion, mucosal perforation, capnoperitoneum, and/or a complication related to general anesthesia.

In the immediate postoperative period, the occurrence of digestive bleeding, sepsis, in connection with a possible perforation, pain, was collected as well as the time for refeeding and discharge from the hospital.

These complications were classified in terms of severity according to the Clavien–Dindo classification (see Table 1). This classification categorizes perioperative AEs into grades according to their severity and the intensity of the treatments required.[41,42] Grades 1 and 2 represent minor complications and grades 3 to 5 represent major complications. It should be noted that in this classification only the most serious complication is retained.

In the late postoperative period, the need for re-hospitalization, endoscopic re-intervention, and reoperation, as well as the existence of long-term adverse effects were collected.

Objectives

The primary objective was to evaluate the frequency of serious AEs occurring during G-POEM

Table 1. Classification of Clavien–Dindo.

Grade	
1	Any variation in the postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological procedures Accepted treatments are as follows: antiemetics, analgesics, antipyretics, electrolytes, and physiotherapy
2	Complication requiring pharmacological treatment with drugs other than those authorized for Grade 1. Blood transfusions, antibiotics, and total parenteral nutrition are also included
3	Complication requiring a surgical, endoscopic, or radiological procedure
3a	Procedure under local/locoregional anesthesia
3b	Procedure under general anesthesia
4	Life-threatening complication requiring intensive care/resuscitation
4a	Single organ failure
4b	Multiple organ failure
5	Death of the patient

procedure in an expert center. A serious AE was defined by a Clavien–Dindo score of 3 or more.[41]

The secondary objectives were to document all other AEs that could occur postoperatively, to classify them based on their severity, and to identify predictive factors of occurrence and to document the clinical efficacy for interpreting the AEs rate, defined as a GCSI decrease greater than 1 from baseline.

Statistical analysis

The databases used were the local databases specific to each site, all of which meet the French National CNIL standards in terms of anonymization and data protection. Statistical analyses were performed with Excel software (Microsoft, Redmond, WA, USA). Data were expressed as mean with extremes and percentages. Frequencies and percentages were expressed as mean with extremes and percentages. Medians and means were used for quantitative variables.

Fisher's exact tests were performed with BiostaTGV software (Inserm Sorbonne, Paris, France) to determine the possible risk factors for the occurrence of complications, knowing that the effects were sometimes less than 5. Results were expressed as an odds ratio (OR) with confidence interval and p value is significant when less than 0.05.

A multivariate analysis by logistic regression was not performed because it was not relevant, as the small number of events did not allow the identification of statistically significant risk factors in multivariate analysis.

Results

Patients and procedural characteristics

Between February 2015 and March 2021, 217 patients received G-POEM: 81 men and 136 women, with a mean age of 52 ± 17 years. Their characteristics are detailed in Table 2. The etiology of gastroparesis was idiopathic in 38.3% (83/217) of cases, diabetic in 29.5%. (64/217) of cases, post-surgical in 24% (52/217) of cases, secondary to systemic scleroderma in 4.1% (9/217) of cases and related to various causes in 4.1% (9/217) of cases. The latter included gastroparesis secondary to Goujerot–Sjögren's syndrome, paraneoplastic and associated with parkinsonian syndrome. 31% (67/217) of the patients had weight loss of more than 10% of their initial weight after the onset of their digestive symptoms, related to the symptoms of gastroparesis.

Regarding to prior treatments, 16.5% (36/217) of patients were taking antiplatelet agents (APA) and 3.7% (8/217) anticoagulants. Only 0.9% (2/217) of patients were taking both APA and anticoagulants. These treatments have been stopped in all the patients based on recommendations.

Notable characteristics of the procedure are collected in Table 3. The mean duration of the procedure was 34 ± 14 min (12–78). 28.6% (62/217) of patients had significant gastric stasis at the beginning of the procedure. 21.7% (47/217) of patients had significant submucosal vascularity noticed by the operator. 24.9% (54/217) of patients had significant submucosal fibrosis. The average postoperative length of stay was 3.7 ± 2.3 days.

The mean preoperative GCSI score was 3.57 ± 1.7. The efficacy rate was 67.3% ($n = 146$) after a mean follow-up time of 20 ± 12 months.

Adverse events

Per-endoscopic complications. A rate of 3.7% ($n = 8$) of mucosotomies was observed, all closed by the placement of a clip with 100% technical success and without clinical consequences postoperatively. A capnoperitoneum occurred during four procedures, systematically exsufflated by needle with success and without hemodynamic impact or on the ventilatory mechanics of the patients.

There was no bleeding responsible for hemodynamic instability, significant blood loss greater than 2 g/dl of hemoglobinemia or requiring a transfusion during or after the procedure. No significant anesthetic complications were reported.

Early postoperative complications. First, 14.7% ($n = 32$) of the patients reported postprocedural significant pain requiring stage 1 or 2 analgesics, classified as grade 1 of the Dindo–Clavien classification. The length of stay was prolonged in these cases to 5.8 days compared to 3.7 days, due to an extended refeeding time. Two patients underwent a computed tomography (CT) scan because of severe abdominal pain with peritoneal irritation, demonstrating a moderate pneumoperitoneum. They were treated by fasting, antibiotic therapy, PPI, and nasogastric tube placement with a favorable evolution within 5 days allowing for being discharged.

Bleeding occurred in five patients, in four of them within 24 h, without hemodynamic instability and with spontaneous cessation of bleeding without recourse to hemostasis endoscopy. These patients were classified as grade 2 of the Dindo–Clavien classification. The length of stay for these patients was extended to an average of 5.25 ± 3 days.

Table 2. Patient characteristics.

Patient characteristics	
Gender (%)	Men 37.3%, women 62.7%
Average age (years)	52 (12–85 years)
Etiology % (n)	
Idiopathic	38.3% (83)
Diabetes	29.5% (64)
Post-surgical	24% (52)
Scleroderma	4.1% (9)
Others	4.1% (9)
Use of antiplatelet agents % (*n*)	16.5% (36)
Use of anticoagulants % (*n*)	3.7% (8)
Use of antiplatelet agents and anticoagulants % (*n*)	0.9% (2)
Involuntary weight loss of more than 10% since onset of symptomatology % (*n*)	31% (67)
Average length of stay after surgery (days)	3.7 (1–23 days)

Table 3. Notable features in relation to procedure.

Characteristics of the procedure	
Average duration of the procedure (min)	44 (12–78)
Presence of significant gastric stasis at the beginning of the procedure % (*n*)	28.6% (62)
Presence of significant submucosal vascularization % (*n*)	21.7% (47)
Presence of significant submucosal fibrosis % (*n*)	24.9% (54)

Table 4. Classification of early postoperative complications according to the Dindo–Clavien classification.

No complications % (*n*)	**81.5% (175)**
Grade 1	15.2% (33)
Grade 2	3.7% (8)
Grade 3	0.4% (1)
Grade 4	0% (0)
Grade 5	0% (0)

One patient had a postoperative peripyloric abscess discovered by CT scan performed for pain and an inflammatory syndrome. The evolution was promptly favorable under antibiotic therapy, with a discharge at postoperative day 15. He was therefore classified as Clavien–Dindo grade 2. One patient developed with dumping syndrome with episodes of severe hypoglycemia, which had a favorable evolution without recurrence after introduction of hygienic-dietary measures and without delay of discharge.

There were no deaths among the 217 patients included in the study. Similarly, no patient was admitted to intensive care or resuscitation. Importantly, 175 of the 217 patients in the series were free of pain and early postoperative complications.

The summary of early postoperative complications, classified according to the Dindo–Clavien classification, is reported in Table 4.

Late postoperative complications. One patient presented with melena within 12 days post-G-POEM, with blood loss, without hemodynamic instability. A gastroscopy was performed, finding a hemorrhagic suffusion at the level of the most distal clip in the pre-pyloric region, treated by the placement of three clips allowing hemostasis. He was therefore classified as Clavien–Dindo grade 3 because of the need for endoscopic revision.

Concerning the long-term complications, two cases of dumping syndrome later, in the month following the procedure, were notified. These cases were transient and rapidly improved in less than 5 days after appropriate management.

Table 5. Summary of complications of endoscopic pyloromyotomy.

Intraoperative complications	
Mucosotomies % (*n*)	3.7% (8)
Capnoperitoneum % (*n*)	1.8% (4)
Significant bleeding* % (*n*)	0% (0)
Early postoperative complications	
Pain	14.7% (32)
Hemorrhage	1.8% (4)
Abscess	0.4% (1)
Dumping syndrome	0.4% (1)
Late postoperative complications	
Dumping syndrome	0.9% (2)
Hemorrhage	0.4% (1)

*Hemorrhage resulting in hemodynamic impact, loss of more than two hemoglobin points or the need for a blood transfusion.

A total of four patients were rehospitalized, for non-specific abdominal pain, relieved by level 1 and 2 analgesics, with a hospital stay of less than 72 h. There was no need for surgery during the follow-up. The overall summary of all these complications is recorded in Table 5.

The complications were also classified according to the classification of the American Society for Gastrointestinal Endoscopy Lexicon Adverse Events (Table 6).

Factors associated with complications

Because of the low rate of occurrence of the events, the predictive factors for occurrence that could be identified were as follows:

- For mucosal perforation, the presence of significant submucosal fibrosis was significantly associated with the occurrence of this event (OR: 4.1, [0.7461; 23.0923], $p=0.05$).
- Regarding postoperative hemorrhage, no predisposing factors could be demonstrated, in particular the use of anticoagulants and antiplatelet agents.

Table 6. Classification of postoperative complications according to the ASGE adverse events lexicon.

No complications	81.6% (177)
Minor complications	16.2% (35)
Moderate complications	1.8% (4)
Severe complications	0.4% (1)
Fatal complications	0% (0)

ASGE, American Society for Gastrointestinal Endoscopy

Discussion

G-POEM is one of the most promising minimally invasive procedures to treat refractory gastroparesis, which is a chronic pathology,[13] difficult to treat, responsible for altered quality of life, undernutrition, and increased frequency of hospitalizations.

Many studies have focused on the efficacy of the procedure,[28–39] and side effects were evaluated as secondary endpoints, with few side effects being identified such as bleeding, capnoperitoneum, and prepyloric ulcer. In the only study specifically evaluating the subject, Ichkanian *et al.* reported severe complications in two patients out of 216 included.[40]

However, the safety profile of such a procedure is a major question, since it is a minimally invasive treatment of a functional pathology.

In a similar way, with regard to esophageal POEM, the first studies focused on the efficacy of the procedure, taking AEs as a secondary endpoint. However, complications have been specifically evaluated more recently, in a retrospective monocenter study involving 1680 patients. This study found no mediastinitis or death, and demonstrated only 3.3% of serious AEs, with a rate that dropped to about 1% after 3.5 years of operator experience.[27]

We therefore propose here this study specifically evaluating the safety profile of G-POEM, in a multicenter manner in expert centers. This setting allowed for including a large number of operators (eight operators) and thus to validate a wide use of the procedure, in spite of the fact that all the operators had a notable expertise in submucosal dissection and esophageal POEM.

This study shows a very low rate of serious complications, with only 0.4% classified as Clavien–Dindo 3, and an absence of AEs classified as Clavien–Dindo 4 and 5, confirming the safety of G-POEM. This rate of serious AEs appears to be even lower than that demonstrated in previous safety studies of esophageal POEM. Importantly, in the meantime, the efficacy rate in our cohort is the same than in the published literature, allowing for a reliable interpretation of the AEs rate.

In addition, most patients in the study (81.5%) did not experience any AEs, including simple pain. The average hospital stay was very short, less than 4 days, with a very low rate of re-hospitalization and re-intervention, which could allow in the future to think about performing this procedure in ambulatory setting. Moreover, all AEs occurring during endoscopy were successfully managed conservatively. Indeed, mucosal wounds (3.7% of patients) were closed by the application of clips, without clinical impact. The occurrence of preoperative bleeding, reported in 21% of patients, is considered as part of the procedure and not as a complication in the absence of hemodynamic instability, significant blood loss greater than 2 g/dl or the need for a transfusion, as seen in surgery or during endoscopic submucosal dissection procedures.

Interestingly, three cases of dumping syndrome were identified in patients without diabetes, all within 1 month of the procedure, maybe due to the acceleration of the gastric emptying following the pylorotomy. They were quickly improved in less than 5 days with appropriate management and education of patients on how to avoid major glycemic peaks. In our study, this AE appeared to be rare, but it is important to be aware of it in the event of postprandial clinical signs of hypoglycemia.

Regarding the risk factors for complications, few were significantly identified, due to the very low overall rate, and a larger population would be necessary to identify the predictive factors for complication. However, logically, the presence of significant submucosal fibrosis multiplies the risk of mucosal breach by 4. Similarly, the presence of important submucosal vascularization was significantly associated with the occurrence of per procedural bleeding. No other risk factors were statistically significantly associated with the occurrence of AEs in the subgroup analyses.

The noteworthy limitation is the retrospective design of the study, with the risk of missing data inherent in this type of study.

Conclusion

Our study confirms the safety of G-POEM with less than 0.5% of serious AEs, medically managed. This figure should be weighed against the efficacy of approximately 50–65% at 1 year,[28–39] making this a procedure with a good benefit–risk ratio. These data can be confirmed by larger prospective studies.

Declarations

Ethics approval and consent to participate

According to the French law, no ethical committee approvement nor IRB is requested in the case of retrospective studies. However, our database was anonymized and declared and approved by the French National Commission for Information Technology and Civil Liberties (CNIL). As a retrospective study, according to the Declaration of Helsinki, informed consent was not required from patients.

Consent for publication

Not applicable.

Author contribution(s)

Florian Baret: Conceptualization; Methodology; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Jeremie Jacques: Resources; Software; Supervision; Validation; Visualization.

Mathieu Pioche: Resources; Validation; Visualization.

Jeremie Albouys: Resources; Validation; Visualization.

Véronique Vitton: Resources; Software; Validation; Visualization.

Geoffroy Vanbiervliet: Resources; Supervision; Validation; Visualization.

Antoine Debourdeau: Resources; Software.

Marc Barthet: Conceptualization; Methodology; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Jean-Michel Gonzalez: Conceptualization; Methodology; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The databases used were the local databases specific to each site, all of which meet the French National Commission for Information Technology and Civil Liberties standards in terms of anonymization and data protection.

ORCID iD

Florian Baret https://orcid.org/0000-0001-7460-5190

Supplemental material

Supplemental material for this article is available online.

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