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Outcome of peroral endoscopic myotomy in children with achalasia

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Abstract

Background and aims Achalasia cardia is rare in children and optimum endoscopic management options are not well known. Peroral endoscopic myotomy (POEM) is a novel treatment modality for achalasia with excellent results in adult patients. The long-term outcomes of POEM are not well known in children. In this study, we aim to evaluate the outcome of POEM in children with idiopathic achalasia.

Methods We analyzed the data of children (≤ 18 years) diagnosed with achalasia from September 2013 to January 2018. Technical success, clinical success, and adverse events were assessed. Post-POEM, gastroesophageal reflux (GER) was assessed with 24-h pH-impedance study and esophagogastroduodenoscopy.

Results A total of 44 children (boys—23, girls—21) with mean age of 14.5 ± 3.41 years (4–18) were diagnosed with achalasia during the study period. Of these, 43 children underwent POEM. The subtypes of achalasia according to Chicago classification were type I—11, type II—29, type III—2, and unclassified—2. Eighteen children (40.9%) had history of prior treatment. POEM was successfully performed in 43 children (technical success—97.72%). Intra-operative adverse events occurred in 11 (25.6%) children including retroperitoneal CO2 (7), capnoperitoneum (3), and mucosal injury (1). Clinical success at 1, 2, 3, and 4 years' follow-up was 92.8%, 94.4%, 92.3%, and 83.3%, respectively. Erosive esophagitis was detected in 55% (11/20) children. On 24-h pH study, GER was detected in 53.8% (7/13) children.

Conclusion POEM is a safe, effective, and durable treatment for achalasia in children. However, GER is a potential concern and should be evaluated in prospective studies before adopting POEM for the management of achalasia in children.

Keywords Achalasia · Child · Endoscopy · Myotomy

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Achalasia is a neurodegenerative disease characterized by aperistalsis and absence of lower esophageal sphincter relaxation. Achalasia is rare in children with a mean incidence of 0.1 to 0.18/10^5 children/year and a mean prevalence of 0.9/10^5 children [1, 2]. The presentation of achalasia is distinct in children and therefore, often misdiagnosed as gastroesophageal reflux and bronchopneumonia leading to diagnostic delay [3].

The management options for achalasia include pneumatic dilatation (PD) and Heller's myotomy. However, PD is often not effective in long run and repeated dilatations are required [4, 5]. Moreover, pneumatic balloons have not been specifically designed for pediatric use and therefore, not recommended in small children. In the absence of an effective endoscopic treatment option, Heller's myotomy is often performed in pediatric patients with achalasia [4].

Per-oral endoscopic myotomy (POEM) is a relatively new technique and has been effectively used in adult patients [6,

7]. However, the literature regarding the utility of POEM in children is limited. Few small studies with short-term follow-up show favorable results of POEM in children and adolescents as well [8–11]. The long-term outcomes of POEM and the incidence of post-operative gastroesophageal reflux (GER) are not known in children.

In this study, we aimed to analyze the long-term outcome of POEM and objectively assess post-operative GER in children with achalasia.

Materials and methods

The data of all the children who were diagnosed with achalasia from September 2013 to January 2018 were analyzed, retrospectively. Informed consent was obtained from the parents/legal guardians and the study was approved by the institution's review board (AIG/AHF IRB: 34/2015).

The diagnosis of achalasia was established using esophagogastroduodenoscopy (EGD), high-resolution esophageal manometry, and barium swallow. The sub-typing of achalasia was done using Chicago classification for esophageal motility disorders [12]. Clinical symptoms were assessed and graded using Eckardt score [13].

Technical and clinical success

Technical success was defined as accomplishment of entire POEM procedure from mucosal incision to closure of incision with endoclips. Unsuitability for POEM due to any reason like contraindication to general anesthesia or low weight was considered as failure.

Clinical success was defined as improvement in Eckardt score (≤ 3). Objective parameters of clinical success included improvement in esophageal emptying of $> 50\%$ at 5-min on timed barium esophagogram. In addition, high-resolution manometry was performed and reduction in lower esophageal sphincter pressure was assessed.

Instruments and accessories

The following instruments and accessories were utilized for the procedure—gastroscope equipped with water jet (Olympus GIF HQ 190; Olympus Corp., Tokyo, Japan), tapered tip transparent cap (DH-28GR; Fujifilm, Tokyo, Japan), electrosurgical generator (VIO300D; ERBE, Tübingen, Germany), triangular tip knife [TT, KD-611L; Olympus Corp.], triangular knife with water jet [TriangleTipKnife J (TTJ), KD-645L, Olympus, Tokyo, Japan], insulated tip knife (KD-611L; Olympus Corp.), spray catheter, CO_2 insufflator (UCR; Olympus Corp.), endoscopic clips (EZ Clip, HX-610-090L; Olympus Corp.), and coagulation forceps (Coagrasper G, FD-412LR, Olympus, Japan).

Intra-operative details

All the POEM procedures were performed in an endoscopy suit. EGD was performed under light sedation for the clearance of esophago-gastric contents prior to the administration of general anesthesia and commencing the POEM procedure.

The technique of POEM has been described in detail in our previous studies [9, 14]. POEM was performed under general anesthesia with the child in supine position. In brief, the steps of POEM were as follows: submucosal injection with saline and indigocarmine solution (~ 10 cc), mucosal incision (~ 2 cm long), submucosal tunneling, myotomy, and closure of mucosal incision with endoclips (Fig. 1). POEM was performed via an anterior (2 o'clock) or posterior (5 o'clock) approach. Posterior approach was used in children with previous history of Heller's myotomy. Intra-procedural details including operative time, length of myotomy, and adverse events were recorded.

Definition of adverse events

Adverse events were defined as those requiring an intervention (like needle drainage of capnoperitoneum or closure of mucosal injuries with clips) or temporary cessation of POEM procedure (high-end tidal CO_2, significant abdominal distension). Events associated with hemodynamic compromise or resulting in abortion of the procedure were considered as severe adverse events. Partial thickness mucosal injuries and insufflation related events not requiring an intervention were not considered as adverse events.

Post-operative care and follow-up

The children were kept nil by mouth for 24 h after the procedure. Thin barium swallow was performed on next morning to rule out any leak. Subsequently, oral liquids were initiated followed by soft pureed diet for 1 week. Intravenous antibiotics were continued for 2 days.

The children were followed up at 1 month, 3 months, 1 year, and every year thereafter. Clinical symptoms were recorded at each visit. Objective evaluation of success with esophageal manometry and timed barium swallow were performed at 1 year.

Esophageal manometry [15]

We have described the technique of high-resolution manometry (HRM) previously [15]. HRM was carried out with a 16-channel water-perfused catheter that has 8

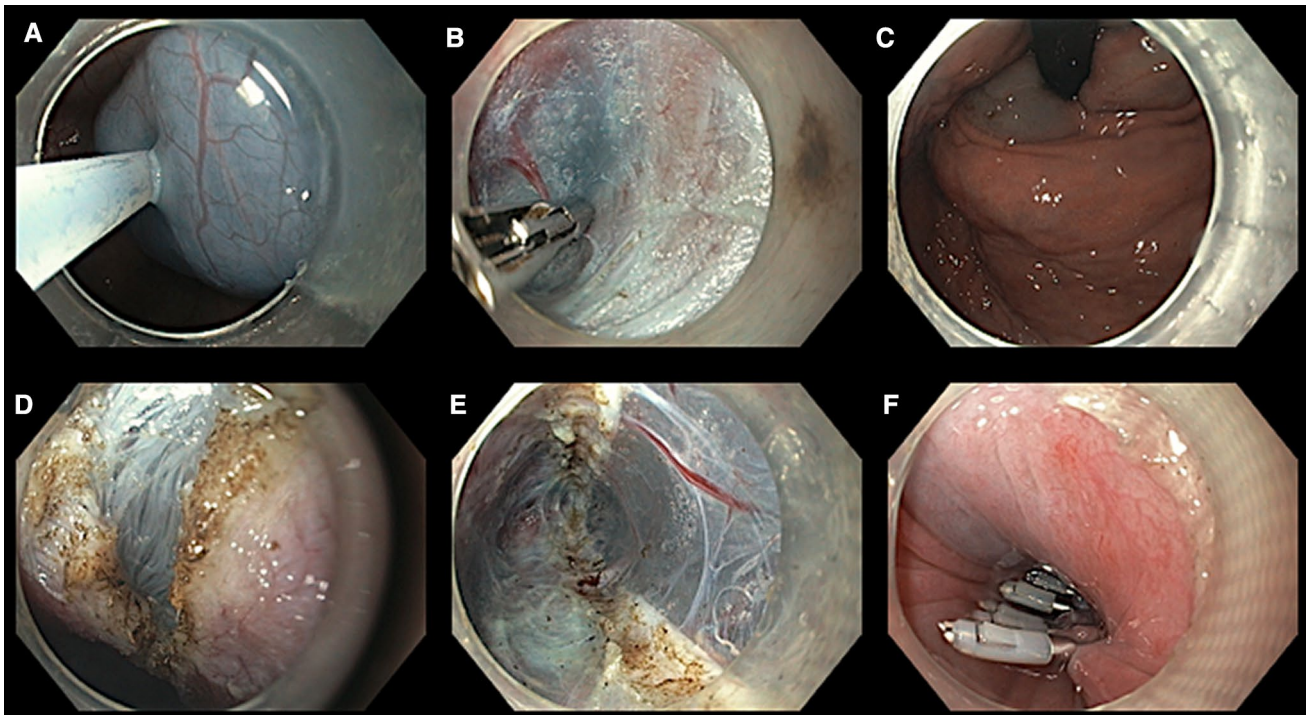

Fig. 1 Technique of peroral endoscopic myotomy. **A** Submucosal lifting injection of saline mixed with indigocarmine dye. **B** Submucosal tunneling (note the coagulation of a vessel using coagulation forceps). **C** Blanching of gastric mucosa confirming the adequate extension of submucosal tunnel into the stomach. **D** Partial thickness or circular only myotomy in the upper part of the submucosal tunnel. **E** Full thickness myotomy in the lower part of submucosal tunnel. **F** Closure of mucosal incision using endoclips

channels 1 cm apart at the lower end and the remaining 8 channels 3 cm apart (Dentsleeve International Pty Ltd.; Mui Scientific, Ontario, Canada). Data were analyzed using Trace 1.2 V software (Geoff Hebbard, Royal Melbourne Hospital, Victoria, Australia). Patients were classified into achalasia subtypes according to the Chicago classification of esophageal motility disorders (V 3.0) [12].

Evaluation of gastroesophageal reflux

GER was evaluated with symptoms, esophagogastroduodenoscopy (EGD), and 24-h pH-impedance study at 3 months after the POEM procedure.

The evaluation of reflux with 24-h pH impedance was performed as follows. The pH probe was placed transnasally and connected to a pH data acquisition device (ZepHr pH monitor with ComforTEC disposable catheters, Sandhill Scientific, Highlands Ranch, CO, USA). Total number of reflux episodes, acid exposure time, and composite DeMeester score were measured [15]. Esophageal acid exposure time (pH < 4) of > 7%, a DeMeester score > 14.7, and erosive esophagitis on EGD were considered as indicative of GER [16].

Management of gastroesophageal reflux

All children received oral proton pump inhibitors (PPIs) for 3 months after the procedure. PPIs were stopped 1 week prior to the 24-h pH-impedance study. Subsequently, PPIs were continued in only those with symptoms suggestive of reflux and or objective evidence of reflux, i.e., erosive esophagitis and or increased esophageal acid exposure time.

Statistics

The data are presented as median (range) or mean (± SD). Student's paired t test was used for continuous variables and proportion test for categorical variables. p values of < 0.05 were considered statistically significant. The data were analyzed using MedCalc for Windows, version 12.2.1.0 (MedCalc Software, Ostend, Belgium).

Results

Demographic characteristics

A total of 44 children were diagnosed with achalasia during the specified period. Of these, 43 children (22 boys, 21 girls) with median age of 14.5 ± 3.41 years (4–18) underwent POEM. In one 11-month-old infant, POEM was deferred due to low weight (7 kg).

Table 1 Demographics of study patients

No. of children	44
Mean age, years ± SD	14.58 ± 3.41 (4–18)
Male:female	22:21
Achalasia cardia	40.90%
Type I	11
Type II	29
Type III	2
Unclassified	2
Median disease duration (months)	24 (2–96)
Previous therapy	
Balloon dilatation	15
Heller's myotomy	1
Balloon dilatation and Heller's myotomy	2

Eighteen children (40.90%) had received prior treatment including balloon dilatation in 15, HM in 1, and both balloon dilatation and HM in 2 children.

The subtypes of achalasia as per the Chicago classification were—type I 11(25%), type II 29 (65.9%), type III 2(4.5%), and unclassified 2 (4.5%). Esophageal manometry could not be performed in two children (Table 1).

Intra-operative details

POEM was successfully performed in 43 (97.72%) children. POEM was performed via an anterior approach in majority of the children (66%). Mean total length of myotomy was 10.09 ± 2.53 cm (5–15).

Mean procedure time was 65.46 ± 42.05 (18–240) min. Mean procedure time reduced significantly with the operator's experience and use of new triangular knife equipped with water jet facility (Table 2). Operative time was significantly less in cases, where TTJ knife was used as compared to those in whom TT knife was used (mean, 42.72 ± 14.92 vs. 97.05 ± 47.30 min, $p < 0.05$).

Overall, insufflation-related events were noticed in 21 children (48.83%). Of these, an intervention was required in ten children (23.25%) and were considered as insufflation-related adverse events. These adverse events included accumulation of retroperitoneal CO_2 ($n = 7$) and capnoperitoneum ($n = 3$). Intra-procedural mucosal injury requiring closure with clips occurred in one child ($n = 1$) (Table 2).

Table 2 Operative finding of children who underwent peroral endoscopic myotomy

Mean operating time in minutes (range)	65.46 ± 42.05 (18–240)
Case 1–15	106 ± 46.27
Case 16–30	48.66 ± 17.94
Case 31–43	38.08 ± 9.84
Mean operating time with TT knife ($n = 18$)	97.05 ± 47.30
Mean operating time with TTJ knife ($n = 25$)	42.72 ± 14.92
Site of myotomy	
Anterior	33
Posterior	10
Total length of myotomy (cm) (range)	10.09 ± 2.53 (5–15)
Esophageal (cm)	7.09 ± 2.31
Gastric (cm)	2.98 ± 0.64
Intra-operative events (adverse events)	27.9%
Retroperitoneal CO_2 (temporary cessation of procedure)	11 (7)
Capnoperitoneum (drainage)	10 (3)
Mucosal injury	1
No. of clips, median (range)	6 (4–10)
Technical Success	97.7% (43/44)
Hospital stays, mean (range)	3 (2–4)
Median follow-up days (range)	540 (30–1594 days)
Clinical success	90.90 (40/44)

Clinical success and follow-up

Overall, clinical success (Eckardt ≤ 3) was achieved in 90.90% (40/44) children. There were four failures. Of these, two clinical failures (Eckardt > 3) were detected at 1 and 3 years' follow-up, respectively. One child was lost to follow-up and POEM was not performed in one child due to small size. Both of these cases were considered as clinical failures in the final analysis. The median follow-up duration was 540 days (range 30–1594). Clinical success at 1, 2, 3, and 4 years' follow-up was 92.8% (26/28, one clinical failure, one technical failure), 94.4% (17/18, one lost to follow-up), 92.3% (12/13, one clinical failure), and 83.3% (5/6, one clinical failure), respectively. Mean Eckardt score was significantly less at each of the follow-up periods (Table 3).

Management of relapses

In two children with clinical and objective failure after POEM, pneumatic dilatation was performed. Of these, one child did not respond to dilatation. This child underwent re-POEM via an alternate route subsequently. The other child responded well to two sessions of pneumatic dilatation (30 and 35 mm) and did not require re-treatment.

Gastroesophageal reflux disease

GER was assessed with symptoms, EGD and 24-h pH-impedance study at 3 months. The symptoms of GER including heartburn and or regurgitation were found in four children (10%). Twenty children underwent EGD, out of which 11 had evidence of erosive esophagitis (Los Angeles grade A = 3, grade B = 8). Thirteen children underwent 24-h pH-impedance study. Of these, three children had high esophageal exposure time (> 7%). Seven children were found to have elevated DeMeester scores (> 14.7). Five children had both elevated DeMeester scores and erosive esophagitis. In three children, erosive esophagitis was present with normal pH study. Of four children with symptomatic GER, objective evidence of GER (erosive esophagitis or positive Ph-impedance study) was detected in two children (Table 4).

Table 4 Evaluation of gastroesophageal reflux disease after peroral endoscopic myotomy at 3 months

	No. of patients
Total no. of patients at 3 months of follow-up	40
Symptoms (heartburn and regurgitation)	4 (10%)
Gastroscopy	20
Erosive esophagitis	11
Grade A esophagitis	3
Grade B esophagitis	8
24-h pH-impedance study	13
DeMeester score > 14.7	7
Esophageal acid exposure time %, median	4.7(0–26.9)
Esophageal acid exposure time > 7%	3
Both gastroscopy and 24-h pH study	12
Erosive esophagitis with abnormal pH impedance study	5
Abnormal pH study with normal endoscopy	2
Erosive esophagitis with normal pH impedance study	3

Discussion

In the present study, we found that POEM is a safe, effective, and durable management option for achalasia in children.

Achalasia is a neurodegenerative disease, which implies that it cannot be cured with the presently available treatment options which aim at reducing the lower esophageal sphincter pressure. The endoscopic armamentarium for the management of achalasia in children is limited to pneumatic dilatation and botulinum toxin injection. Both of these modalities do not have long-lasting efficacy and re-treatment is often required [5, 17]. In the absence of an effective and durable endoscopic treatment, Heller's myotomy is arguably the gold standard for the management of achalasia in children [18].

Table 3 Comparison of objective parameters of success before and after peroral endoscopic myotomy

	Pre procedure ($n = 42$)	Post procedure				p value
		1 years ($n = 28$)	2 years ($n = 18$)	3 years ($n = 13$)	4 years ($n = 6$)	
Eckardt score	6.86 ± 1.67	1.03 ± 0.88	1.33 ± 0.68	1.38 ± 0.87	1.33 ± 1.03	0.0001
LES pressure	36.25 ± 16.49	11.83 ± 5.68	–	–	–	0.0001
Integrated relaxation pressure (IRP)	33.45 ± 17.37	7.59 ± 3.32				0.0001
Timed Barium (> 50% emptying)	–	92.85%				

LES lower esophageal pressure

Table 5 Studies demonstrating the outcome of peroral endoscopic myotomy in children

Study	*n*	Prior treatment	Age in years mean/median (range)	Operative Time and orientation	Success (technical/clinical %)	Intra-operative adverse events	GERD Symptoms/esophagitis	Follow-up Days/months
Chen et al. (2015) [10]	27	Pharmacologic 8 BD-5 Botox inj.—1 Stenting—1	13.8 (6–17) (median)	39.4±17.4 (21–90)	96.3/100	33.3% Mucosal injury—5 Pneumothorax—1 Pain—2	19.2% Symptoms—2 Reflux esophagitis and Symptoms—1 Esophagitis—2	24.6 (15–38) months
Li et al. (2015) [26]	9	All treatment naïve	14.1 (10–17) (mean)	56.7 (40–105)	100	1% Subcutaneous emphysema—1	1% Reflux esophagitis	16.3 (3–30)
Tan et al. (2016) [27]	12	–	13.7 ± 2.6		100/100	8.3% subcutaneous emphysema	2 (16.7%) Symptoms and Reflux esophagitis	3–36 months
Nabi et al. (2016) [9]	15	BD—6 HM—1 BD and HM—1	14 (9–18) (median)	100 (38–240) Anterior—13 Posterior—2	100/100	46.7% Capnoperitoneum—1 Retroperitoneal air—3 Subcutaneous emphysema—2 Mucosal Injury—1	Symptoms − 3 (30%) Reflux esophagitis 2 (20%)	15 (12–20) months
Kethman et al. (2017) [22]	10	–	13.4 (median) (7–17)	142 (60–259) 3–4 o'clock	100/80	30% Pneumothorax Pneumoperitoneum Mucosal injury	–	1 month
Miao et al. (2018) [11]	21	BD—1	5.5 (median) (0.9–18)	40 (30–55)	100/100	57% Subcutaneous emphysema—4 Pneumoperitoneum—1 Mediastinal emphysema—4 Pneumonia—1 Mucosal injury—1	6 (28.57%) Symptoms	13.2 months (3–24)
Nabi et al. (2018)	10	BD—2	14.2 ± 2.74 (9–18)	47.6 ± 19.74 (30–98) Anterior—70%	100/90	40% (insufflation related)	–	131 days (39–255)

BD balloon dilatation, *HM* Heller's myotomy, *GERD* gastroesophageal reflux

POEM is a minimally invasive endoscopic treatment for achalasia. There is ample evidence the efficacy and safety of POEM in adult patients with achalasia [6, 19, 20]. However, the current body of evidence is limited to small case series with short follow-up in pediatric age group (Table 5) [8–11, 21, 22]. Moreover, the incidence of GER after POEM has not been objectively assessed in children.

In this study, we comprehensively analyzed the outcomes of POEM in a relatively large cohort ($n = 43$) of children with achalasia. POEM could be successfully performed in most of the children, implying that in expert hands POEM is technically feasible in pediatric population as well. We did not attempt POEM in one child due to small size (weight 7 kg). In another child, POEM was deferred for 4 weeks due to aspiration pneumonia and severe stasis esophagitis. The child was managed with nasogastric tube feeding and subsequently POEM was successfully performed. POEM is difficult to perform in infants due to several reasons. The accessories used in POEM including coagulation forceps and electrosurgical knives are not compatible with pediatric gastroscopes. In the absence of dedicated accessories designed for pediatric use, it may not be advisable to perform POEM in small infants. Another potential reason for technical difficulty and failure to perform POEM is the

presence of submucosal fibrosis [6, 10, 23]. Prior treatment with balloon dilatation or botulinum toxin injection have been proposed as potential risk factors for submucosal fibrosis. However, we did not encounter severe submucosal fibrosis in any of the children who received prior treatment (41%, mainly pneumatic dilatation). In our opinion, long duration of disease is a more relevant factor predisposing to submucosal fibrosis [23]. Therefore, the technical feasibility of POEM may not be hampered by previous treatment.

The mean procedure time in the present study was little over an hour (65.46 ± 42.05 min). Operating time reduced with the operator's experience and the use of a new triangular knife. The new triangular knife is equipped with water jet and therefore, reduces the need to exchange accessories. Another potential advantage of the new knife is that it is more compact than the standard triangular knife. This in turn allows for effective spray coagulation with little collateral damage to the mucosa. We have previously demonstrated the utility of new triangular knife in children with achalasia [8]. In future, further refinement of accessories may decrease the technical challenges of POEM in this special age group.

We established the safety of POEM procedure in the present study. There were no major intra-operative adverse events. Minor complications were noticed in about one-fourth of the children. In our previous study, the occurrence of intra-procedural adverse events was higher (46.7%) [9]. Unlike the previous study, we used a standard definition of adverse events in the present study and did not consider clinically insignificant insufflation related occurrences as adverse events [24]. Out of 21 insufflation related events, nearly half did not require an intervention and therefore, were not regarded as adverse events. Adverse events have been variably defined in previous studies. Consequently, the reported rate of adverse events is widely variable (8.3–57%) (Table 5). A relatively high incidence of adverse events has been noticed in the study by Chen et al. The main reasons include the use of air instead of CO_2 for insufflation, and the use of post-operative CT scan [10]. CO_2 is absorbed much faster than air from the gastrointestinal tract and therefore, preferred over latter for insufflation. We do not recommend routine use of post-procedure CT scan as it increases the radiation exposure and usually does not aid in decision making.

The clinical efficacy of POEM was high in both short-term (92.8% at 1 year, 94.4% at 2 years) and long-term follow-up (92% at 3 years, 83% at 4 years). In previous studies, the clinical success has been 80–100% in short- and mid-term follow-up [8–11, 22, 25–27] (Table 5). In comparison to our study, clinical success was not determined objectively with timed barium swallow and esophageal manometry in previous studies. The success rate after POEM appears to be comparable to laparoscopic Heller myotomy (85%) [18]. Caldaro and colleagues compared POEM with Heller myotomy in 18 children with achalasia [25]. Mean operation time was shorter despite longer myotomy length in the POEM group. There was no manometric or clinical difference in the two groups on follow-up [25]. In contrast to Heller myotomy, relapse is frequent after balloon dilatation and re-treatment may be required in up to 71–90% of children [28].

In the present study, there were two relapses after POEM at 1 and 3 years of follow-up, respectively. Recurrence of symptoms to variable extent do occur in some patients with achalasia irrespective of the treatment modality used. Incomplete myotomy (< 2 cm) and fibrosis are responsible for majority of the failures after Heller's myotomy [29]. An extended gastric myotomy (3 cm) has been shown to improve the outcomes of myotomy for achalasia [30]. In POEM, difficulty in accurately identifying gastroesophageal junction and subsequently extending the myotomy may result in subsequent relapse of symptoms. The management strategy in patients with relapse after POEM has not been well studied. In adults, pneumatic dilatation, Heller's myotomy, and re-POEM have been performed with variable outcomes [31–33].

POEM was equally effective in prior treatment failure cases. These results are in concordance with previous studies in adult patients which conclude that POEM is efficacious in the management of prior treatment failure cases [7].

In the present study, we evaluated GER at 3–6 months after POEM. It is important to assess GER early to avoid delay in diagnosis and look for the need of long-term need of PPI therapy. GER was detected in over half of the children as assessed by 24-h pH-impedance study and EGD. On the contrary, clinical symptoms were found in only 2 children with objective evidence of GER. Therefore, it is important to objectively assess GER as the correlation between symptoms and objective evidence of GER is poor like in adults [34]. GER is an important adverse event after myotomy, be it endoscopic or surgical. Unlike Heller's myotomy, where fundoplication is usually performed to prevent post-operative GER. POEM is not accompanied with any anti-reflux procedure. Therefore, the occurrence of GER is probably more after POEM as compared to Heller's myotomy with fundoplication [35, 36]. In contrast to adults, the occurrence of GER with or without fundoplication (2.5% vs. 3%) did not differ significantly in a recent review [18]. Previous studies in children have evaluated GER with either symptomatology or EGD and may have underestimated the actual occurrence of GER. 24-h pH-impedance analysis is the gold standard for the evaluation of GER and should be performed when feasible. Consequently, the incidence of GER was higher in the current study as compared to previous studies (Table 5). In a study by Chen et al., clinical GER was found in 19% of children [10]. In our previous study, erosive esophagitis and clinical symptoms of GER were noticed in 20% and 30% of

children, respectively [9]. The long-term consequences of GER arising after POEM are not well known in pediatric patients. We routinely prescribe proton pump inhibitors to all the patients for first 3 months. Subsequently, medications are continued in children with objective evidence of GER. Endoscopic anti-reflux therapies including trans-oral fundoplication appear an attractive alternative to long-term PPIs in older children and deserve evaluation in future [37].

The strengths of our study include—large population size, long follow-up, standardized reporting of adverse events, and comprehensive evaluation of success and GER. The noteworthy drawbacks are—retrospective design, lack of objective confirmation of GER in about half of the children, and small number of children who completed 3 or more years of follow-up. The normative values of 24-h pH-impedance study have not been established in pediatric population. Therefore, we may have either underestimated or overestimated the occurrence of GER. There were no infants or children weighing less than 10 kg in our cohort. Therefore, the feasibility and safety of POEM in this subgroup of very small children cannot be ascertained from the present study.

Conclusion

POEM is a safe, effective, and durable treatment for achalasia in children. However, GER is a potential concern and should be evaluated in prospective studies before adopting POEM for the management of achalasia in children.

Author contributions RC and US were involved in collection and interpretation of data; ZN, MR, DNR, SD, RK (Rama Kotla) were involved in performing the procedure and drafting and revision of the article; MT and RK (Rakesh Ralapala) were involved in the conception and revision of the article.

Compliance with ethical standards

Disclosures Zaheer Nabi, Mohan Ramchandani, Radhika Chavan, Santosh Darisetty, Rakesh Kalapala, Upender Shava, Manu Tandan, Rama Kotla, and D.Nageshwar Reddy have no conflicts of interest or financial ties to disclose.

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