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ORIGINAL ARTICLE

Long-term outcomes of Heller's myotomy and balloon dilatation in childhood achalasia

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Abstract Achalasia is a rare esophageal motility disorder: its optimal treatment in children is still a matter of debate. Records of children treated for achalasia, over an 18-year period, were reviewed.

Forty-eight children (median age at diagnosis 10 years; range 3–17 years) were identified. Twenty-eight patients were initially treated with Heller's myotomy (HM) and 20 with balloon dilatation (BD). At last follow-up (median 3 years; range 1–5.5 years), 43.8% (21/48) of children were symptom free. The number of asymptomatic children was significantly higher among those treated initially with HM compared to BD (HM 15/28, 53.6% BD 6/20, 30%, $p < 0.05$). All children who underwent BD required HM due to symptom recurrence. The median (range) total number of procedures was significantly higher in the BD group (BD 3 (1–7); HM 1 (1–5); $p < 0.05$) with a shorter time to the second intervention (BD 14 months, 95%CI 4–24; HM 58 months, 95%CI 38–79; $p < 0.05$). Of 108 procedures, esophageal perforation occurred in two children after HM (two out of 48 HM procedures in total, 4%) and one child after BD (1/60, 1.7%).

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Conclusion: Less than half of children with achalasia are symptom free after initial treatment with either BD or HM. HM, however, when performed as first procedure, provided longer symptom-free period and reduced need for subsequent intervention.

What is Known:
• *Balloon dilatation (BD) and Heller's myotomy (HM) are safe and effective treatment options for achalasia.*
• *Controversy, however, exists regarding the most effective initial therapeutic approach.*

What is New:
• *HM with or without fundoplication may represent the initial therapeutic approach of choice.*
• *Initial BD may negatively affect the outcome of a subsequent HM.*

Abbreviations

BD	Balloon dilatation
CI	Confidence interval
DAS	Discharged to adult services
EBTI	Endoscopical botulinum toxin injection
EGD	Esophagogastroduodenoscopy
EGJ	Esophagogastric junction
F/U	Follow-up
GER	Gastro-esophageal reflux
GT	Gastric transposition
HM	Heller's myotomy
HR	Hazard ratio
LES	Lower oesophageal sphincter
SD	Standard deviation
Tx	Treatment

Introduction

Achalasia is an esophageal motility disorder characterized by defective relaxation of the lower esophageal sphincter (LES) during swallowing along with various degrees of esophageal body motility impairment [5, 43]. It is commonly accepted that the degeneration and dysfunction of the nitrinergic inhibitory neurons in the esophageal myenteric plexus results in an imbalance between the excitatory and inhibitory motor inputs, which in turn leads to eventual aperistalsis of the esophageal body and impaired LES relaxation [16, 19].

In the pediatric age group, achalasia is extremely rare, with an estimated incidence of 0.18/100.000 children per year in the UK [32, 33]. Progressive dysphagia for solids and liquids, chest pain, regurgitation of undigested food, cough and weight loss represent the most frequently occurring symptoms [36].

The specific diagnostic work-up includes imaging studies to rule out obstruction at the level of esophagogastric junction (EGJ), esophagoscopy with biopsy to rule out inflammatory pathologies and esophageal manometry to confirm the presence of impaired LES relaxation and define the patterns of esophageal body dysmotility [52].

The arsenal available for the management of childhood achalasia comprises a range of treatments including pharmacologic therapies, balloon dilatation (BD), Heller's myotomy (HM) and the novel technique of peroral endoscopic myotomy (POEM) [5, 15, 18, 31]. None of the aforementioned treatments are curative, but rather provide symptomatic relief by reducing LES pressure and, consequently, the EGJ outflow obstruction. Whilst the long-term pharmacologic treatments are not generally recommended [3, 6, 28, 51, 57], HM and BD are considered the main procedures for treating achalasia in both adults and children [1, 2, 4, 8, 10, 13, 14, 17, 21, 24, 27, 30, 35, 39, 42, 45–47, 52, 54, 56, 57]. In the absence of randomized controlled trials, limited data from retrospective reviews are available in children comparing the long-term outcome between the two therapeutic approaches [34, 49, 55].

The aims of the present study were to review our experience in the treatment of achalasia in a large cohort of children and compare the long-term outcomes of BD and HM.

Methods

A retrospective review of the medical records of children diagnosed and treated for esophageal achalasia at our institution (January 1995 to December 2012) was performed. Patients were identified from the Hospital's database and information collected included gender, age at the time of diagnosis, presenting symptoms, duration of symptoms, diagnostic modalities, initial and subsequent treatments (BD, HM), peri- and post-interventional/operative complications and outcomes. The diagnosis of achalasia was suspected on the basis of clinical history and barium contrast study showing the characteristic "bird's beak" appearance of the distal esophagus. The diagnosis was then confirmed with esophageal manometry (conventional or high resolution) showing defective LES relaxation with different degrees of esophageal body dysmotility. All patients had also undergone upper gastrointestinal endoscopy and biopsy to rule out other causes of dysphagia.

The study was approved by the Institutional Review Board of Great Ormond Street Hospital (registration number 13GA09).

Clinical assessment and therapeutic management

Our institution has not implemented a standardized protocol for the diagnosis, treatment and follow-up for patients with

esophageal achalasia. After the initial evaluation and confirmation of the diagnosis, the decision for the most appropriate management was mainly gastroenterologist and surgeon specific. It was based upon the presenting symptoms, the state of patient's health and the preferences of the child and its family. Follow-up was performed by either a gastroenterologist and/or surgeon, and treatment outcomes were assessed by utilizing Eckardt score as published elsewhere [10, 11]; standard post surgery/intervention follow-up appointments were organized initially at 1, 6 and 12 months and afterwards on a yearly basis or upon symptom recurrence. Eckardt score classified the clinical outcome as follows: stage 0 (scores 0–1), stage I (scores 2–3), stage II (scores 4–6), stage III (score >6). Children in stages 0 and I were considered to be in clinical remission whereas these in stages II and III were classified as treatment failure [10, 11].

Balloon dilatation

BD was performed under general anesthesia with endotracheal intubation. The balloon catheter was positioned fluoroscopically by an interventional radiologist over a guide wire at the level of LES. When no single balloon catheter was available in an appropriate size, two (or on one occasion three) balloons were simultaneously inflated (with dilute radiographic contrast, using 10-ml syringes) across the EGJ. The balloon was inflated until its walls appeared parallel on fluoroscopy (i.e. until any "waist" was abolished), left inflated for a maximum of 30 s and then deflated and removed. The effective diameter of the inflated balloon(s) was chosen according to the child's size and ranged from 14 to 39 mm. No routine post-interventional esophagograms were performed. Patients were treated as day cases as long as the procedure was uneventful.

Over the years, the balloon catheters used were Cristal (Balt Extrusion, Montmorency, France), Accent, Valvuloplasty and Omega NV (William Cook Europe, Bjaeversko, Denmark), XXL (Boston Scientific, Galway, Ireland), Maxi LD (Cordis, Cashel, Ireland) and Atlas (Bard Peripheral Vascular Inc., Tempe, AZ, USA).

Surgical technique

The institution's approach to the surgical esophagomyotomy (HM) has evolved over the years from an open abdominal procedure to the current laparoscopic approach. In the majority of cases, the HM was combined with an antireflux procedure. Details of the laparoscopic technique can be found in the article published by Pachl et al. in which the authors explored the outcome of HM in a group of children initially treated with surgery [37]. This group of patients is a subset of the cohort analyzed in the present study.

Statistical analysis

Patient and disease characteristics are expressed as mean ± standard deviation and as median (range) dependent on the normality of the distribution as assessed with Kolmogorov-Smirnov test. Patients were divided according to the type of initial treatment into two groups (HM, BD). Comparisons between groups for continuous variables were performed using t test or Mann-Whitney test as appropriate. Categorical variables were compared using chi-square or Fisher's exact test as appropriate. Furthermore, the adjusted effect of different factors (gender, age at onset of symptoms, time from onset of symptoms until initial intervention, age at first procedure and type of initial treatment) on the outcome (need for additional treatment after the initial management) was explored using logistic regression and Cox regression analysis. Kaplan-Meier curves were also derived by the type of initial management with mean times to second intervention and p values based on the log-rank test. Statistical analysis was performed with SPSS version 17.0 software (SPSS Inc., Chicago, IL). Statistical significance was set at the $p < 0.05$ level.

Results

Forty-eight children (21 male, 43.8%) with a diagnosis of esophageal achalasia were identified and included in the analysis. Four children were diagnosed as Allgrove syndrome (alacrima, achalasia, adrenal insufficiency). Dysphagia to either solids or liquids was the chief symptom prior to treatment. The median age at diagnosis was 10 years (range 3.2–17.4 years) with a median time (range) from the occurrence of initial symptoms suggestive of achalasia to initial treatment of 13 (7–22) months. The median follow-up duration after initial treatment was 3 years (range 1–5.5 years).

There were no statistically significant differences between the age at diagnosis, time from diagnosis to treatment, duration of follow-up and the choice of initial treatment, i.e. HM or BD. Baseline disease characteristics of the study population are summarized in Table 1.

Sixteen children were treated with calcium channel blockers or nitrates before surgery or balloon dilatation; two children had a single uneventful intrasphincteric (LES) endoscopical botulinum toxin injection as an interim measure for symptom alleviation prior to the definitive therapeutic procedure (HM and BD, respectively).

Twenty-eight patients (58%) were initially treated with HM and 20 with BD. Amongst children who underwent BD, two were under the age of 6 years (4 and 5 years old). Sixteen out of 18 children who underwent open HM also received concomitant antireflux procedures, whereas 10 out of 30 children had a combined HM with fundoplication in the laparoscopic

Table 1 Symptoms of the study population prior to the diagnosis of achalasia (number and percentage)

Presenting symptoms	Numbers (%)
Dysphagia	48 (100)
Regurgitation/vomiting	28 (58)
Weight loss	9 (20)
Cough	9 (20)
Failure to thrive	6 (13)
Chest pain	6 (13)
Prolonged feeding time	3 (7)
Abdominal pain/post-prandial distress	3 (7)
Stridor/hoarse voice	2 (4)
Odynophagia	1 (2)
Heart burn	1 (2)
Recurrent chest infections	1 (2)

approach. Noteworthily, in two children, an antireflux procedure (one Nissen and one Thal, respectively) was performed independent of HM for the treatment of gastro-esophageal reflux (GER) which was refractory to medical treatment.

At the last follow-up, 21 children in total (44%) were asymptomatic (Eckardt clinical stage: 0), within which there was a statistically significant higher proportion of those who underwent HM as the initial intervention (HM 15/28, 54% BD 6/20, 30%, $p < 0.05$). Subsequent procedures were required in 28 children, of whom 13 underwent HM and 15 BD as a second intervention. Twenty-two patients had more than three procedures. The median (range) number of total interventions was significantly higher in children initially managed with BD compared to the HM group (BD 3 (1–7); HM 1 (1–5); $p < 0.05$). Table 2 presents the outcome at last follow-up compared to the initial treatment. A subgroup analysis revealed that the proportion of symptom-free children was significantly lower in the group that had undergone BD as first and HM as subsequent (second) treatment (6/16, 37%) as compared to patients who had HM as first procedure (15/28, 54%) ($p < 0.01$). Patient flow through the study is shown in Fig. 1, which summarizes the initial and subsequent treatments.

Logistic regression analysis was performed to assess the effect of various factors on the need for a second intervention. The type of first procedure was the only factor found to significantly determine the outcome (HR 0.08, 95%CI 0.01–0.40, $p < 0.01$) (Table 3). Survival analysis with log-rank test demonstrated that patients undergoing BD as first procedure had a higher rate of second intervention (BD 17/20, 85%; HM 11/28 39%; $p < 0.01$) with shorter time to it (mean time BD 14 months, 95%CI 4–24; HM 58 months, 95%CI 38–79; $p < 0.001$) (Fig. 2).

Peri- and immediate post-operative/interventional complication rate was 2.7% overall. Specifically of a total of 108 procedures, esophageal perforation occurred in two children after HM (2/48) and in one child after BD (1/60).

After treatment, 11 patients (11/48, 23%) reported symptoms suggestive of GER, which was objectively proven by either esophagogastroduodenoscopy (EGD), pH-metry or pH-Impedance in five of them. There were no deaths.

Discussion

Current treatments available for childhood achalasia rely on improvement of symptoms by relieving the EGJ outflow obstruction induced by the defective LES relaxation during swallowing, rather than establishing esophageal peristaltic motor sequences [5, 16].

The optimal initial procedure for childhood achalasia remains a matter of debate and controversy with several studies reporting conflicting results [1, 10, 25, 26, 29, 37, 38]. However, whilst BD achieves short-term symptomatic improvement, there is a high requirement for subsequent interventions [40]. This finding was supported in our cohort too, as the total number of procedures was significantly higher in children initially managed with BD. Of children who underwent HM as initial treatment, 53.6% were asymptomatic requiring no further intervention whereas 85% of patients who had BD as the initial procedures required subsequent treatment. These results are in agreement with other published studies although the recurrence of symptoms in our cohort was higher for the BD group [1, 29, 37, 38]. Our findings
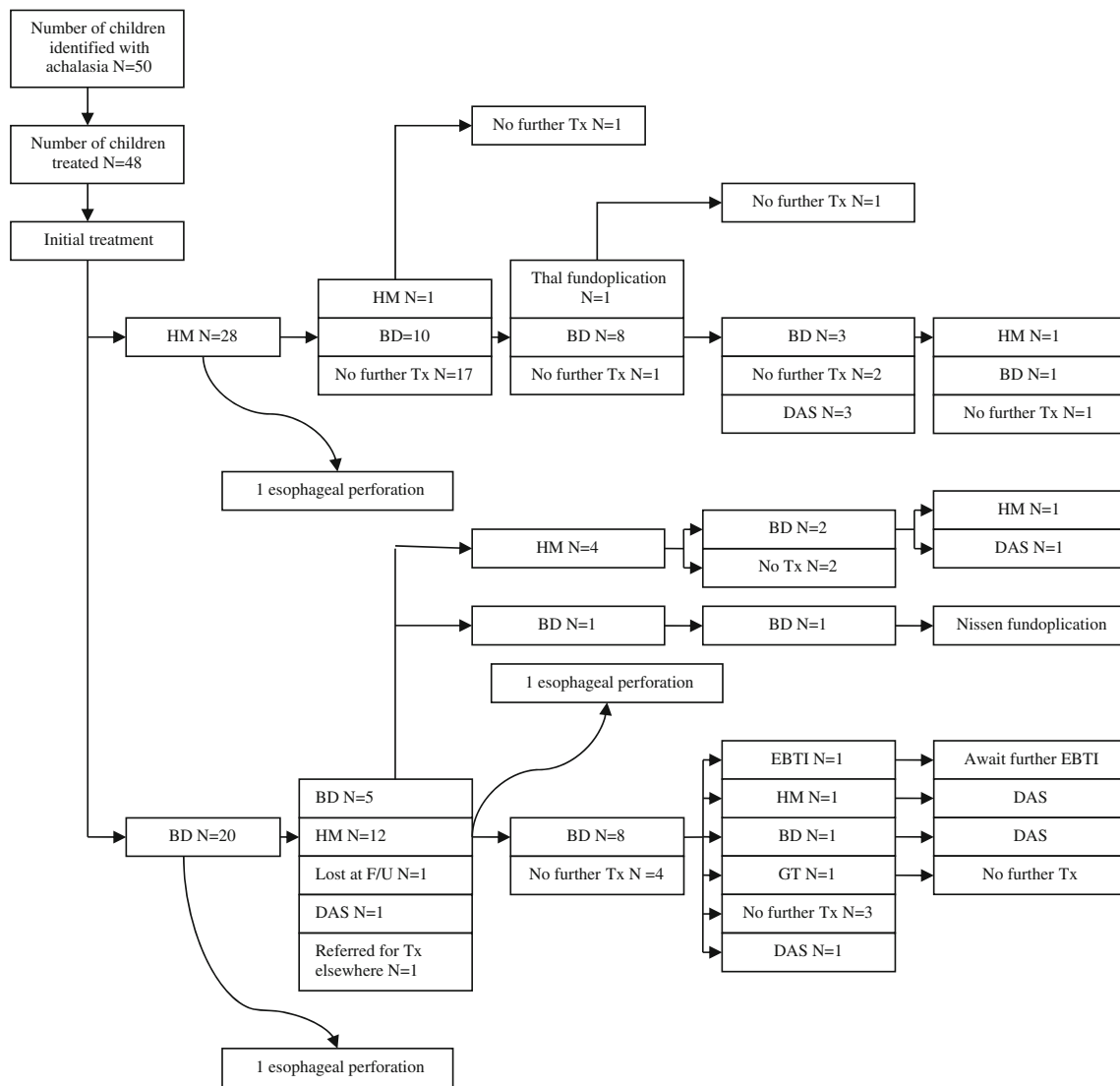
Table 2 Effect of the initial treatment on the patients' outcome

	Eckardt clinical stage at last follow-up				Eckardt score	
	0 No. of patients (%)	I No. of patients (%)	II No. of patients (%)	III No. of patients (%)	Baseline median (range)	Last follow-up median (range)
HM (n = 28)	15 (54) *	12 (43)	1 (4)	0	7 (5–9)	0.5 (0–4)[a]
BD (n = 20)[b]	6 (30)	6 (30)	5 (25)	1 (5)	7 (5–8)	2 (0–7)

*$p < 0.05$ versus BD by Fisher's exact test

[a] $p < 0.05$ versus BD by Mann-Whitney test

[b] Two patients were lost at follow-up

Fig. 1 Flow-chart of initial and subsequent treatments in the cohort of achalasia patients (*Tx* treatment, *GT* gastric transposition, *EBTI* endoscopical botulinum toxin injection, *DAS* discharged to adult services, *F/U* follow-up)

contradict two recent studies in children, which report a long-term remission rate of 66.7% after a single BD and a complete remission of 65% after a 2-year follow-up period after repeated BD [10, 26]. Furthermore, our data do not compare favourably with the long-term results of the European

Table 3 Effect of different variables on the need of a second intervention (logistic regression model)

Covariates	HR	95%CI	*p* value
Gender	1.07	0.38–2.96	0.8
Age at onset of symptoms	1.41	0.32–6.23	0.6
Time from onset of symptoms until treatment	0.49	0.91–1.19	0.4
Age at first procedure	0.90	0.19–4.13	0.8
Type of initial intervention	0.08	0.01–0.40	0.002

HR hazard ratio, *CI* confidence interval

achalasia trial, which, after at least 5 years of follow-up, revealed comparable success rate for both HM and BD [35]. Differences in the dilatation protocol (e.g. implementation of a graded BD with re-assessment of the patient at regular intervals to decide whether an additional BD is required) and the dilatation technique per se (e.g. size of the balloon, number of dilatations per session, maximum balloon pressure, duration of dilation at maximum balloon pressure) between various centers could explain these discrepancies as they may account for variable effect on the disruption of the LES fibers during the procedure [12, 48]. Clearly, the HM group had the most favourable outcome with the highest remission rate and a longer period before a subsequent intervention compared to BD. The therapeutic efficacy of HM in the present cohort is in agreement with that shown in other studies in both pediatric and adult populations [1, 8, 17, 29, 37, 46, 55]. HM's superiority in terms of favourable outcome compared to BD could

Fig. 2 Kaplan-Meier curve of the time from first to second intervention by type of initial management
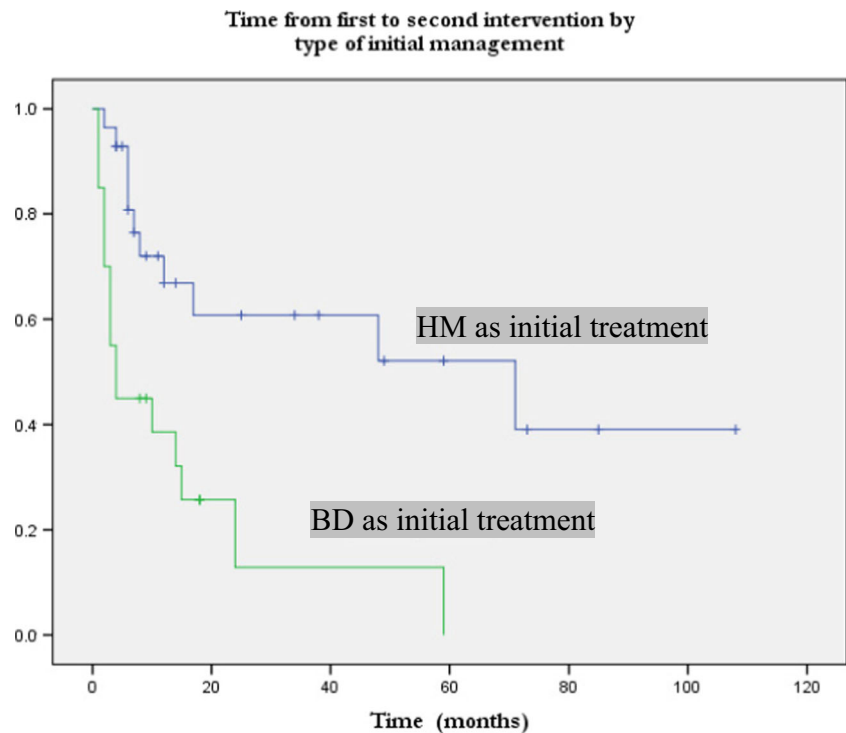
be explained by the fact that it offers a more complete dissection of the LES fibers and, consequently, a more efficient esophageal clearance and relief of dysphagia [8, 50]. In this series, 16 patients underwent HM after a non-relieving initial BD. At the last follow-up, 6/16 (37%) were at Eckardt clinical stage 0, 5/16 (31%) were at stage I and 5/16 (32%) at stage II. Children who underwent HM as their initial procedure were asymptomatic in a significantly higher percent (15/28 Eckardt clinical stage 0, 12/28 stage I, 1/28 stage II) (Fisher's exact test, $p < 0.01$). Our data raise the possibility that a history of a previous BD may negatively affect the success of a future HM and do not demonstrate the favourable outcome shown by others [20, 22, 29]. It has been speculated that this could be because BD scars the submucosal layers of the esophagus by causing microhemorrhages, inflammation and subsequent formation of fibrotic tissue which may make a future HM technically more difficult, less effective, with an increase in intra-operative complications [23, 41]. Nonetheless, BD may be utilized as an appropriate second-line intervention, especially in symptomatic patients who were initially managed with HM to further widen the already divided esophageal musculature and to distract any fibrotic tissue or adhesions which may have formed post initial HM. The latter was also reported in the study published by Pachl et al. [37].

In the present cohort, more than half of the esopha-gomyotomies (26 out of 48) were combined with a fundoplication. The majority of the antireflux surgery (16 out of 26 procedures) took place during the open abdominal HM procedure. Eleven out of 48 children reported symptoms

indicative of GER, which was objectively demonstrated in five patients (10.4%); the latter is in accordance with the results published by other researchers [24, 38, 53, 57]. However, we did not identify any significant association between the occurrence of post-intervention GER and type of initial treatment (BD, HM), type of HM (open or laparoscopic approach, combined or not with fundoplication) and the type of fundoplication (Nissen or Dor). It has been shown that the dissection of the LES fibers is less extensive during a laparoscopic HM, i.e. the myotomy is adequate to alleviate dysphagia but not so extensive to compromise the physiological barriers against GER (especially the angle of His) which are therefore preserved [44]. Although a recent systematic review with meta-analysis in adults supported HM with fundoplication as the best initial treatment for esophageal achalasia, there are several studies in pediatrics suggesting that HM without fundoplication is an adequate and effective initial treatment [9, 53, 54]. This area is controversial and open to opinion.

We did not find any statistically significant differences between HM and BD in peri- or post-operative adverse events. In our series of patients, three procedural esophageal perforations were observed (three complications out of 108 procedures in total) which accounts for a complication rate of 2.7%. Two perforations occurred after HM (one HM was the primary procedure and the other after a BD) and one after BD (initial procedure). Perforations after HM were diagnosed peri-operatively whereas in BD, this complication was diagnosed within an hour post procedure. All perforations were

managed conservatively and the patients recovered without any further events. The adverse events and the complication rates in the present cohort compare favourably with previous published data [29, 40].

Undoubtedly, this study bears certain limitations that affect the significance of our results. Firstly, this is a retrospective study embracing the well-known limitations of this type of methodology, such as incomplete data, and reliance on child and parental recall. However, using different strategies for data extraction, such as a structured form created a priori, we aimed to minimize the limitations and increase the reliability of our data. Secondly, despite describing the largest single-center cohort in pediatric achalasia, the number of patients is relatively small. Thirdly, the surgical approach has changed over the time from an open abdominal procedure to the current laparoscopic approach. Although no differences were found on the outcome between patients treated with different therapeutic techniques, suggesting that different types of surgery do not seem to affect the final outcome, the sample size and potential skewing of the data might be the source of a type II error that has affected our findings. Finally, there was neither randomization of patients to different therapeutic modalities nor a standardized algorithm/protocol for the evaluation, management and follow-up of patients. As a result, a potential bias on the outcomes amongst treatment groups cannot be excluded. However, we do believe that our study adds important data on a rare condition and aids to further enlighten clinicians on the best initial approach of an entity with a continuously evolving management [7].

In conclusion, our data indicate that both HM (with or without an antireflux procedure) and BD are safe and effective for the treatment of childhood esophageal achalasia. However, in the absence of any evidence from randomized controlled trials, HM with or without fundoplication may be the favoured initial therapeutic approach for childhood achalasia, as it may lead to a higher remission rate, a longer symptom-free period and a more favourable long-term outcome. A well-designed multicenter randomized controlled study is, however, needed to definitively confirm our findings.

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