Endoscopic Electrocautery Incisional Therapy as a Treatment for Refractory Benign Pediatric Esophageal Strictures

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See ''Cutting-edge Treatment for Benign Pediatric Esophageal Strictures, a Step Forward, More to Go'' by Mark and Narkewicz on page 433.

ABSTRACT

Background and Aim: Refractory esophageal strictures are rare conditions in pediatrics, and are often due to anastomotic, congenital, or caustic strictures. Traditional treatment options include serial dilation and surgical stricture resection; endoscopic intralesional steroid injections, mitomycin C, and externally removable stents combined with dilation have had variable success rates. Although not as widely used, endoscopic electrocautery incisional therapy (EIT) has been reported as an alternative treatment for refractory strictures in a small number of adult series. The aim of the study was to evaluate the safety and efficacy of EIT in a pediatric population with refractory esophageal strictures.

Methods: A retrospective chart review was conducted on all patients who underwent EIT for esophageal strictures (May 2011–September 2017) at our tertiary-care referral center. A total of 57 patients underwent EIT. Procedural success was defined as no stricture resection, appropriate diameter for age, and fewer than 7 dilations within 24 months of first EIT session. This corresponded to the 90th percentile of the observed number of dilations in the data. All patients included in the study had at least 2-year follow-up.

Results: A total of 133 EIT sessions on 58 distinct anastomotic strictures were performed on 57 patients (24 girls). The youngest patient to have EIT was 3 months old and 4.8 kg. There were 36 strictures that met the criteria for refractory stricture and 22 non-refractory (NR) strictures. The median number of dilations before EIT therapy was 8 (interquartile range [IQR]: 6–10) in the refractory group and 3 (IQR: 0–3) in the NR group. In the refractory group, 61% of the patients met the criteria for treatment success. The median number of dilations within 2 years of EIT in the refractory group was 2 (IQR: 0–4). In the NR group, 100% of the patients met criteria for success. The median number of dilations within 2 years of EIT in the NR was 1 (IQR: 0–2). The overall adverse event rate was 5.3% (7/133), with 3 major (2.3%) and 4 minor events (3%).

Conclusions: EIT shows promise as an adjunct treatment option for pediatric refractory esophageal strictures and may be considered before surgical resection even in severe cases. The complication rate, albeit low, is significant, and EIT should only be considered by experienced endoscopists in close consultation with surgery. Further prospective longitudinal studies are needed to validate this treatment.

Key Words: dilation, esophageal atresia, esophageal dilation, esophageal Stricture, esophagus, incisional therapy, recalcitrant stricture, refractory stricture

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What Is Known

- First-line treatment for esophageal strictures is balloon or savory dilation.
- There is no accepted pediatric definition for refractory esophageal stricture.
- The success rate of currently available adjunct treatments to esophageal dilation is variable in the literature, and therefore, none are universally recognized as first-line adjunct therapy to dilation.

What Is New

- Endoscopic electrocautery incisional therapy shows promise as an adjunct treatment option for pediatric refractory esophageal strictures and may be considered before surgical resection.
- We have proposed a stricture classification system to help standardize future studies.
- Endoscopic electrocautery incisional therapy complication rate is higher than standard dilation, and therefore should be undertaken only by an endoscopist with therapeutic experience.

BACKGROUND

Esophageal stricture in pediatrics is a rare but difficult condition to treat. A common cause of strictures requiring therapy in pediatrics is anastomotic, secondary to esophageal atresia (EA) repair (1). Other benign strictures include caustic, peptic, eosinophilic esophagitis, and congenital. Traditional treatment options include balloon or mechanical dilation of the esophagus.

In adults, a proposed definition of a refractory stricture is when there is an inability to remediate the esophageal lumen to a diameter of 14 mm during 5 dilation sessions at 2-week intervals (2,3). An alternate definition that has been reported is requiring ≥7 dilations without time frame with an inability to maintain a lumen size to allow passage of solid food (4). There are no agreed-upon definitions for refractory strictures in pediatrics.

Adjunct treatments to esophageal dilation include intralesional steroid injections, topical application or intralesional

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injection of mitomycin C, and placement of externally removable stents. The success rate of these treatments is variable in the literature, and therefore, none of these therapies are universally recognized as first-line adjunct therapy to dilation. If these treatments are not successful, many patients with refractory strictures will opt for surgical stricture resection. These surgeries are, however, not without risk, and patients may still suffer from recurrent strictures afterwards. Endoscopic electrocautery incisional therapy (EIT) has been reported in a small number of adult series as an alternative treatment for refractory strictures. We retrospectively looked at our experience as a tertiary-care referral center that provides endoscopic treatment for pediatric esophageal strictures to evaluate the efficacy and safety of EIT.

METHODS

We performed an institutional review board-approved retrospective chart review on all patients who underwent EIT for esophageal strictures from May 2011 to September 2017 at our institution. Pertinent clinical data were recorded from patient charts, and endoscopy, surgical, and radiology reports. Recorded patient information included sex, age, weight, number of balloon dilations, and number of EIT sessions per patient. The diameter of the esophagus was based on a combination of measurements taken with fluoroscopy, which was performed on all patients at the time of dilation and endoscopy, using the diameter of the scope and radiographic ruler as a reference. A refractory stricture for this study was defined as inability to remediate the esophageal lumen with 5 dilatations performed within 5 months to a diameter of

A. 8 mm or greater in children <9 months of age
B. 10 mm or greater in children 9 to 23 months of age
C. 12 mm or greater in children 24 months to 5 years of age
D. 14 mm or greater in children 6 years or greater

Our second definition for refractory stricture was the requirement of ≥7 dilations, regardless of time frame, with an inability to maintain the lumen to the above-mentioned sizes.

There are variations in the EIT technique reported in the literature. Our EIT technique involves the use of a needle knife to make incisions into a stricture at its most dense points. We use the Huibregtse needle knife papillotome (Cook Medical, Winston-Salem, NC) to perform EIT. This needle knife can pass through a 2.0-mm working channel, allowing the pediatric endoscopist to perform EIT with a slim pediatric endoscope. The ERBE electrosurgical generator (ERBE, Tübingen, Germany) applies a cut current to make the incision. We use either the ERBE ICC 200 or ERBE VIO 300 D generator. When using the ERBE ICC 200, we use settings of 100W with effect 2 or 3, and when using the ERBE VIO 300 D, we use Endo Cut I (effect 2, cut duration 2, cut interval 3). After one or more incisions are made, balloon dilation is usually performed to cause preferential tearing at those incision sites (Fig. 1) (5,6).

Our primary outcome was treatment success at 2 years defined by the following: ability to maintain a lumen size appropriate for age as described above, whether or not a stricture resection was required, and by the number of dilations within 2 years of the first EIT session. Using the observed data, we determined a dilation cutoff corresponding to the 90th percentile of the number of observed balloon dilations among the EIT patients. This statistical approach resulted in a cutoff of 7 dilations. Thus, a treatment success at 2 years following EIT was defined as no stricture resection, appropriate diameter for age, and fewer than 7 dilations in the 2 years following the first EIT session.

Patients in general were referred for stricture resection in the refractory group after the first or second EIT session, if we did not see any improvement in esophageal diameter or if there was worse narrowing. Therapy with further EIT or balloon dilation typically continued if we saw interval improvement in clinical symptoms and esophageal diameter. Patients who continued with further dilations or EIT past the number 4 were either showing clinical improvement or refused surgical resection despite our recommendation.

All statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, TX). Normality was assessed by the Shapiro-Wilk test for each variable. Due to skewedness of all variables, values for continuous variables are reported as medians and interquartile ranges (IQR; 25th–75th percentile). Categorical variables are reported as frequencies and percentages. Median values of continuous variables were compared between the refractory group and the non-refractory (NR) group using the Wilcoxon rank-sum test, and categorical variables were compared between the 2 groups using the Chi-square test. Statistical significance was set at $P < 0.05$.

Secondary outcomes of the study were adverse events. A minor adverse event (MAE) was defined as a contained esophageal leak. Major complications were defined as a non-contained esophageal leak and/or significant bleeding requiring an intervention such as a blood transfusion, or endoscopic or surgical therapy.

RESULTS

Clinical Characteristics

We have summarized the clinical characteristics of our patients in Table 1. A total of 133 EIT sessions on 58 distinct anastomotic strictures were performed on 57 patients. One of the 57 patients had EIT performed on their refractory stricture that failed to remediate the stricture and subsequently had a stricture resection. This patient then developed another anastomotic stricture that was also treated with EIT, which gave us the total number of 58 strictures. There was no statistically significant difference in age, weight, or sex between the refractory and NR group. The youngest patient to have EIT was 3 months old and 4.8 kg. There were 36 strictures that met the criteria for refractory stricture and 22 NR strictures. In the refractory group 30 of the 36 patients met the primary definition for refractory stricture of a minimum of 5 dilations within a 5-month period and 6 met the second definition for refractory stricture. The median number of dilations before EIT therapy was 8 (IQR: 6–10) in the refractory group and 3 (IQR: 0–3) in the NR group.

Treatment Outcomes

EIT procedural success is summarized in Table 1. In the refractory group, 61% of the patients met the criteria for treatment success. The median number of dilations within 2 years of EIT therapy in the refractory group was 2 (IQR: 0–4). Looking further into the refractory group, the number of dilations before EIT was not associated with success ($P = 0.412$). The median number of dilations before EIT in the refractory group was 8 (IQR: 6–9) among successes and 9 (IQR: 6–10) among non-successes. The median number of EIT sessions performed in the refractory group was 2 (IQR: 1–3). The median change in diameter of the stricture between the start of EIT and at conclusion of therapy was an increase of 6 mm (IQR: 1–7).

In the NR group, 100% of the patients met criteria for success. The median number of dilations within 2 years of EIT in the NR group was 1 (IQR: 0–2). The median number of EIT sessions performed in the NR group was 1 (IQR: 1–2). In looking at

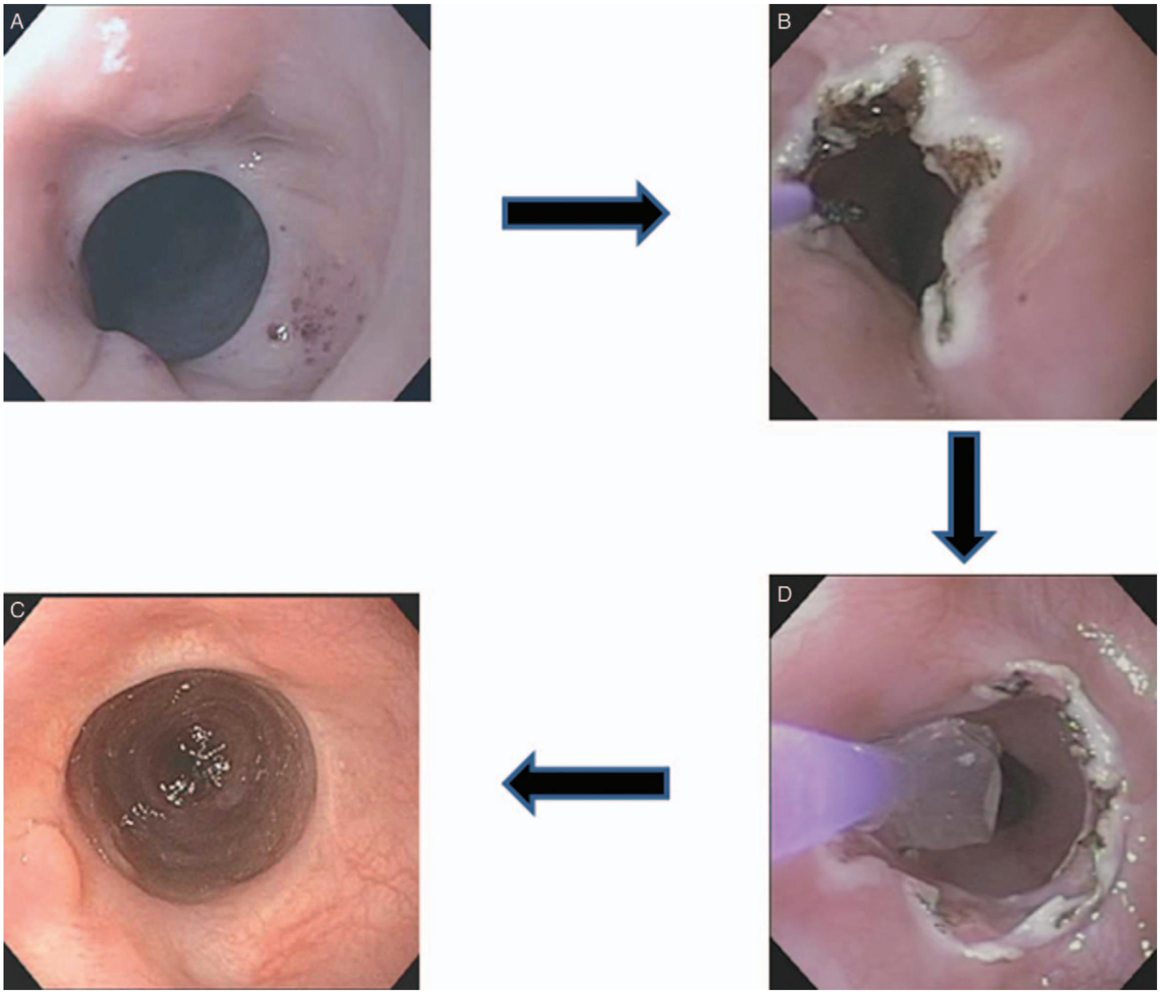

FIGURE 1. Technique of endoscopic electrocautery incisional therapy. A, Esophageal anastomotic stricture with incomplete ring or ''shelf'' of scar tissue. B, Incisional therapy is performed only on the area of the incomplete ring using a needle knife and a cutting electric current. C, After incisional therapy, a balloon dilator is past across the area and inflated to extend the tearing initially done by the needle knife. D, Follow-up endoscopy shows a widely patent anastomosis with minimal evidence of a ring or shelf.

the increase in esophageal diameter, the median change in diameter of the stricture in the NR group was a 7 mm increase (IQR: 5–8).

Comparison of Groups

In comparing the refractory stricture group to the NR group, there were statistically significant differences in both groups. As expected, the number of dilations before EIT was statistically higher in the refractory group ($P < 0.001$). The increase in diameter post-EIT was higher in the NR group, 7 (IQR: 5–8) versus 6 (IQR: 1–7; $P < 0.001$). Lastly, treatment success was significantly higher in the NR group, 100% versus 61% ($P < 0.001$). There was no statistical difference in the median number of EIT sessions or

TABLE 1. Comparison of refractory versus non-refractory groups.

	Refractory (n = 36)	Non-refractory (n = 22)	Total (n = 58)	*P*
Age, months	23 (15–40)	24 (13–37)	24 (14–39)	0.898
Weight, kg	11 (8–14)	11.5 (9–14)	11 (9–14)	0.631
Number of dilations before EIT	8 (6–10)	3 (0–3)	5 (3–8)	<0.001*
Number of dilations within 2 year following EIT	2 (0–4)	1 (0–2)	1 (0–2)	0.085
Total number of EIT sessions	2 (1–3)	1 (1–2)	2 (1–2)	0.215
Change in diameter (mm)	6 (1–7)	7 (5–8)	6 (3–8)	0.049*
Treatment success at 2 years	22 (61%)	22 (100%)	44 (76%)	<0.001*

Values are median (interquartile range) for continuous variables and frequency (percent) for categorical variables. *P* values comparing refractory group to non-refractory group obtained using the Wilcoxon rank-sum test or the Chi-square test as appropriate. EIT = endoscopic electrocautery incisional therapy.
*$P < 0.05$.

TABLE 2. Adverse events secondary to endoscopic electrocautery incisional therapy

Adverse event rate	n (%)
Overall adverse event rate	7/133 (5.3%)
Minor adverse event rate	
Contained leak	4/133 (3%)
Major adverse event rate	
Non-contained leak	3/133 (2.3%)

median number of dilations within 2 years following EIT between both groups (see Table 1).

Adverse Events

The overall adverse event rate for EIT was 5.3% (7/133). There were 3 major adverse events and 4 MAEs. All minor events were small contained leaks that required no intervention; patients were discharged home within 24 hours of the procedure. All major adverse events were non-contained esophageal leaks, which occurred in 2.3% (3/133) of the EIT cases. There were no bleeding events associated with EIT. All patients with a major adverse event healed without surgical intervention (Table 2).

DISCUSSION

The use of incisional therapy in the esophagus was first described in the treatment of Schatzki's rings and an esophageal stricture of unknown origin (7,8). It has been subsequently reported in small case series of the treatment of esophagogastric and esophagojejunal anastomoses with good success (5,9). Hordijk et al (10) performed a prospective randomized study comparing EIT to Savary bougienage for treatment of naïve esophagogastric strictures. In this study of 62 patients (n = 31 in each study arm), there was no significant difference between groups in the mean number of dilations at 6-month follow up (2.9 vs 3.3; $P = 46$). Both Simmons and Hordijk, however, demonstrated improvement of refractory strictures using EIT with 12 to 14-month follow-up in retrospective studies (6,11). The largest study to date looking at refractory strictures was Muto et al (12), who performed EIT in 32 patients with refractory esophagojejunal strictures. Long-term follow-up was available for 21 patients at 12 months with a 62% success rate. In pediatrics, there is a paucity of literature on EIT. To date there is only 1 published case series in children, which looks at 7 patients. In this series, all children showed symptomatic improvement after EIT (13).

Our study demonstrates 61% treatment success in children with refractory anastomotic strictures. If we compare EIT to other adjunct therapies for refractory strictures, we see that EIT is comparable or superior. The use of intralesional steroid injection has long been reported as an adjunct therapy for refractory strictures. In the largest study to date, in adults with anastomotic strictures, the reported success rate was 45% (14). The success of mitomycin C in the literature has been variable. In one study of 16 patients, the reported success rate was 62.5%; however, this was a mixed stricture population, and the subgroup success for EA strictures was lower at 50% (15). The largest published study to date looking at mitomycin C in EA patients looked retrospectively at 21 patients. In this study, 11 patients received mitomycin C topically, and were compared to 10 historical EA controls. The authors demonstrated that the results were not significantly different to the control group (16). There are also reports of mixed success with esophageal stenting. Most positive outcomes in pediatrics have been with small case series (17–19). Our group has published the largest study to date, retrospectively looking at self-expanding stents for the treatment of EA anastomotic strictures (20). In our study, 23 patients with EA underwent a total of 40 stenting sessions. The success rate for stent placement of $\geq$30 days was 39% (9/23), and the 90-day success rate was only 26% (6/23).

Weaknesses of all these studies are lack of consensus on the definition of a refractory stricture, pooling strictures of different etiology into 1 category, and having no clear definition of treatment success. One significant obstacle of our study is the lack of a definition of pediatric refractory strictures. The adult definition, which is not universally accepted, is also not completely applicable to pediatrics. In this study, we attempted to define refractory stricture based on a modification of the adult criteria as previously defined. The authors hope that our proposed definitions can serve as the basis to standardize future research in the field of refractory esophageal strictures. To determine treatment success, we looked at all patient dilations in patients who had EIT. To eliminate the extremes of treatment we chose the 90 percentile as our cutoff for success. This came to <7 dilations in 2 years. It is important to note that the median number of dilations after the first EIT for both the refractory and NR group was much lower than this cutoff, at 2 dilations and 1 dilation, respectively.

Although the NR group had a 100% success rate, the authors acknowledge that without a randomized study we cannot prove that EIT directly caused success. We do want to point out, however, that median dilation after EIT was 1, and there was also a large increase of diameter at 7 mm. This data could imply that attempting EIT earlier may be beneficial, but further studies are needed. In the refractory group, there was no difference between success and non-success based on prior number of dilations, so this infers that EIT can still be attempted even in cases where numerous dilations have previously been tried.

The authors believe that, more important than the prior number of dilations, the contours of the stricture are a better predictor of success rather than prior number of dilations. Many strictures are not symmetrical. Many times thick scar tissue is adjacent to more normal tissue, which gives a shelf-like appearance to the stricture. This can certainly be the case in patients who have undergone multiple esophageal dilations; however, this can also be seen early on, depending on how the anastomosis was initially sutured and how it healed. This shelf of scar tissue is particularly amenable to EIT, more than a completely circular stricture. In the asymmetric stricture, the needle allows us to cut directly into the shelf to widen this area, whereas a balloon or bougie, which exerts force equally in all directions, will more likely tear less dense tissue adjacent to the thicker shelf. Many patients will have multiple dilations and make minimal to no progress because the same less-dense scarred area is tearing repeatedly, while the denser esophageal scar sections that are contributing most to the narrowing go unaddressed. The use of fluoroscopy in this process is extremely helpful to identify asymmetry of the stricture: When an indentation or shelf is seen on x-ray that is a good indication EIT could be successful. In addition, it is helpful to understand that EIT does not always end with the incisions. In many instances after the incision has been made, we follow with balloon dilation, which further tears the esophagus where the incisions were made. The balloon is analogous to blunt dissection in the way it spreads open the scar tissue. Understanding that balloon dilation will expand and deepen the incisions allows us to make shallower incisions to minimize perforation.

We report a severe adverse event rate of 2.3%, which is higher than the reported pediatric literature perforation rate with balloon dilation of 0.9% to 1.8% (1). Therefore, EIT should be performed by endoscopists with advanced training and utilizing fluoroscopy during the procedure. We also want to stress the importance of surgical consultation before performing EIT in pediatric patients. Although none of our 3 patients with complications required surgery, it was our fallback treatment option had endoscopic interventions failed. Fortunately all these children healed with endoscopic intervention only, including clipping of the perforation, stent, or endoscopic vacuum sponge therapy. We reported a 3% MAE rate. Due to the retrospective nature of the data it is possible that MAE could be underreported. This study is limited by its retrospective look at the data and a lack of control group. In addition, there is no standard definition of pediatric refractory strictures.

Furthermore, we did not have any reliable dysphagia scoring data to report for our patients. This is partially due to a lack of standardized dysphagia scoring systems that can adequately capture all the variables associated with pediatric patients with EA. We can anecdotally report, however, that the majority of patients showed improvement in eating after completing EIT.

Our study is the largest to date regardless of patient age to look at EIT in refractory esophageal strictures. We also have significant long-term follow-up, with a minimum of 2 years for all reported patients. Our data suggests that EIT is useful in the treatment of esophageal anastomotic strictures and is at a minimum comparable to other adjunct therapies. With a complication rate higher than balloon or bougie dilation, children undergoing EIT warrant closer monitoring than standard dilations, and EIT should be undertaken only by an endoscopist with significant therapeutic experience. Accumulation of experience may allow endoscopists to better determine whether a stricture will respond best to dilation, EIT, or surgical resection. Randomized prospective studies will be required to confirm that EIT is superior to continued balloon dilation in patients with refractory esophageal strictures, but we believe we have demonstrated that EIT should be considered in refractory esophageal strictures before performing a surgical stricture resection.

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