Botulinum Toxin as a Treatment for Feeding Difficulties in Young Children

Suzanna Hirsch, MD[1], Samuel Nurko, MD[1], Paul Mitchell, MS[2], and Rachel Rosen, MD, MPH[1]

Objective To determine the effectiveness of intrapyloric botulinum toxin injection (IPBI) for treatment of feeding disorders and associated gastrointestinal symptoms in very young children.

Study design A single-center retrospective study of patients 2 months to 5 years old who received IPBI at Boston Children's Hospital from May 2007 to June 2019 was performed. Charts were reviewed for demographic data, comorbidities, symptoms leading to IPBI, oral and tube feeding data, symptom improvement after IPBI, and need for repeat injections. The primary outcome was symptom improvement at the first gastroenterology clinic visit following IPBI. Secondary outcomes included improvement in oral feeding, decreases in tube feeding, and need for repeat injections. The χ^2 or Fisher exact tests and multivariate logistic regression were used to identify factors associated with symptomatic improvement.

Results A total of 85 patients who received 118 injections were included in the final analysis; 57 patients (67%) had partial or complete improvement in symptoms after IPBI. Among the 55 patients with enteral tubes, there was an improvement in feeding, with more patients receiving at least some oral feeds after IPBI compared with before (26/55 vs 15/55; $P = .004$) and fewer patients receiving postpyloric feeds after IPBI compared with before (12/55 vs 21/55; $P = .01$). Twenty-six patients (31%) received repeat IPBI within 1 year, with only 6 patients receiving IPBI more than twice.

Conclusions IPBI is safe and effective in young children. Children with enteral tubes show improvement in oral feeding and reduction in need for postpyloric feeding after IPBI. *(J Pediatr 2020;226:228-35)*.

Feeding difficulties are common in children, affecting up to 20% of typically developing children and up to 80% of children with developmental disabilities or medical complexities.[1-3] These feeding problems have a negative physical and psychosocial impact on patients and families, and currently there is no straightforward treatment algorithm. Management often involves multiple medication trials and procedures including enteral tube placement.[4,5] These measures are variably effective and can result in adverse side effects or complications, underscoring the need for further evidence-based treatment options.

Intrapyloric botulinum toxin injection (IPBI) has been used for the treatment of nausea and vomiting in older children and adults, particularly those with gastroparesis.[6] The use of this therapy has been extended in our tertiary care center to include the treatment of infants and young children with feeding disorders and gastrointestinal (GI) comorbidities, such as vomiting, retching, and abdominal pain. Although several observational studies show symptomatic improvement after IPBI in adult patients with gastroparesis, 2 underpowered small randomized controlled trials failed to demonstrate a difference between IPBI and sham saline injections.[7-14] One study of IPBI in children with mean age of 10 years and intractable gastroparesis showed safety and efficacy of the therapy for this population.[15] Therefore, the primary aim of this study was to determine the efficacy of IPBI in the treatment of feeding disorders and associated GI symptoms in young children ages 5 years and under at Boston Children's Hospital. The secondary aim was to determine predictors of clinical response to IPBI in this patient population.

Methods

Institutional review board approval was obtained for this retrospective, open-label study of patients undergoing endoscopic IPBI from May 2007 to June 2019 at Boston Children's Hospital. CPT codes (codes 43235 to 43270) and searches for administration of botulinum toxin were used to identify all patients who underwent IPBI. Inclusion criteria included all patients age 5 years or younger undergoing IPBI for the first time. Patients were excluded if they had no follow-up within 1 year of IPBI, if follow-up notes were insufficient to determine clinical outcome, if the patient had

GI	Gastrointestinal
IPBI	Intrapyloric botulinum toxin injection

From the [1]Aerodigestive Center, Center for Motility and Functional Gastrointestinal Disorders, Division of Gastroenterology, Hepatology & Nutrition; and the [2]Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Boston, MA

Supported by National Institutes of Health R01 DK097112-01 and the Translational Research Program Senior Investigator Award. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.06.063

pseudo-obstruction (ie, evidence of small bowel dysmotility), or if significant interval patient illness (eg, acute infection, major surgery, or a new GI diagnosis, such as protein-losing enteropathy) precluded interpretation of the effect of IPBI on outcome.

Botulinum Administration

Intrapyloric botulinum injections were administered during an upper endoscopy under direct visualization using a sclerotherapy needle as previously described.[15] The botulinum vial of 100 U was diluted in 1 mL of normal saline to create a 10 U/0.1 mL solution. A dose of 6 U/kg was used up to a maximum of 100 U. The dose was divided in 4 injections around the pylorus.

Data Collection

Patient records were reviewed for age, sex, weight z-score, comorbidities, baseline medications, past surgeries, past imaging studies including gastric emptying scans, and oral and tube feeding data. Age was categorized as a continuous variable and as a categorical variable, classified as children age less than 3 years or age 3 or more years based on the age at which patients are most verbal. Comorbidities were characterized as GI, pulmonary, cardiac, neurologic, metabolic or genetic, endocrine, or prematurity (defined as gestational age of <37 weeks). Prior upper endoscopies and upper GI series were recorded. Upper endoscopies were considered abnormal if there was gross or microscopic esophagitis, gastritis, or duodenitis. Upper GI series were considered abnormal if there was malrotation, other anatomic abnormalities, or poor clearance of barium from the esophagus. Gastroesophageal reflux on upper GI series was not classified as abnormal. To determine the impact of dysmotility on IPBI response, we reviewed the charts for evidence of dysmotility on gastric emptying scans and motility studies. In the subset of patients who had gastric emptying scans, 2 types of scans were obtained depending on the age of the patients. Patients less than 3 years of age underwent a 1-hour study and patients 3 years of age or older underwent either a 1-hour or a 4-hour study. To perform the gastric emptying study, technetium-99m sulfur colloid was mixed with the patient's formula (for liquid studies) or a standard egg meal (for solid studies). For 1-hour studies, dynamic imaging was performed over the 1-hour period. For 4-hour studies, static images were obtained immediately and at 1, 2, 3, and 4 hours after meal ingestion. Studies were considered abnormal if there was more than 60% gastric residual at 1 hour for 1-hour studies or more than 10% gastric residual at 4 hours for 4-hour studies. Multichannel intraluminal impedance with pH was considered abnormal if (1) there was pH less than 4 for more than 6% of the time for children more than 1 year of age and more than 12% of the time for children under 1 year of age, or if (2) there were more than 72 impedance-detected episodes of reflux per 24-hour study for children more than 1 year of age or more than 100 impedance-detected episodes of reflux for children less than 1 year of age. Antroduodenal manometry was considered abnormal if there was postprandial antral hypomotility, which was defined as a decreased motility index of postprandial distal antral contractions following administration of a meal.[16] Patients with pseudo-obstruction (ie, evidence of small bowel dysmotility) were not included in this study. To assess for aspiration, videofluoroscopic swallow studies were recorded, and these studies were considered abnormal if there was laryngeal penetration or aspiration with any consistency.

Feeding data were characterized by the presence or absence of an enteral tube at the time of follow-up and the relative contribution of each feeding route (oral, gastric, or postpyloric) to the patient's total intake. Patients with enteral tubes were divided into 4 categories: (1) those receiving some oral feeds along with tube feeds, (2) those receiving only gastric tube feeds, (3) those receiving combined gastric and postpyloric tube feeds, and (4) those receiving only postpyloric tube feeds. Indications for IPBI as provided in the referring physician's chart note were recorded and these included vomiting, retching, reflux, poor oral intake, rumination, abdominal pain, volume intolerance, abdominal distension, nausea, and early satiety. Data on the IPBI procedure were recorded, including the endoscopist who completed the procedure, the dose of botulinum toxin administered, and need for repeat injections during the year after the initial injection.

Outcomes

Response to IPBI treatment was assessed at the first gastroenterology clinic follow-up appointment within 1 year after IPBI, with supplemental information taken from documented phone calls with GI providers or appointments with non-GI providers. At the time of follow-up, records were reviewed for symptomatic response to IPBI, oral and tube feeding data, weight z-score changes, and medications. Symptomatic response to IPBI was defined as improvement or no improvement in the symptoms that were the indication for IPBI. Patients with improvement were subcategorized as those with partial improvement or complete resolution of symptoms. Patients were categorized as having no improvement if the chart indicated the symptoms were the same as before IPBI. They were categorized as having partial improvement if the chart indicated that the patient had some degree of symptom improvement (ie, mild or moderate improvement was mentioned in the chart review) after IPBI. Patients were categorized as having complete resolution of symptoms if the chart stated that the patient was no longer having the symptoms that prompted IPBI. Oral and tube feeding data at the time of the first follow-up appointment were characterized by the presence or absence of an enteral tube and relative contribution of oral, gastric, and postpyloric feeds. The procedure note and the first gastroenterology follow-up note were reviewed for complications from the IPBI procedure.

Statistical Analyses

For statistical analysis, continuous variables are expressed as means with SDs, and categorical variables are expressed as number (%). Comparisons of continuous variables were completed using *t* tests. Comparisons of categorical variables were completed using the χ^2 tests or Fisher exact tests when any expected cell count was less than 5. Comparison of feeding route before and after IPBI was made with the Bowker test for symmetry, followed by pairwise McNemar tests with Bonferroni adjustment to determine which off-diagonal pairs were statistically different. A multivariable logistic regression model using Firth's penalized likelihood was used to investigate factors associated with symptomatic improvement after IPBI. Model fit was confirmed with the Hosmer-Lemeshow goodness-of-fit test. The sensitivity of the results to a lack of balance in the groups with and without symptomatic improvement after IPBI was investigated by applying stabilized inverse probability of treatment weights to the logistic regression models. All tests were 2-sided with *P* values of less than .05 considered statistically significant. ORs are expressed with 95% CI. Statistical analysis was conducted using Stata (StataCorp, College Station, Texas) and SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

A total of 112 patients ages 5 years and under received IPBI during the study period. Twenty-seven patients were excluded due to absent or insufficient follow-up data (n = 17), an underlying diagnosis of pseudo-obstruction (n = 3), or significant interval illness that precluded interpretation of the outcome (n = 7), with these illnesses including acute gastroenteritis, severe pneumonia, new diagnosis of protein-losing enteropathy, or interval surgery for tracheoesophageal fistula. A total of 85 patients who received 118 injections were included in the final analysis. The demographic and clinical characteristics of these 85 patients are summarized in Table I. The mean age at the time of first IPBI was 2.9 ± 1.6 years, and 50 patients (59%) were 3 years of age or younger. Seven patients (8%) were less than 1 year of age. Fifty-five patients (65%) had an enteral tube at the time of IPBI. Of these, 46% had a gastrostomy tube (n = 25), 6% had a nasogastric tube (n = 3), 47% had a gastrojejunostomy tube (n = 26), and 2% had a nasojejunal tube (n = 1). Fifty-one patients (60%) had undergone a baseline gastric emptying study before IPBI. Forty-seven patients underwent a 1-hour gastric emptying study, and 4 patients underwent a 4-hour study. Thirty-four studies (67%) were liquid gastric emptying studies and 17 (33%) were solid gastric emptying studies. The mean 1-hour gastric residual was 58.96 ± 19.00% and the mean 4-hour gastric residual was 43.95 ± 36.69%. Baseline gastric emptying was abnormal in 49% of those who underwent a gastric emptying study. Two patients had previously undergone pyloroplasty, which was performed 1.5 and 5.0 years before the IPBI in these patients.

Table I. Baseline characteristic at the time of IPBI

Characteristics	Values (n = 85)
Age, years	2.9 ± 1.6
Female sex	32 (38)
Weight, z-score	−1.02 ± 1.49
Comorbidities	
GI	85 (100)
Pulmonary	20 (24)
Cardiac	18 (21)
Neurologic	15 (18)
Metabolic/genetic	25 (29)
Endocrine	7 (8)
Prematurity	24 (28)
Surgeries	
Enteral tube	51 (60)
Fundoplication	13 (15)
Pyloroplasty	2 (2)
Other surgeries*	36 (42)
Prior testing	
Upper endoscopy	49 (58)
Abnormal	15/49
Upper GI series	62 (74)
Abnormal	5/62
Gastric emptying	51 (60)
Abnormal	25/51
pH-MII	22 (23)
Abnormal	7/22
Antroduodenal manometry	13 (15)
Abnormal	12/13
Videofluoroscopic swallow study	55 (65)
Abnormal	27/55
GI medications at the time of IPBI	
PPI	66 (78)
H2 blocker	21 (25)
Cyproheptadine	37 (44)
Erythromycin	29 (34)
Metoclopramide	3 (4)
Ondansetron	7 (8)
Gabapentin	7 (8)

H2-blocker, histamine-2 receptor blocker; *pH-MII*, multichannel intraluminal impedance with pH; *PPI*, proton pump inhibitor.
Values are mean ± SD or number (%).
*Other surgeries included esophageal atresia and/or tracheoesophageal fistula repair, resection of bowel, Ladd procedure, umbilical hernia repair, Kasai procedure, repair of congenital cardiac disease, heart transplant, lung transplant, nephrectomy, tracheostomy, laryngeal cleft repair, cleft lip or palate repair, supraglottoplasty, adenoidectomy, tonsillectomy, tympanostomy tubes, tethered cord release, imperforate anus repair, and orchidopexy.

Primary or secondary symptoms leading to IPBI included vomiting (n = 66), retching (n = 25), reflux (n = 11), poor oral intake (n = 28), rumination (n = 5), abdominal pain (n = 10), volume intolerance (n = 12), abdominal distension (n = 6), nausea (n = 3), or early satiety (n = 2); because patients often had more than 1 presenting symptom, the total number of symptoms in this analysis was more than 85. Some symptoms were only reported in older children. For example, nausea was reported in children with a mean age of 5.2 ± 0.9 years of age, and early satiety was reported in a mean age of 5.4 ± 0.6 years. Of the 11 patients with reflux, 8 patients (73%) had a baseline gastric emptying study, 2 of which were abnormal. The average time from the first GI clinic visit to receiving IPBI was 387 ± 406 days. Two patients received IPBI before their first GI clinic visits, as they were initially seen by the gastroenterology team while

admitted to the hospital. The mean botulinum toxin dose received was 6.2 ± 1.2 U/kg. A total of 9 endoscopists performed the botulinum injections, with 4 endoscopists performing 87% of the injections. No patients received pyloroplasty or pyloric dilation at the time of botulinum injection.

Symptomatic Response to IPBI

Outcomes were assessed at a mean of 76 ± 59 days after initial IPBI. Fifty-seven patients (67%) had an improvement in symptoms at the time of follow-up. Of those with improvement, 47 patients (82%) had partial improvement and 10 patients (18%) had complete resolution of symptoms. There was a trend toward a small increase in mean weight z-score after IPBI compared with before IPBI, but this did not reach statistical significance (−0.99 ± 1.5 vs −1.13 ± 1.7; $P = .07$). There was no association between the endoscopist performing the procedure and the response to IPBI on a χ^2 test ($P = .59$). There was no difference in the mean time to GI follow-up in patients who responded to IPBI (mean of 80 ± 66 days from IPBI to follow-up) compared with those who did not respond to IPBI (mean of 65 ± 40 days from IPBI to follow-up; $P = .28$). No patient had documented complications or side effects after IPBI.

The rates of improvement by indications for IPBI are shown in Figure 1. Univariate and multivariate analyses of factors that may be associated with a response to IPBI are shown in Table II. Based on the univariate analysis, patients less than 3 years of age had a higher rate of improvement than those 3 years of age or greater (76% in patients less than 3 years vs 54% in patients 3 years or greater; $P = .04$). Patients with rumination had a lower rate of improvement than those without rumination (0% in patients with rumination vs 71% in patients without rumination; $P = .003$), as did patients with early satiety, although this difference did not reach statistical significance (0% in patients with early satiety vs 69% in patients without early satiety; $P = .11$). There was a trend toward greater improvement in males compared with females (74% in males vs 56% in females; $P = .10$), and in those with congenital cardiac disease compared with those without congenital cardiac disease (83% in those with congenital cardiac disease vs 63% in those without; $P = .10$). On multivariate logistic regression, no single variable predicted IPBI response.

In an effort to assess other confounders that could affect outcomes, we examined medication changes and modifications to thickening of oral feeds between IPBI and first GI follow-up. Twelve patients (14%) had an additional medication added between IPBI and follow-up. These medications included cyproheptadine (5 patients), erythromycin (3 patients), acid suppression (3 patients), and gabapentin (1 patient). Patients with a new medication added had the same rate of improvement as patients who did not have a medication added (8/12 [67%] for patients with medication added vs 49/73 [67%] for patients with no medication added; $P = .975$). Eleven patients (13%) were receiving thickened feeds at the time of undergoing IPBI, and all of these patients were still on thickening at the time of follow-up. No patients were started newly on thickening between IPBI and follow-up. Four patients did have a change in their thickening between the time of IPBI and follow-up; 2 of these patients had a decrease in thickening and 2 had an increase in thickening. Of the 2 patients who had an increase in

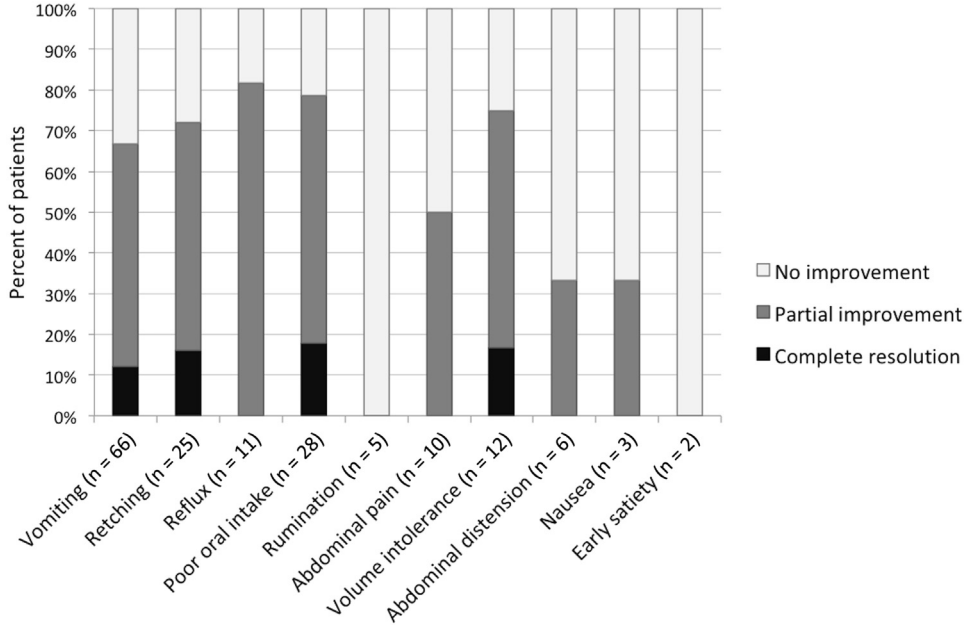

Figure 1. Response to intrapyloric botulinum injection by presenting symptom.

Table II. Predictors of IPBI response

	Unadjusted		Multivariable		Multivariable (sIPTW)	
	Improved with IPBI	*P* value	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age, years						
<3	38/50 (76%)	.04	.31	0.54 (0.17-1.76)	.49	0.66 (0.20-2.18)
≥3	19/35 (54%)					
Sex						
Male	39/53 (74%)	.10	.09	0.41 (0.14-1.16)	.83	0.89 (0.32-2.51)
Female	18/32 (56%)					
Vomiting						
Yes	44/66 (67%)	.89	.55	0.66 (0.17-2.55)	.33	0.46 (0.10-2.15)
No	13/19 (68%)					
Retching						
Yes	18/25 (72%)	.53	.70	0.78 (0.22-2.79)	.48	0.64 (0.18-2.21)
No	39/60 (65%)					
Rumination						
Yes	0/5 (0%)	.003	.08	0.05 (0.002-1.35)	.08	0.04 (0.001-1.40)
No	57/80 (71%)					
Congenital cardiac disease						
Yes	15/18 (83%)	.10	.42	1.84 (0.42-8.09)	.61	1.48 (0.33-6.63)
No	42/67 (63%)					
Neurologic comorbidities						
Yes	8/15 (53%)	.24	.75	0.80 (0.20-3.21)	.78	1.22 (0.31-4.87)
No	49/70 (70%)					
Enteral tube						
Yes	39/55 (71%)	.31	.65	0.76 (0.23-2.49)	.58	0.71 (0.22-2.36)
No	18/30 (60%)					
Delayed gastric emptying (ref = N/A)						
Yes	16/25 (64%)	.29	.45	0.48 (0.14-1.69)	.55	0.79 (0.22-2.84)
No	15/26 (58%)			0.49 (0.13-1.85)		0.48 (0.13-1.81)
N/A	26/34 (76%)					

N/A, not applicable; *sIPTW*, standardized inverse probability of treatment weight.
Unadjusted *P* value from Pearson χ^2 test or Fisher exact test. Adjusted *P* value from logistic regression with Firth's penalized likelihood.

thickening, 1 had symptomatic improvement after IPBI and the other did not have symptomatic improvement.

Feeding Response to IPBI

At baseline before receiving IPBI, 30 patients (35%) were receiving full oral feeds and 55 patients (65%) were receiving some amount of enteral tube feeds. Changes in the route of feeding before and after IPBI for patients with enteral tubes are shown in Figure 2. On the Bowker test for symmetry, there was a significant change in the proportion of patients in each feeding category before and after IPBI (P = .01). More patients were receiving at least some oral feeds after IPBI compared with before (26/55 after vs 15/55 before; P = .004), and fewer patients were receiving exclusively postpyloric feeds after IPBI compared with before IPBI (12/55 after vs 21/55 before; P = .01).

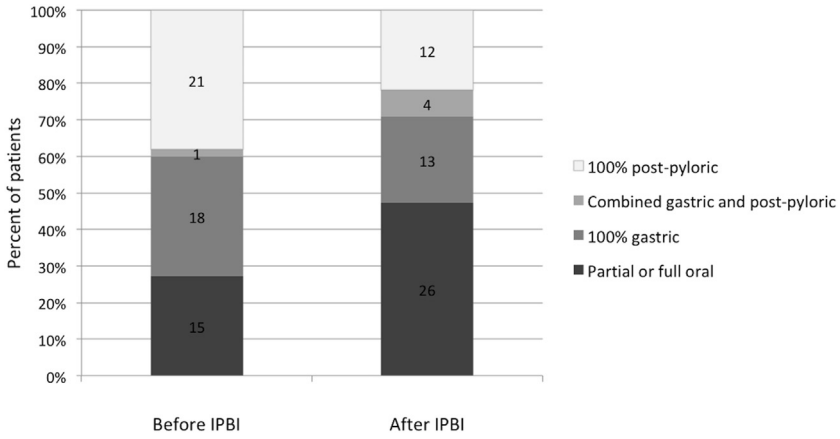

Figure 2. Feeding route before and after IPBI in patients with enteral tubes.

Gastric Emptying after IPBI

Of the 51 patients who underwent baseline gastric emptying studies, 15 patients had a follow-up gastric emptying study after receiving IPBI. All follow-up gastric emptying studies were 1-hour studies. There was no difference between the mean 1-hour gastric residual before and after IPBI in these patients (62% before vs 56% after; $P = .34$); however, there was wide variability in the timing of the follow-up studies in relation to IPBI (range, 13 days to 4.8 years after IPBI). Only 3 of the 15 patients had a gastric emptying study within 3 months of initial IPBI.

Repeat IPBI

Twenty-five patients (29%) underwent repeat IPBI within 1 year after the first IPBI. Patients who had improvement after initial IPBI were more likely to receive repeat IPBI than those who did not have improvement after initial IPBI (23/57 patients with improvement on initial IPBI had a repeat injection vs 2/28 without improvement on initial IPBI had a repeat injection; $P = .002$). Nineteen patients (22%) received only a second IPBI within 1 year of follow-up, 5 patients (6%) received IPBI 3 times, and 1 patient (1%) received IPBI 4 times within 1 year. The average time to second IPBI was 5.5 ± 2.5 months from initial IPBI. The average time to third IPBI was 4.5 ± 1 months from second IPBI.

Discussion

We investigated the use of IPBI in very young children with feeding disorders and associated GI symptoms. We found that this treatment was safe and effective in these young children, with 67% of patients showing improvement in GI symptoms after their first injection. This rate of symptomatic improvement is similar to that demonstrated in prior observational studies of older children and adults who received IPBI.[8,11,12,15] In our population, the most common indications for IPBI were vomiting, retching, and poor oral feeding. These symptoms can be intractable and difficult to treat in young children; the majority of our cohort had received substantial prior workup and interventions by the time of IPBI, including medications, previous endoscopies, upper GI series, gastric emptying studies, and surgeries.

In addition to assessing for symptomatic improvement, this study investigated IPBI as a novel treatment option for refractory feeding disorders in medically complex patients. Pediatric feeding disorders are characterized by a disturbance in nutritional intake that surpasses typical variations in childhood food preferences and appetite.[4,17-19] When severe, this can result in malnutrition and reliance on enteral tube feedings for all or part of a child's caloric intake. Feeding disorders can be seen in healthy children, but are even more common in those with chronic medical problems, where vomiting, pain, and fatigue can affect eating patterns.[20,21] Research on feeding disorders and tube dependence in children is limited and has focused largely on behavioral interventions.[4,5] Research on intensive inpatient treatment programs have shown promising results with high levels of tube weaning, but these programs are resource intensive and not available in all centers.[22] Additionally, comorbid GI symptoms, as seen in our cohort, may preclude participation in many of these programs, so finding an effective therapy for symptoms is critical before patients can attend these feeding programs.[23,24] Reflecting the intractable nature of feeding disorders in our cohort, 65% of the study population was using an enteral tube for all or part of their nutrition at the time of IPBI. After receiving IPBI, children with feeding tubes showed an increase in oral feeding and decreased need for postpyloric feeding. There was a small increase in weight z-scores at follow-up; however, this did not reach statistical significance and is difficult to interpret in the setting of variable and often short time from IPBI to follow-up. Nevertheless, the clinical feeding outcomes demonstrated in this study are important, given that tube dependence can result in patient morbidity and decreased quality of life, as well as parental stress and anxiety.[25-27] Postpyloric feeding tubes in particular can predispose to complications, such as displacement or intussusception, and can have an impact on mobility and hunger cues because of the continuous feeding requirement.[17,28,29]

Prior research on IPBI has focused primarily on adult patients with gastroparesis. Multiple observational studies have demonstrated a reduction in gastroparesis symptoms after IPBI.[7-10,12] However, the treatment remains somewhat controversial given that 2 very small randomized controlled trials failed to show a benefit of IPBI when compared with a saline control.[13,14] Although some researchers have used these trials to argue against the practice of IPBI, others have critiqued the studies for their small sample sizes, with samples of 23 and 32 total patients in each study (with 11-16 patients in each arm).[11,15] Data on the use of IPBI in children is quite limited with only 1 case study and 1 prior retrospective study examining IPBI in pediatric populations.[15,30] The retrospective study, also from our group, looked at patients with intractable gastroparesis with a mean age of 10 years and found that 30 of 45 patients had improvement in GI symptoms, but no feeding outcomes were assessed as these were older patients.

Given that the effects of botulinum toxin wane over time, a theoretical concern regarding the extension of use of IPBI to infants and young children is a potential need for repeat injections. Studies in adults have demonstrated symptomatic improvements from IPBI lasting about 3-5 months.[6,8,15] In the current study, the majority of patients did not require more than 1 injection and, in those who did, a majority required only 1 additional injection within 1 year. This minimal need for repeat injections may indicate that IPBI is more effective in younger patients than in adults, or it may be that even a few months of improvement after IPBI allows other medications and treatments to become more efficacious in this patient population. Given that many of these patients had undergone endoscopies and other procedures before receiving IPBI, it also is likely that the need for recurrent

anesthesia could be decreased by a proactive effort to combine IPBI with other planned sedated interventions. Future research would be helpful in further delineating the duration of effect of IPBI in children.

In the current study, baseline gastric emptying results did not predict IPBI response. There also was no significant difference between baseline and follow-up gastric emptying studies, although the interpretation of this finding is limited by the fact that only a small subset of patients underwent follow-up gastric emptying studies, and most of these were performed many months after IPBI so may no longer reflect an IPBI effect. In prior studies of IPBI, gastric emptying has not always been measured, and, when it has been measured, results have been mixed.[9,12-15,31] The observed lack of association between symptoms and gastric emptying in this and some prior studies may suggest that IPBI works through mechanisms beyond a motor effect on pyloric muscle, for example, through modulating sensory perception. This idea is supported by successful use of botulinum toxin for neuropathic pain in other areas of the body, such as for postherpetic neuralgia, complex regional pain syndrome, and diabetic neuropathy.[32,33] This hypothesized mechanism of action may help to explain why in our study IPBI was useful even in children who were being fed primarily with a postpyloric feeding tube, because sensory modulation may allow for an increased tolerance of normal sensory stimuli associated with enteral feeding, such as the presence of gastric fluid, formula, or food in the stomach. A similar mechanism may underlie treatment of other sensory-driven symptoms, such as abdominal pain, retching, or nausea.

There are several limitations to this study. The primary limitation was the retrospective nature of the study. Given that all information was taken from the medical chart, some patient details were not always accessible. For example, specific details on patients' feeding behaviors, such as the precise amount of oral intake, barriers to oral feeding progress, and use of speech and feeding therapies, could not always be ascertained from chart review. The retrospective nature of the study also introduced the potential for subjectivity in the interpretation of symptomatic outcomes, particularly in quantifying the degree of symptomatic improvement. Future research using validated questionnaires and symptom scores will be important in addressing this limitation. A related limitation is the possibility of recall bias in parents' and doctors' interpretation of whether IPBI was successful, particularly in the setting of variable time from procedure to follow-up. We attempted to address this by examining whether there was a relationship between time to follow-up and response to IPBI, and there was no such relationship, suggesting that time to follow-up did not systematically affect perception of response to IPBI. Another limitation was the lack of a control group, which raises the possibility that the observed benefits of IPBI could be due to the passage of time or placebo effect. The issue of passage of time is potentially important given that the natural history of feeding disorders are not well-characterized. However, these patients had a high level of medical complexity with long-standing symptoms based on the length of time from first GI appointment to first injection, so we think it is unlikely that time alone led to the observed improvements. Additionally, the general practice at our institution is to pursue IPBI when other medical interventions have failed, and indeed these patients had been followed by our group for an average of slightly more than 1 year before receiving IPBI. An effect from placebo cannot entirely be ruled out, although the likelihood of a sham injection study in pediatrics being approved through an institutional review board is extremely unlikely. A final limitation of the study is that our hospital is a tertiary referral center, so it is possible that the study population may differ in some ways from the general population of young patients with vomiting, retching, and feeding difficulties seen in pediatric gastroenterology or general pediatrics practices.

In conclusion, this study found that IPBI was successful in a group of young patients at reducing symptoms and improving oral and tube feeding. These findings suggest that IPBI in combination with a multidisciplinary approach may represent a novel treatment option for young patients with feeding disorders and chronic vomiting or retching. Further prospective research will be helpful for defining the ideal population and timing for this intervention. ■

Submitted for publication Feb 29, 2020; last revision received May 28, 2020; accepted Jun 19, 2020.

Reprint requests: Rachel Rosen, MD, MPH, Aerodigestive Center, Boston Children's Hospital, 300 Longwood Ave, HUN Ground, Boston, MA 02115. E-mail: Rachel.Rosen@childrens.harvard.edu

References

1. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PSW, Boyd RN. Oropharyngeal dysphagia and gross motor skills in children with cerebral palsy. Pediatrics 2013;131:e1553-62.
2. Sullivan PB, Lambert B, Rose M, Ford-Adams M, Johnson A, Griffiths P. Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. Dev Med Child Neurol 2000;42:674-80.
3. Equit M, Pälmke M, Becker N, Moritz A-M, Becker S, von Gontard A. Eating problems in young children - a population-based study. Acta Paediatr 2013;102:149-55.
4. Sharp WG, Volkert VM, Scahill L, McCracken CE, McElhanon B. A systematic review and meta-analysis of intensive multidisciplinary intervention for pediatric feeding disorders: how standard is the standard of care? J Pediatr 2017;181:116-24.e4.
5. Benoit D, Wang EEL, Zlotkin SH. Discontinuation of enterostomy tube feeding by behavioral treatment in early childhood: a randomized controlled trial. J Pediatr 2000;137:498-503.
6. Pasricha TS, Pasricha PJ. Botulinum Toxin Injection for Treatment of Gastroparesis. Gastrointest Endosc Clin N Am 2019;29:97-106.
7. Arts J, Van Gool S, Caenepeel P, Verbeke K, Janssens J, Tack J. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. Aliment Pharmacol Ther 2006;24:661-7.
8. Bromer MQ, Friedenberg F, Miller LS, Fisher RS, Swartz K, Parkman HP. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. Gastrointest Endosc 2005;61:833-9.
9. Hooft N, Smith M, Huang J, Bremner R, Walia R. Gastroparesis is common after lung transplantation and may be ameliorated by botulinum toxin-A injection of the pylorus. J Heart Lung Transplant 2014;33:1314-6.

10. Lacy BE, Crowell MD, Schettler-Duncan A, Mathis C, Pasricha PJ. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care 2004;27:2341-8.
11. Coleski R, Anderson MA, Hasler WL. Factors associated with symptom response to pyloric injection of botulinum toxin in a large series of gastroparesis patients. Dig Dis Sci 2009;54:2634-42.
12. Miller LS, Knight LC. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. Am J Gastroenterol 2002;97:8.
13. Arts J, Holvoet L, Caenepeel P, Bisschops R, Sifrim D, Verbeke K, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. Aliment Pharmacol Ther 2007;26:1251-8.
14. Friedenberg FK, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. Am J Gastroenterol 2008;103:416-23.
15. Rodriguez L, Rosen R, Manfredi M, Nurko S. Endoscopic intrapyloric injection of botulinum toxin A in the treatment of children with gastroparesis: a retrospective, open-label study. Gastrointest Endosc 2012;75:302-9.
16. Rosen R, Garza JM, Tipnis N, Nurko S. An ANMS-NASPGHAN consensus document on esophageal and antroduodenal manometry in children. Neurogastroenterol Motil 2018;30:e13239.
17. Manikam R, Perman J. Pediatric feeding disorders. J Clin Gastroenterol 2000;30:34-46.
18. Wright CM, Parkinson KN, Shipton D, Drewett RF. How do toddler eating problems relate to their eating behavior, food preferences, and growth? Pediatrics 2007;120:e1069-75.
19. Rommel N, De Meyer A-M, Feenstra L, Veereman-Wauters G. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. J Pediatr Gastroenterol Nutr 2003;37:75-84.
20. Sdravou K. Children with diseases of the upper gastrointestinal tract are more likely to develop feeding problems. AOG. 2019, http://www.annalsgastro.gr/files/journals/1/earlyview/2019/ev-01-2019-12-AG4329-0348.pdf. Accessed January 3, 2020.
21. Zangen T, Ciarla C, Zangen S, Di Lorenzo C, Flores AF, Cocjin J, et al. Gastrointestinal motility and sensory abnormalities may contribute to food refusal in medically fragile toddlers. J Pediatr Gastroenterol Nutr 2003;37:287-93.
22. Hartdorff C, Kneepkens CF, Stok-Akerboom AM, van Dijk-Lokkart EM, Engels MA, Kindermann A. Clinical tube weaning supported by hunger provocation in fully-tube-fed children. J Pediatr 2015;60:538-43.
23. Brown J, Kim C, Lim A, Brown S, Desai H, Volker L, Katz M. Successful gastrostomy tube weaning program using an intensive multidisciplinary team approach. J Pediatr Gastroenterol Nutr 2014;58:743-9.
24. Davis AM, Dean K, Mousa H, Edwards S, Cocjin J, Almadhoun O, et al. A randomized controlled trial of an outpatient protocol for transitioning children from tube to oral feeding: no need for amitriptyline. J Pediatr 2016;172:136-41.
25. Dunitz-Scheer M, Levine A, Roth Y, Kratky E, Beckenbach H, Braegger C, et al. Prevention and treatment of tube dependency in infancy and early childhood. ICAN: Infant Child Adolesc Nutr 2009;1:73-82.
26. Pahsini K, Marinschek S, Khan Z, Dunitz-Scheer M, Scheer PJ. Unintended adverse effects of enteral nutrition support: parental perspective. J Pediatr Gastroenterol Nutr 2016;62:169-73.
27. Ojo O, Keaveney E, Wang X-H, Feng P. The effect of enteral tube feeding on patients' health-related quality of life: a systematic review. Nutrients 2019;11:1046.
28. Morse J, Baird R, Muchantef K, Levesque D, Morinville V, Puligandla PS. Gastrojejunostomy tube complications — a single center experience and systematic review. J Pediatr Surg 2017;52:726-33.
29. Niv E, Fireman Z, Vaisman N. Post-pyloric feeding. World J Gastroenterol 2009;15:1281.
30. Woodward MN, Spicer RD. Intrapyloric botulinum toxin injection improves gastric emptying. J Pediatr Gastroenterol Nutr 2003;37:201-2.
31. Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc 2002;55:920-3.
32. Park J, Park H. Botulinum toxin for the treatment of neuropathic pain. Toxins 2017;9:260.
33. Oh H-M, Chung M. Botulinum toxin for neuropathic pain: a review of the literature. Toxins 2015;7:3127-54.