Comparison of Symptom Control in Pediatric Gastroparesis using Endoscopic Pyloric Botulinum Toxin Injection and Dilatation

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Abstract

Objectives The objective of this study was to assess the tolerance and efficacy of endoscopic intrapyloric botulinum toxin injection compared with pyloric dilatation in children with gastroparesis.

Methods This was a retrospective descriptive multicentre study that included pediatric patients treated between 2010 and 2018 at four tertiary hospitals.

Results Data were collected for 24 patients. The median age at diagnosis was 2.5 years (range 0.5–4.7). A total of 46 endoscopic procedures were performed. The endoscopic procedure was multiple in 63% of patients. Among the interventions, 76% were successful and 15% were unsuccessful. The recurrence rate was 57% and the median time to recurrence was 3.7 months (0.1–73). The efficacy did not differ significantly between the two methods at the first intervention and as a second-line treatment. The recurrence rate also did not differ significantly between the two methods. No complications were reported. The median follow-up was 19.8 months (1.7–61.7).

Conclusions In this retrospective multicentre study, endoscopic management of gastroparesis by balloon dilatation or botulinum toxin was safe in children and seemed to be partially efficient within the first months. Symptoms recurred frequently and required repetition of the interventions.

Keywords Gastroparesis, Child, Endoscopy, Botulinum toxin, Pyloric, Balloon dilatation

What is known?

- Gastroparesis in child is infrequent and treatment is far from being consensual.
- Endoscopic procedures are available, such as pyloric balloon dilatation or botulinum toxin injection.

What is new?

- Endoscopic procedures of pyloric balloon dilatation and toxin botulinum injection are safe.
- There is no superiority of either treatment.
- Effectiveness is short-term and transitory.

Introduction

Gastroparesis in children is a rare entity and its prevalence is unknown [1]. Although the etiologies are multiple, gastroparesis in children is frequently idiopathic [2]. The diagnosis is based on clinical signs (nausea, vomiting, abdominal pain, failure to thrive) and a scintigraphy gastric-emptying study is the reference examination [3]. There is at present no consensus about the best treatment in children, which is complex and involves dietary measures, drug therapy (antiemetics, prokinetics), enteral or parenteral nutrition, and often endoscopic and surgical techniques. In the past few years, advances in endoscopic techniques have focused on the hypertonic component and relaxation anomalies of the pylorus and include intrapyloric injection of botulinum toxin [4], mechanical pyloric dilatation [5] and, more recently, gastric pyloromyotomy [6]. Experience of the use of these techniques in children remains limited [7]. Despite limited data in children, these techniques are occasionally used to improve the clinical impact of gastroparesis in these patients. Their main advantages are simplicity and ease of use, low risk, and the possibility of repeated procedures if needed.

The objective of this study was to examine the tolerance and efficacy of endoscopic intrapyloric botulinum toxin injection compared with pyloric dilatation in children with gastroparesis.

Materials and methods

This was a retrospective descriptive multicentre study. Four centres participated: Jeanne de Flandre Lille University Children's Hospital (Lille, France); Trousseau Hospital (Paris, France); La Timone Hospital (Marseille, France); and Christian Hospital (Liège, Belgium).

Patients

All patients younger than 18 years with gastroparesis who received endoscopic treatment involving pyloric dilatation and/or botulinum toxin injection between 2010 and 2018 were

included consecutively. There were no exclusion criteria. The diagnosis of gastroparesis was based on the combination of clinical symptoms and at least one of the following objective signs of slow gastric emptying: scintigraphy evidence of delayed gastric emptying based on the retention values (liquid and/or solid scintigraphy, reference for gastric retention value: residue >90% at 1 h, 60% at 2 h, and 10% at 4 h, based on the adult standardized values) or observations from an gastrointestinal transit study (delayed gastric emptying, gastric distension). All children underwent gastroscopy to rule out obstruction.

Procedures

All procedures were performed with the patient under general anaesthesia and with orotracheal intubation under endoscopic control. Botulinum toxin was diluted with saline serum and injected using a sclerotherapy needle into the four quadrants of the pyloric mucosa at a dose of 6 IU/kg (maximum 100 IU per child per injection). Dilatation was performed using hydrostatic balloons of increasing size from 6 to 20 mm. The size was adapted to the child's weight and age (balloons < 10 mm in diameter were used for weight <10 kg, 10 to 20 mm in diameter for children weight from 10 to 30 kg, and 20-22 mm for weight >30 kg). The dilatation time was set at one minute, the effectiveness being judged on the dilaceration and the increase in the diameter of the pylorus. Each patient could receive different interventions over time (e.g., botulinum toxin followed by dilatation or vice versa); the choice was at the discretion of the clinician.

Intervention success was defined *a priori* as a clinical improvement occurring during the immediate postoperative period (within 1 week after the intervention). Success was considered as total when there were no more digestive symptoms after the intervention and partial when symptoms improved partially but not fully. Failure of intervention was defined *a priori* as unchanged symptoms and/or the need for a new treatment in the immediate

postintervention period. Recurrence was defined as the reappearance of symptoms at least 1 week after a successful intervention.

Statistical analysis

Categorical variables are expressed as percentages and continuous variables are expressed as mean and standard deviation or median, quartiles, and minimum/maximum values. Fisher's exact test or the Wilcoxon signed-rank test was used to compare the two treatment groups (pyloric dilatation versus botulinum toxin injection at the first intervention). A trend test was used to compare the efficacy between the two techniques. The alpha level was set at 5%.

Ethical considerations

IRB approval was not required. Because the study was observational and the data were obtained without any additional intervention or monitoring procedure and according to French regulations on research, formal ethics committee approval was not required [8]. Nevertheless, parents and children received written information about the study. The data was de-identified.

Results

Demographics

Twenty-four patients were included (Table 1). Median age at diagnosis was 2.5 years (range 0.5–4.7). Twenty children had chronic symptoms for at least 6 months (83%). There were no significant differences in demographic characteristics between the two treatment groups at the first intervention.

Treatment before endoscopy included dietary measures (split meals, low fibres and lipids content) in six patients (25%), enteral nutrition in 10 patients (42%), and parenteral nutrition in two patients. Drug therapy was prescribed in 23 patients: proton pump inhibitors (PPIs, n = 19/24, 79%), prokinetics (erythromycin or domperidone: n = 15/24; 62%), and antiemetics in only one patient. Drug therapy was considered unsuccessful in 13/23 patients (57%).

Endoscopic procedures

Table 2 shows the results of the endoscopic procedures. A total of 46 endoscopic procedures were performed. The median age at the first intervention was 2.9 years (range 1–5.8). The endoscopic procedure was performed once in nine patients (37%) and at least once more in the other 15 patients (63%): twice in eight patients (8/24, 33%), three times in six patients (6/24, 25%), and four times in one patient. Balloon dilatation alone was used in 12 patients (50%). Botulinum toxin alone was used in six patients (25%). Six patients (25%) received both endoscopic techniques consecutively because of failure or recurrence after the previous procedure.

Success was undocumented in four interventions. Success was observed in 35 interventions (76%), either total (13/35, 37%) or partial (22/35, 63%) and failure was observed in the remaining seven interventions (15%). The recurrence rate was 57%. The median time to recurrence was 3.7 months (range 0.2–73).

Table 3 shows a comparison between the two treatment groups. The patient characteristics did not differ between groups. The efficacy of treatment did not differ significantly between the two methods at the first and second intervention or when all interventions were combined. Similarly, the rate of recurrence did not differ significantly between the two methods.

After the first procedure, only 5 patients underwent a re-evaluation scintigraphy because of clinical recurrence (all remained abnormal). Because few patients had an objective re-evaluation study of the gastroparesis after the intervention, evaluation of the results was based on clinical criteria such as weight and height gain, frequency of vomiting and weaning from enteral/parenteral nutrition.

No complications such as perforation, haemorrhage or sepsis were reported in either of the treatment groups.

Follow-up

The median follow-up time was 19.8 months (range 1.7–61.7). One patient was lost to follow-up. One child had a history of neurofibromatosis and died of an unknown reason at 21 months of age, 16 months after the procedure (botulinum toxin).

At the last follow-up consultation, 12 patients still had symptoms suggestive of gastroparesis such as nausea, vomiting, abdominal pain, or failure to thrive (12/22, 55%). Anthropometric parameters (weight, height, body mass index (BMI), and Z scores) did not differ between the date of diagnosis and the last visit.

Oral feeding was possible in 87% of patients and was associated with enteral nutrition in 39% of patients. No child required parenteral nutrition. Five patients had oral feeding difficulties (23%). Drug therapy was prescribed in 52% of patients, 48% of whom were given PPIs. Three patients required secondary surgical treatment at the age of 5, 8, and 11 years: two received a gastric peroral endoscopic pyloromyotomy (G-POEM) and one received a surgical pyloroplasty. No surgical complications were reported.

Discussion

Childhood gastroparesis is a rare and poorly investigated disorder that is difficult to manage. Endoscopic techniques have been developed but are poorly described in the pediatric population. There are few studies reporting on the safety and efficacy of endoscopic management of pediatric gastroparesis [9,10]. To our knowledge, this observational study is the first to compare the results of balloon dilatation and botulinum toxin injection.

In this series, these two endoscopic techniques appeared to be safe, and no complications were reported in the short, medium, or long term. Despite the small size of this sample and the retrospective and multicentric nature of the study, we found no obvious difference in efficacy between the two methods. However, the efficacy of these procedures was transient and early recurrence was frequent.

These results are consistent with those of other pediatric studies. However our study differs from others [2,11] by the significant lower age of our population (2.5 years compared to 7.9 to 9 years); this may lead to different outcomes since etiologies, duration of gastroparesis and its transient or permanent nature, as well as treatment modalities may differ.

Endoscopic treatments of gastroparesis have produced contradictory results in adult patients. Retrospective studies show a temporary efficacy of botulinum toxin that correlates with age <50 years, female sex, idiopathic cause, toxin dosage, and repeated administration [12]. In randomized double-blind studies, toxin was no more effective than placebo [13,14]. These studies involved a small number of patients (31 and 32 patients, respectively) and were based on scintigraphy data and not on data about clinical efficacy [15]. The heterogeneous results of botulinum toxin may be explained, in part, by the pyloric anatomy, which leads to diffusion of the product into adjacent areas [16]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends against botulinum toxin injection in the treatment of unselected adult patients with gastroparesis. The ESGE stipulates that the toxin should be considered only in patients with symptoms suggestive of gastroparesis in combination with objective proof of delayed gastric emptying in a validated test, and only when medical therapy has failed [17]. Botulinum toxin is recommended only for adult patients with refractory gastroparesis, which is defined as gastroparesis refractory to several pharmacological treatments for at least 1 year. This is due to safety and simplicity of toxin administration [18], which may allow for avoidance of the need for more invasive surgical treatment [15].

In 2012, Rodriguez et al. reported a retrospective series of 47 pediatric patients with gastroparesis who received a total of 70 botulinum toxin injections [10]. The authors reported that 67% of the patients had a partial or total response but that the mean duration of the

response was only 3 months. More recently, Hirsch et al. reported a retrospective of 85 pediatric patients with gastroparesis who received a total of 118 botulinum toxin injections : the rate of effectiveness was similar and injections allowed an improvement in feeding with fewer patient needing post pyloric feeds after injections compared with before [19].

In adults, pyloric balloon dilatation is not recommended for the treatment of gastroparesis [17]. This procedure was first described in children with pyloric obstruction [20], peptic stenosis [21], or caustic stenosis of the esophagus [22]. Israel et al. reported a retrospective pediatric series of 19 patients with gastroparesis who underwent pyloric dilatation. Thirteen patients had complete resolution of symptoms and five patients experienced transient improvement requiring additional surgical treatment [9]. As for botulinum toxin, the long-term effectiveness of pyloric dilatation seems to be limited [23].

Taken together, our results and those of previous studies suggest that these two endoscopic treatments are transiently effective by providing an initial improvement, which may serve as a bridge to spontaneous resolution of gastroparesis or to the need for more invasive management.

As our study was not randomized, we cannot exclude that the natural history of gastroparesis or a placebo effect could explain the efficacy of endoscopic intervention. However, most of the patients reported herein had a long duration of symptoms and failure of several drugs and enteral nutrition with a significant impact on nutritional status and growth before they underwent endoscopic treatment. More than 2/3 of the patients clinically improved, could be discharged from hospital or further be weaned from parenteral nutrition suggesting these interventions may be of interest in refractory or chronic gastroparesis, with a

significant positive clinical impact. Moreover, the endoscopic approach is simple and safe, and does not compromise further more invasive treatment.

Other therapeutic strategies are currently under development. Gastric electrical stimulators are at the research stage in the context of treatment for refractory gastroparesis in children and there are anecdotal reports of beneficial effects on symptoms and quality of life [24]. The current major advance concerns G-POEM, which was first described in 2013 for adult gastroparesis [25]. Several studies have shown its safety and efficacy for treating adult gastroparesis [26]. Because G-POEM is an emerging procedure, the ESGE recommends consideration of its use only in carefully selected patients and in expert centres in the context of a clinical trial [17]. The use of G-POEM in children should be extended before any recommendations can be made. There are currently no available data on G-POEM in the treatment of gastroparesis in children despite the use of peroral endoscopic myotomy (POEM) for pediatric achalasia [27].

In conclusion, this study shows that endoscopic pyloric dilatation and botulinum toxin injection are both safe and are equally effective for treating gastroparesis in children. Recurrence of symptoms is frequent in the first months after the procedure. These endoscopic techniques may be an acceptable treatment as the bridge between spontaneous improvement and more invasive treatment, such as G-POEM.

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Figure legends

Table 1 Characteristics of the patients

Table 2 Results of the treatments

Table 3 Comparison of the two treatment groups at the time of the first-line intervention

Table 1 Characteristics of the patients

	Number (%)
Boys	16 (67)
History	
Encephalopathy	2 (8)
Anti-reflux surgery	5 (21)
Constipation	4 (17)
Hypertrophic pyloric stenosis	3 (13)
Overweight	1 (4)
Age at the beginning of symptoms, years (SD)	2.7 (± 4.2)
Weight, kg (SD)	17.2 (± 21.8)
Z-score weight/age, mean (SD)	–1.8 (± 2)
BMI, kg/m² (SD)	15.2 (± 3.8)
Z-score BMI/age, mean (SD)	–1.5 (± 2.5)
Symptoms	
Vomiting	21 (88)
Abdominal pain	12 (50)
Faltering growth	12 (50)
Nausea	5 (21)
Dysphagia	5 (21)
Early satiety	5 (21)
Respiratory symptoms	5 (21)
Weight loss	2 (8)
Imaging results	
Abdominal ultrasound	17 (71)
Normal	12/17 (71)
Upper GI series	23 (96)
Normal	3/23 (13)
Delayed gastric emptying	13/23 (57)
Gastric scintigraphy	18 (75)
Normal	1/18 (6)
Delayed gastric emptying	16/18 (89)
Endoscopy	24 (100)
Macroscopically normal	8 (33)
Pylorus not passable	6 (25)
Presence of food residues	5 (21)

Table 2 Results of the treatments

	Dilatation						Botulinum toxin					
	Total success	Partial success	Failure	Unknown	**Total**	Recurrence	Total success	Partial success	Failure	Unknown	**Total**	Recurrence
First-line treatment	7	8	1	0	**16**	11	2	3	3	0	**8**	5
Second-line treatment	2	4	2	3	**11**	4	1	1	1	1	**4**	2
Third-line treatment	1	2	0	0	**3**	1	0	4	0	0	**4**	1
TOTAL, n (%)	10 (33)	14 (47)	3 (10)	3 (10)	**30/46**	16 (53)	3 (19)	8 (50)	4 (25)	1 (6)	**16/46**	8 (50)

Success: clinical improvement during the immediate postoperative period. *Total success*: no more digestive symptoms after the intervention. *Partial success*: symptoms partially improved. *Failure*: unchanged symptoms and/or need for a new treatment. *Recurrence*: reappearance of symptoms at least 1 week after a successful intervention.

Table 3 Comparison of the two treatment groups at the time of the first-line intervention

	Treatment		p
	Dilatation n = 16	Toxin n = 8	
Boys, n (%)	10 (62%)	6 (75%)	0.67
Age at first intervention, months, median (SD)	45.9 ± 57.4	3.7 ± 6.1	0.3
Weight at diagnosis, kg, mean (SD)	21.7 ± 25.9	8.7 ± 5.3	0.26
First intervention	Success: 15 Failure: 1	Success: 5 Failure: 3	0.17
Recurrence	Yes: 11 No: 4	Yes: 5 No: 0	0.23