

# Outcomes of combined pyloric botulinum toxin injection and balloon dilation in dyspepsia with and without delayed gastric emptying

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**Abstract** **Background:** Pyloric botulinum toxin injection has improved symptoms in children with delayed gastric emptying. We aimed to determine the clinical response to combined endoscopic intra-pyloric botulinum toxin injection and pyloric balloon dilation (IPBT-BD) in patients with dyspepsia. **Methods:** Electronic medical records were reviewed to gather demographic data, symptoms, and follow-up on patients with dyspepsia. Cases were defined as those who underwent IPBT-BD in addition to their ongoing management. Controls received pharmacotherapy, behavioral intervention, or dietary management alone. Clinical response was defined as no change, partial, or complete improvement in symptoms within 12 months. Propensity score matching based on age, gender, and symptom duration was used to pair cases and controls. **Results:** In total, 79 cases and 83 controls were identified. After propensity matching, 63 patients were included in each group. The mean age for cases was  $14.5 \pm 3.9$ y; 62% were females and 98% were Caucasian. Further, 83% of 46 cases and 94% of 49 controls who had scintigraphy scans showed delayed gastric emptying. After matching, 76% of cases showed partial or complete improvement compared with 49% controls within 12 months ( $P = 0.004$ ). Younger children tended to respond more favorably to the procedure ( $P = 0.08$ ). **Conclusions:** In our propensity-matched analysis, combined IPBT-BD in addition to pharmacotherapy, behavioral, or dietary management clearly showed a benefit over these modalities alone. This favorable response lasted up to 12 months.

**Keywords:** Delayed gastric emptying, dyspepsia, pediatric, pyloric Botox, pyloric dilation

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## INTRODUCTION


Dyspepsia is a common pediatric condition, and symptoms include nausea, emesis, early satiety, bloating, postprandial

pain, and weight loss.<sup>[1,2]</sup> There is a significant overlap in the symptoms, epidemiology, and pathophysiology of functional dyspepsia and gastroparesis.<sup>[3,4]</sup> Recent studies

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consider them to be a part of a spectrum of gastroduodenal sensorimotor dysfunction.<sup>[3-5]</sup> A wide array of treatments are employed (pharmacotherapy such as prokinetics, proton pump inhibitors, antidepressants, and eradication of *Helicobacter pylori*; dietary modifications; and behavioral interventions).<sup>[1]</sup> Studies have reported suboptimal outcomes or side effects with pharmacotherapy,<sup>[5-9]</sup> and evidence-based data for these treatments in the pediatric population remain lacking.

One potential therapy is the injection of intra-pyloric botulinum toxin (IPBT) injection, which has been shown to improve symptoms in patients with gastroparesis.<sup>[10-16]</sup> Botulinum toxin A inhibits the release of acetylcholine into the neuromuscular synaptic cleft, resulting in decreased muscle contractility. This, in turn, is thought to improve pyloric function and improve the symptoms related to delayed gastric emptying.<sup>[17,18]</sup> However, pediatric data is scarce with only a couple of retrospective studies evaluating the efficacy of IPBT in gastroparesis and feeding disorders. These have shown promising results with a 67% response rate in each study.<sup>[19,20]</sup> Another treatment targeting pyloric dysfunction is pyloric balloon dilation (BD), which has been performed for anatomic gastric outlet obstruction in adults as well as children secondary to strictures, peptic ulcer disease, post-acid ingestions, and congenital pyloric stenosis.<sup>[21-25]</sup> Pyloric balloon dilation has also improved outcomes in gastroparesis in adults, likely by improving pyloric compliance,<sup>[26]</sup> but data in pediatrics is limited. There are no studies on the combination of IPBT injection and pyloric BD for pediatric dyspepsia with or without delayed gastric emptying. Therefore, the primary aim of this study was to analyze the long-term response rates of dyspeptic symptoms to the combination of intra-pyloric botulinum toxin injection and pyloric balloon dilation (IPBT-BD) in addition to conventional management, and compare the results with those for children who received conventional management alone. We also sought to assess factors that predicted response to IPBT-BD and conventional treatment. Lastly, we compared the response of combined IPBT-PD from our cohort to two previously published pediatric studies on IPBT to assess the possible added effect of pyloric dilation.

## PATIENTS AND METHODS

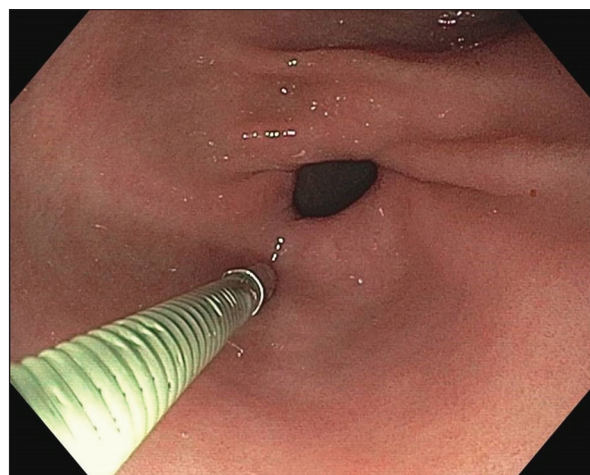
After obtaining approval from the institutional review board, we reviewed the electronic medical records (EMR) and identified all patients aged 0–25 years with ICD 10 codes of dyspepsia, abdominal pain, nausea, vomiting, early satiety, and weight loss without any organic etiology, between January 2012 and May 2019. We excluded patients

who had previous IPBT procedures outside our institution and those who did not follow up. We separated them into two groups: those that underwent a single IPBT-BD procedure and those that did not. A standard protocol was used for IPBT-BD. A total of 100 units of botulinum toxin A was injected into the submucosa by using a sclerotherapy needle (Carr-Locke needle, Steris/US Endoscopy, Mentor, OH) and divided into four quadrants of the pylorus (25 units of botulinum toxin A diluted in 0.5mL of NS in each quadrant) [Figure 1]. This was followed by balloon dilation with a controlled radial expansion (CRE) balloon dilator (Boston Scientific, Marlborough, MA @2015) up to 20 mm Hg for 2 min [Figure 2]. The final balloon size for dilation depended on the pyloric diameter measured relative to the size of the scope tip. We performed IPBT injection first, followed by pyloric dilation which allowed the botulinum toxin to dissipate over a larger surface area.

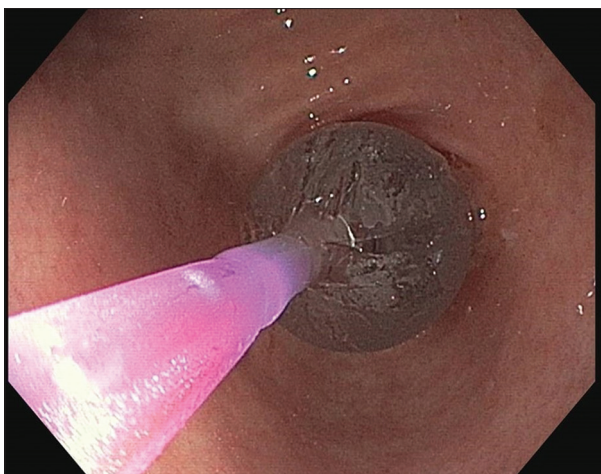
Controls included patients with dyspepsia who received conventional therapy but no IPBT-BD. We collected data on demographics (age, gender, and race), presenting symptoms, symptom duration, scintigraphic gastric emptying scan (GES) results when done, the presence or absence of joint hypermobility syndrome, and psychiatric comorbidities. A delayed GES was defined as <40% emptying at 2 h or <90% at 4 h after a solid meal. A standard meal per divisional radiology protocol was used for GES. Symptom improvement was assessed at the follow-up visit for both groups.

## Outcome

The primary outcome measure was the response to combined IPBT-BD and was classified as follows: 0 = no change, 1 = partial improvement (patient felt better but



**Figure 1:** Intra-pyloric botulinum toxin injection (IPBT). Endoscopic image of botulinum toxin A injection into the pyloric submucosa via a sclerotherapy needle



**Figure 2:** Pyloric dilation. Endoscopic image of balloon dilation of the pylorus using a controlled radial expansion (CRE) balloon dilator

still had some symptoms), and 2 = complete resolution of symptoms within 12 months, as reported by the patient or caretaker. Secondary outcomes included assessment of response based on follow-up duration and rate of gastric emptying. Factors that predicted response to combined IPBT-BD and to conventional treatment were also identified.

As an exploratory analysis, response rates were compared between this cohort, which included the total number of IPBT-BD patients, and the combined response rates of the two previously published pediatric studies of IPBT.<sup>[19,20]</sup> Response rates and 95% confidence intervals were calculated between the number of patients who had a partial or complete response and non-responders and were used to compare with the published response rates.

### Statistical analysis

The IPBT-BD treated (case) patients were matched to

control patients according to age ( $\leq 5$  years and  $> 5$  years), gender, and duration of symptoms. This matching was carried out to reduce potential bias in analysis and interpretation due to baseline and disease characterizations because of the non-randomized nature of the study. Propensity score matching was performed, with a propensity score model fit using logistic regression with the group status (case/control) as the response and the above mentioned matching variables as the independent variables. Each case was matched within 0.1 SD of the propensity score. The response at follow-up was compared between the matched case and control groups using the t-test, Chi-Square test, or Fisher's exact test as appropriate. To determine the predictors of response to treatment in each group, a proportional odds regression model with single predictors was used for univariate analysis. Fisher's exact test was used to assess the difference between the response rate of IPBT-BD and the combined response rate from the two previously published pediatric studies of IPBT in the exploratory analysis. Statistical analysis was conducted using R-package "Matching" version 4.9-6 for the matching process on R version 3.6.0. Group comparisons were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). Continuous variables were summarized as mean, standard deviation, or median as appropriate and indicated in the results.

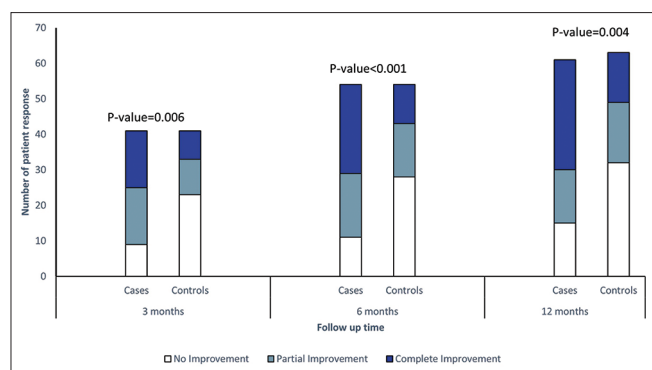
## RESULTS

### Clinical characteristics

A total of 83 controls who underwent conventional management alone and 79 cases with dyspepsia who underwent combined IPBT-BD and conventional management were identified. After a 10% propensity caliper matching for age, sex, and duration of symptoms,

**Table 1: Baseline characteristics, before and after matching, in the 12-month follow-up group**

Demographic Variables	Before Matching			After Matching		
	Control <i>n</i> =83 (%)	Cases <i>n</i> =79 (%)	<i>P</i>	Control <i>n</i> =63 (%)	Cases <i>n</i> =63 (%)	<i>P</i>
Age (Mean, SD)	10.8 (6.3)	14.7 (3.9)	<0.001	13.2 (4.7)	14.5 (3.9)	0.084
Gender						
Female	46 (55.4)	49 (62.0)	0.394	36 (57.1)	39 (61.9)	0.586
Race	79 (95.2)	75 (94.9)	0.524	60 (95.2)	62 (98.4)	0.369
White						
Duration of symptoms prior to presentation (median, Q)	83 (18.0) (5.0, 55.0)	79 (29.0) (9.0, 72.0)	0.158	63 (23.0) (5.0, 63.0)	63 (29.0) (9.0, 64.0)	0.460
Time to follow-up (median, Q)	83 (2.0) (1.0, 4.0)	79 (2.0) (0.0, 4.0)	0.318	63 (2.0) (1.0, 4.0)	63 (2.0) (0.0, 4.0)	0.119
Nausea	33 (39.8)	41 (51.9)	0.121	31 (49.2)	33 (52.4)	0.722
Abdominal pain	48 (57.8)	59 (74.7)	0.024	43 (68.3)	49 (77.8)	0.229
Vomiting	50 (60.2)	36 (45.6)	0.061	34 (54.0)	27 (46.7)	0.212
Early satiety	10 (12.1)	7 (9.0)	0.526	10 (15.9)	5 (7.9)	0.179
Weight loss	2 (2.4)	6 (7.7)	0.158	1 (1.6)	4 (6.5)	0.207
Hypermobility	10 (15.4)	8 (11.9)	0.564	8 (16.0)	8 (15.4)	0.932
Psychiatric comorbidities	22 (26.5)	36 (45.6)	0.011	19 (30.2)	26 (41.3)	0.193
Gastric emptying scans performed	<i>n</i> =55	<i>n</i> =60		<i>n</i> =49	<i>n</i> =46	
Delayed gastric emptying	50 (90.9)	50 (83.3)	0.228	46 (93.9)	38 (82.6)	0.086



**Figure 3:** Clinical response based on follow-up. Clinical response to combined intra-pyloric botulinum toxin injection and pyloric balloon dilation (IPBT-BD) treatment in matched cases based on follow-up duration

63 patients were included in each group. The demographic and clinical characteristics of the patients are shown in Table 1. Only one patient in each group was younger than 5 years of age. Delayed gastric emptying was identified in 83% of 46 cases and 94% of 49 controls who had documented gastric emptying scans. The average duration of symptoms at presentation was 63 days in both groups. Psychiatric comorbidities (anxiety, depression, attention deficit hyperactivity disorder, post-traumatic stress disorder, schizophrenia, and bipolar disorder) were present in 41% of cases and 30% of controls. None of the baseline characteristics (age, gender, race, GES results, symptoms of abdominal pain, nausea, vomiting, early satiety, weight loss, psychiatric comorbidities, present or absence of hypermobility, and duration of symptoms) were statistically different after propensity matching.

### Response

Before matching, 78% of cases showed partial or complete improvement, for those with follow-up within 12 months, compared to 51% of controls ( $P = 0.001$ ). After propensity matching, 76% of cases showed partial or complete improvement compared with 49%

controls ( $P = 0.004$ , Figure 3). Specifically, 26% of cases had partial improvement compared with 27% of controls, and 50% of cases had complete improvement with 22% of controls. No adverse events were reported after the procedure.

We further analyzed patient data for those who were followed up within 3 and 6 months post-intervention (Table 2 and Figure 3). Within 3 months, after propensity matching, 78% of cases showed partial or complete improvement compared to 44% of controls ( $P = 0.006$ ). Within 6 months, 79% of cases showed partial or complete improvement compared to 48% controls ( $P = 0.0002$ ).

Table 3 shows the clinical response based on gastric emptying rates in the 12-month follow-up group. Among patients with delayed gastric emptying, those who got IPBT-BD were more likely to show improvement compared to controls (81.6% vs. 50%,  $P = 0.008$ ). Cases with normal gastric emptying and those with unknown emptying rates also showed improvement compared with controls, although this was not statistically significant.

### Predictors of response

Table 4 summarizes the univariate (logistic) analysis of factors predicting response to IPBT-BD for unmatched cases and conventional treatment for unmatched controls. There was a trend toward younger children responding more favorably to IPBT-BD ( $P = 0.08$ ). Age did not predict the response for controls. Gender, symptoms, comorbidities, and gastric emptying did not significantly affect response to treatment in either group. However, odds ratio point estimates suggested that cases with nausea and vomiting, and controls with nausea only, responded most favorably to the procedure, although this did not reach statistical significance. Similarly, males, patients with hypermobility, delayed gastric emptying, and those without psychiatric comorbidities responded more favorably to

**Table 2: Univariate analysis of clinical response to combined intra-pyloric botulinum toxin injection and pyloric balloon dilation (IPBT-BD) treatment, before and after matching, based on follow-up duration**

Follow-up	Before propensity matching			After propensity matching		
	Control n=56 (%)	Cases n=51 (%)	P	Control n=41 (%)	Cases n=41 (%)	P
Within 3 months			0.004			0.006
No change	31 (55.4)	13 (23.5)		23 (56.1)	9 (22.0)	
Partial improvement	13 (23.2)	19 (37.3)		10 (24.4)	16 (39.0)	
Complete improvement	12 (21.4)	20 (39.2)		8 (19.5)	16 (39.0)	
Within 6 months	n=72	n=69	0.002	n=54	n=54	0.0002
No change	36 (55.4)	16 (23.2)		28 (51.9)	11 (20.4)	
Partial improvement	19 (23.2)	21 (30.4)		15 (27.8)	18 (33.3)	
Complete improvement	19 (21.4)	32 (46.4)		11 (20.3)	25 (46.3)	
Within 12 months	n=83	n=78	0.001	n=63	n=62	0.004
No change	41 (49.4)	17 (21.8)		32 (50.8)	15 (24.2)	
Partial improvement	22 (26.5)	23 (29.5)		17 (27.0)	15 (25.8)	
Complete improvement	20 (24.1)	38 (48.7)		14 (22.2)	31 (50.0)	

**Table 3: Clinical response based on the rate of gastric emptying**

Variables	After matching		P
	Control (n=63) (%)	Botox (n=63) (%)	
Delayed gastric emptying	n=46	n=38	0.008
No change	23 (50.0)	7 (18.4)	
Partial improvement	10 (21.7)	10 (26.3)	
Complete improvement	13 (28.3)	21 (55.3)	
Normal gastric emptying	n=3	n=7	0.700
No change	2 (66.7)	2 (28.6)	
Partial improvement	1 (33.3)	2 (28.6)	
Complete improvement	0 (0.0)	3 (42.8)	
Gastric emptying not known	n=14	n=17	0.106
No change	7 (50.0)	6 (35.3)	
Partial improvement	6 (42.9)	4 (23.5)	
Complete improvement	1 (7.1)	7 (41.2)	

the procedure in both groups, although this did not reach statistical significance.

### Comparison of IPBT-BD with historic IPBT response

The response rate of all unmatched patients receiving IPBT-BD who had a partial or complete response 12 months after treatment was 78% (95% CI: 69–87%), which is close to the response rate of IPBT-BD (76%) in the control-matched patients. Compared to the pooled response rate of 67% (58%–75%) from Rodriguez *et al.*<sup>[19]</sup> and Hirsch *et al.*<sup>[20]</sup> (combined total of 87 responders out of 130 total patients), the difference did not reach a statistical significance ( $P = 0.114$ ) in a Fisher's exact test of 2-by-2 contingency table. There is an obvious trend toward a higher response rate among IPBT-BD patients compared to IPBT only patients in Rodriguez *et al.*<sup>[19]</sup> and Hirsch *et al.*<sup>[20]</sup> (78% vs. 67%).

## DISCUSSION

This is the first study evaluating the response of IPBT injection combined with pyloric balloon dilation in children or adults with dyspepsia, with and without delayed gastric emptying. In a propensity-matched sample, we have shown a response rate of 76% with combined IPBT injection and pyloric dilation in addition to conventional management compared with the latter alone. Two uncontrolled pediatric retrospective studies have each shown a 67% improvement after IPBT injection alone in children with gastroparesis ( $n = 45$ )<sup>[19]</sup> and in younger children with feeding difficulties including delayed gastric emptying ( $n = 87$ ).<sup>[20]</sup> The higher response rate in our sample may be attributed to the inclusion of patients with dyspepsia regardless of gastric emptying status, a propensity-matched control group, a large sample size, and a long duration of follow-up. When comparing our outcome of “any improvement” in the unmatched cohort with the historic studies, we found a 11% higher response, which could be attributed to the effect of pyloric dilation. While open-label studies

in adults have demonstrated 55%–100% improvement in symptoms such as nausea and vomiting,<sup>[14,15,27-29]</sup> two small randomized controlled trials (RCT) did not establish the superiority of IPBT over saline injections in gastroparesis in adults. However, these trials included heterogeneous populations with varied etiologies for delayed gastric emptying that may have confounded the results.<sup>[30,31]</sup> In adults with gastroparesis, 78% of 33 patients showed overall improvement in symptoms and weight gain after receiving either IPBT ( $n = 25$ ) or pyloric balloon dilation ( $n = 8$ ).<sup>[16]</sup> The majority of patients (79%) in this study had idiopathic delayed gastric emptying.

Among our patients with delayed gastric emptying, those with IPBT-BD had significantly more improvements compared with controls ( $P = 0.008$ ). Pyloric spasm or fibrosis has been implicated in the pathophysiology of delayed gastric emptying leading to a functional gastric outlet obstruction.<sup>[32,33]</sup> Studies in adults with delayed gastric emptying have demonstrated decreased pyloric distensibility and compliance, decreased cross-sectional area and diameter, and increased basal pyloric pressure.<sup>[26,34-36]</sup> Dyschalia (premature contraction of the pylorus during antral peristalsis) has also been implicated in the pathophysiology of gastroparesis.<sup>[37]</sup> Based on these studies, the witnessed improvement in symptoms with combined IPBT-BD treatment may be secondary to improved pyloric outflow from increased pyloric distensibility and compliance, as well as improving dyschalia. It is also hypothesized that altering the pyloric dynamics may cause changes in antral contractility, which in turn improves gastric emptying and associated symptoms.<sup>[36]</sup>

It has been reported that symptoms do not often correlate with the severity of delayed gastric emptying.<sup>[38]</sup> Thus, the improvements noted in our cohort with both delayed and normal gastric emptying may be secondary to an altered afferent input from the stomach to the brain. One hypothesis is that IPBT injection may decrease the sensory vagal input from the pylorus to the brain, leading to enhanced symptom response. This is supported by the analgesic effect of botulinum toxin noted in animal studies. Neural evaluation in rat models has shown that botulinum toxin decreases the expression of nociceptors (TRPV1), the secretion of substance P and other pain regulatory neurotransmitters, as well as the peripheral and central sensitization of pain signals in the spinal cord. Direct retrograde axonal transport of botulinum toxin along the branches of nociceptive neurons has also been documented, suggesting its role in treating central neuropathic pain conditions such as post-stroke pain, multiple sclerosis, and complex regional pain syndrome.<sup>[39]</sup>

**Table 4: Univariate analysis of factors predicting response to combined intra-pyloric botulinum toxin injection and pyloric balloon dilation (IPBT-BD) treatment for cases, and conventional treatment for controls, within 12 months of follow-up**

Effect	Unmatched cases				Unmatched controls			
	Odds ratio estimate	95% Wald Confidence Limits of OR		P	Odds ratio estimate	95% Wald Confidence Limits of OR		P
Age (continuous)	0.904	0.806	1.014	0.084	0.992	0.929	1.058	0.802
Children (older than vs. <10 y)	0.437	0.171	1.119	0.085	0.668	0.294	1.522	0.338
Gender (M)	1.975	0.811	4.809	0.134	1.190	0.527	2.687	0.675
Abdominal pain	0.752	0.285	1.983	0.565	0.533	0.234	1.214	0.134
Nausea	1.602	0.691	3.710	0.272	1.257	0.551	2.869	0.587
Vomiting	1.530	0.658	3.555	0.323	0.669	0.293	1.528	0.340
Early satiety	1.358	0.535	3.447	0.519	1.486	0.437	5.059	0.526
Weight loss	1.632	0.432	6.171	0.470	4.764	0.302	75.267	0.268
Hypermobility	1.080	0.431	2.706	0.870	1.309	0.376	4.558	0.673
Psychiatric comorbidities	0.625	0.316	1.236	0.177	0.891	0.354	2.240	0.806
Gastric emptying	0.516	0.137	1.941	0.328	0.207	0.021	2.079	0.181

We noted a similar rate of symptom relief with the combination of IPBT injection and dilation at all three time-points (3, 6, and 12 months) postintervention. Previous studies have demonstrated that IPBT has an expected symptom relief for about 3 months in children and adults with a few studies in adults showing efficacy up to 4–6 months from treatment.<sup>[19,28,29,40]</sup> Some of the improvements noted over time in our cohort can be attributed to the natural history of the disease in children. However, given the severity of the symptoms when present, and a lack of well-established, evidence-based treatments, the combined procedure appears to have an advantage over IPBT or BD alone, with a robust and longer-lasting response.

In terms of factors predicting response, we did not find a gender difference between responders versus non-responders, despite mixed data being reported in previous studies.<sup>[19,28,29]</sup> Younger age (<50 years) and idiopathic etiology have demonstrated a favorable response to IPBT in adults, which is consistent with our findings.<sup>[29]</sup> The study by Rodriguez *et al.*<sup>[19]</sup> showed that children older than 12 years of age responded better to IPBT. In contrast, our study showed that children less than 14 years of age tended to have a better response to IPBT-PD. Rodriguez *et al.* used weight-based dosing for IPBT,<sup>[19]</sup> while we used a fixed dose of 100 units for our entire cohort. As larger doses of Botox as high as 200 units are related to improved responses in adults,<sup>[27,29]</sup> the improvements in our younger patients may be due to a relatively higher dose-for-weight of Botox compared to the prior study. This may also explain our improved outcomes compared to studies in adults. Further elucidation is warranted to evaluate the effect of relative weight-based dosing, especially in combination with pyloric dilation. The type of symptoms and other comorbidities did not significantly affect the response. Though not statistically significant, nausea and vomiting responded more favorably to IPBT-BD. This has been reported in prior studies assessing response to IPBT.<sup>[19,30]</sup>

Our study had a few limitations. The retrospective design of our study may be impacted by the accuracy of EMR documentation. However, a double-blind, placebo-controlled trial is not practical or ethical in children as it has the risk of general anesthesia and would be an invasive procedure in healthy controls. While propensity score-matching employed in our study cannot completely balance known or unknown confounders, it had the advantage of eliminating confounding bias to a degree that closely mimics that of a RCT. Moreover, it was difficult to establish the individual effects of the two procedures as they were combined. However, although not a perfect comparison, we were able to ascertain a higher response of the combined procedure over historic IPBT studies, and this may be attributed to pyloric dilation. A future study could focus on discerning the efficacy of combined pyloric balloon dilation and IPBT compared to IPBT or pyloric dilation alone. We included some patients with delayed emptying of a solid meal at 2h and not 4h exclusively. This is because some patients had their scan done before 4-h scintigraphy was regarded as the gold standard for diagnosing delayed emptying.<sup>[41,42]</sup> However, 2-h abnormal cut-offs have been previously established as >60% retention on scintigraphy, which we used for our study.<sup>[43]</sup> Our cohort included a heterogeneous population with known and unknown gastric emptying. Thus, performing a subgroup analysis for evaluating improvement in those with normal, delayed, and unknown gastric emptying, impacted the numbers in each of these three subgroups. Therefore, it is likely that a lack of statistically significant improvement of the combined intervention in patients with normal and unknown emptying groups is due to smaller sample sizes, than those with delayed emptying. This highlights the need for future large studies of this intervention in patients with normal gastric emptying. Another limitation was our inability to use Rome 4 criteria for patient selection due to the retrospective nature of the study, as these are not consistently documented in the EMR clinic notes. Similarly,

providers included general gastroenterologists as well as neurogastroenterologists.

In conclusion, we demonstrated a significant benefit of combined intra-pyloric botulinum toxin injection and pyloric balloon dilation for children with dyspepsia, especially in those with delayed gastric emptying. The observed response rate of the combined procedure was higher than that reported in previous pediatric studies assessing intra-pyloric botulinum toxin injection alone. Larger scale studies in both children and adults are needed to confirm our findings as this may necessitate a paradigm shift and have a significant impact on the standard of care of patients with dyspepsia.

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### Conflicts of interest

Dr. Kaul has been on the editorial board for the Saudi Journal of Gastroenterology in the past. Other than that, none of the authors have any conflict of interest.

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