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CME

Intralesional Steroid Injection Therapy for Esophageal Anastomotic Stricture Following Esophageal Atresia Repair

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ABSTRACT

Objectives: The role of intralesional steroid injection (ISI) in the treatment of anastomotic stricture in patients with esophageal atresia remains unclear. The aim of this study was to evaluate the efficacy and safety of ISI.

Methods: A total of 158 patients with esophageal atresia with at least 1 ISI for the treatment of esophageal anastomotic stricture between 2010 and 2017 were identified. The change in stricture diameter (ΔD) was compared between procedures with dilation alone (ISI−) and dilation with steroid injection (ISI+).

Results: A total of 1055 balloon dilations were performed (452 ISI+). The median ΔD was significantly greater in the ISI+ group: 1 mm (interquartile range [IQR] 0, 3) versus 0 mm (IQR −1, 1.5) ($P < 0.0001$). The ISI+ group had greater percentage of improved diameter ($P < 0.0001$) and lesser percentages of unchanged and decreased diameters at subsequent endoscopy ($P = 0.0009$, $P = 0.003$). Multivariable logistic regression confirmed the significance of ISI on increasing the likelihood of improved stricture diameter with an adjusted odds ratio of 3.24 (95% confidence interval: 2.15–4.88) ($P < 0.001$). The ΔD for the first 3 ISI+ procedures was greater than the ΔD for subsequent ISI+ procedures: 1 mm (IQR 0, 3) versus 0.5 mm (IQR−1.25, 2) ($P = 0.001$). There was no difference in perforation incidence between ISI+ and ISI− groups ($P = 0.82$).

Conclusions: ISI with dilation was well tolerated and improved anastomotic stricture diameter more than dilation alone. The benefit of ISI over dilation alone was limited to the first 3 ISI procedures.

Key Words: children, endoscopic therapy, esophageal stricture, pediatric, triamcinolone

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What Is Known

- Anastomotic stricture after esophageal atresia repair is a common cause of esophageal stricture in the pediatric population.
- Endoscopic balloon dilation is the mainstay treatment for esophageal anastomotic strictures.
- Efficacy studies on intralesional steroid injection therapy for mixed etiology strictures show conflicting results and pediatric studies have been limited to small case series.

What Is New

- Intralesional steroid injection therapy in addition to stricture dilation improves anastomotic diameter more than dilation alone.
- Our study identifies a limitation of the benefit of continued intralesional steroid injection therapy beyond 3 injections.

Anastomotic stricture following esophageal atresia (EA) repair is the most common cause of esophageal stricture in the pediatric population (1–17). Endoscopic mechanical dilation is the mainstay treatment for these strictures. Several therapies are available as adjuncts to esophageal dilation, including intralesional steroid injection (ISI), topical application or intralesional injection of mitomycin C, placement of externally removable stents, and endoscopic electrocautery incisional therapy (EIT) (1,10). Our group previously reported only 30% success rate with stenting of refractory pediatric anastomotic strictures (18). Although endoscopic EIT shows promise as a previously less utilized treatment of esophageal stricture, this technique likely has an inherently increased risk for perforation and requires more advanced endoscopic training (19). There are no large-scale studies that support the efficacy of topical or injected mitomycin C which may also carry long-term risks for young patients.

The local trauma that occurs with stricture dilation may result in additional collagen deposition and scar formation resulting in stricture recurrence. The proposed mechanism of ISI therapy is the local inhibition of the inflammatory response, which in turn results in reduced collagen formation and therefore less scarring. Although some studies have shown a benefit of intralesional steroids in reducing recurrent stricture formation, others have not demonstrated efficacy (20–27). Most reports are small, uncontrolled

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studies evaluating strictures of diverse etiologies. In addition, the existing literature on ISI for the treatment of esophageal strictures in the pediatric population is limited to small series and case reports (1,10,28–32). In this study, we evaluate the use of ISI in a large number of pediatric anastomotic strictures treated at our specialized esophageal referral center and assess ISI efficacy.

METHODS

Overview and Patients

An institutional review board–approved retrospective review of all patients with EA treated in the Esophageal and Airway Treatment (EAT) Center at Boston Children's Hospital was performed. Patients with at least 1 esophageal ISI for the treatment of esophageal anastomotic stricture between July 2010 and November 2017 were identified. The ISI may have been performed on either a primary anastomosis after EA repair or an esophago-esophageal anastomosis after stricture resection or revision. Congenital esophageal strictures, esophagojejunal, and esophago-colonic anastomoses were excluded.

Intralesional Steroid Injection Procedure

All ISI procedures were performed by 1 of 2 gastroenterology providers in the EAT center under general anesthesia. ISI was performed using an endoscopic injection needle that fits through both 2.8- and 2.2-mm endoscopic channels (Interject, Boston Scientific, Marlborough, MA; 23 or 25 gauge). Triamcinolone acetate (10 mg/mL) was injected into and around the scar tissue at the stricture site at a typical dose of 1 to 2 mg/kg with a usual weight-based maximum of 20 mg and not >40 mg per procedure (typically 10–20 mg). The total injected dose was divided into 4 or more injection sites and administered into the submucosal space. Endoscopic balloon dilation (controlled radial expansion (CRE) 5.5-cm balloons, Boston Scientific, Marlborough, MA) was concurrently performed at each procedure in which ISI was performed with the order of the procedures decided by the endoscopist. ISI was typically performed on strictures that were either deemed to be refractory or responding poorly to prior dilations or anastomoses considered high risk for stricture development and were usually reserved for 4 weeks after surgical anastomosis.

Assessment of Anastomotic Diameter

Anastomotic diameter was determined by the endoscopist at each procedure before any therapeutic intervention and recorded in the operative note. A brief intraoperative contrast esophagram with half-strength ioversol 68% (Optiray 320, Mallinckrodt Pharmaceuticals, Hazelwood, MO) was performed before dilation with a radiopaque ruler placed under the patient. The anastomotic diameter was measured using the fluoroscopic image with the greatest anastomotic diameter with the radiopaque ruler and scope diameter as size references. The endoscope diameter and/or known width of open and closed biopsy forceps were used to determine inner diameter at the narrowest portion of the anastomosis in cases with poor contrast distention.

Data Collection

Recorded data included patient characteristics, presence or absence of long gap EA (LGEA), age at time of procedure, time interval from prior endoscopic stricture therapy, presence of fundoplication, initial anastomotic stricture diameter, maximum balloon dilation diameters, triamcinolone injection dosage, adverse events, and concurrent advanced endoscopic therapy (eg, esophageal stenting, EIT). If a subject's anastomosis underwent surgical stricture resection, the new anastomosis was considered a separate anastomosis. As previously published by our team, a refractory stricture was defined as an inability to remediate the esophageal lumen diameter with 5 dilations performed within 5 months to a diameter of $\geq$8 mm in children <9 months of age, $\geq$10 mm in children 9 to 23 months of age, $\geq$12 mm in children 24 months to 5 years of age, or $\geq$14 mm in children $\geq$6 years (19). Our second definition for refractory stricture was the requirement of $\geq$7 dilations regardless of time frame, with an inability to maintain the lumen to the above-mentioned sizes (19). Documentation of ''leak,'' ''contained leak,'' or ''perforation'' at the time of procedure or in follow-up were considered to be a procedure-related perforation.

Evaluation of the Change in Anastomotic Stricture Diameter

The initial anastomotic stricture diameter was recorded at each individual procedure before endoscopic intervention and compared to the stricture diameter at the subsequent endoscopy. The change in diameter from one procedure to the subsequent procedure was defined as ΔD (recorded in mm) for that specific intervention. ΔD was recorded for procedures with balloon dilation alone (ISI−) and those receiving balloon dilation with steroid injection (ISI+). The median ΔD of the ISI+ and ISI− groups were compared to assess ISI efficacy. ΔDs were also compared in 3 categories: improved ($\Delta D \geq +1$), unchanged ($-1 < \Delta D < +1$), and decreased ($\Delta D \leq -1$). To assess for a change in efficacy, ΔDs were grouped the first 1 to 3 interventions and subsequent interventions (fourth and greater) for both ISI+ and ISI− dilation procedures.

Statistical Analyses

Statistical analyses were performed using IBM SPSS (version 25.0) and GraphPad Prism (version 8.0.2). Categorical variables were reported as frequencies and percentages. Continuous variables were reported as medians and interquartile ranges (IQRs 25th, 75th percentiles). Median values of continuous variables were compared using the Mann-Whitney *U* test, and categorical variables were compared using the chi-square test. A 2-tailed $P < 0.05$ was considered statistically significant. Multivariable logistic regression was performed using generalized estimating equations to account for multiple serial balloon dilations over time within the same patient and the Wald test used to assess significance of the predictor variables regarding the binary outcome of stricture diameter improvement ($\Delta D \geq +1$ mm). Six covariates were tested in the multivariable model to derive adjusted odds ratios and 95% confidence intervals (CIs): ISI+, initial anastomotic diameter $\leq$7 mm, interval from prior dilation in weeks, age in weeks at time of procedure, presence of fundoplication, and advanced endoscopic therapy. Receiver operating characteristic curve analysis using the Youden J-index identified 7 mm as an optimal cut-off value for the initial anastomotic diameter to be used in multivariable analysis.

RESULTS

A total of 158 EA patients (79 boys) were identified who received at least 1 ISI for esophageal anastomotic stricture. Seventy-five (47%) of the patients had LGEA defined as an inability to perform an initial primary esophago-esophageal anastomosis. Tracheoesophageal fistula was present in 109 (69%); and initial EA repair was performed at our EAT center in 79 (50%). Fifty-four of the 158 patients (34%) underwent anastomotic stricture resection at our EAT center.

TABLE 1. Stricture characteristics and change in diameter in (ISI+) versus (ISI−) groups

ΔD	(ISI+)	(ISI−)	*P*
Total number	373	445	
Initial anastomotic diameter, mm, median (IQR)	6 (4, 8)	7 (4, 8)	0.32
Interval from prior dilation, wk, median (IQR)	2 (1, 4)	2 (1, 5)	0.16
Age at procedure, wk, median (IQR)	47 (24, 96)	55 (29, 104)	0.09
Presence of fundoplication, n (%)	117 (31%)	167 (38%)	0.07
Advanced endoscopic therapy, n (%)	52 (14%)	64 (14%)	0.92
Change in diameter, mm, median (IQR)	1 (0, 3)	0 (−1, 1.5)	<0.0001*

ΔD = change in diameter; IQR = interquartile range; ISI = intralesional steroid injection; ISI− = dilation procedure without steroid injection; ISI+ = dilation procedure with steroid injection.
*Statistically significant.

The 158 patients in our study had 211 anastomoses, of which 168 (80%) received at least 1 ISI. These 211 anastomoses cumulatively received 1055 balloon dilation procedures, of which 452 (43%) were ISI+ and 603 (57%) were ISI−. The median number of ISI performed on each anastomosis was 2 (IQR 1, 3; range 0–13) and the median number of balloon dilations was 4 (IQR 1, 6; range 0–25). Triamcinolone was used for ISIs at a median dose of 1.4 mg/kg (IQR 1.0, 1.8). The median age at the time of procedure for all 1055 dilations was 51 weeks (IQR 24, 99).

ΔD was compared between ISI+ dilations and ISI− dilations. ΔD could be calculated for 818 procedures (373 ISI+ and 445 ISI−). No significant difference was found between these 2 groups for initial anastomotic diameter ($P = 0.32$), time interval from prior balloon dilation ($P = 0.16$), age at the time of procedure ($P = 0.09$), presence of fundoplication ($P = 0.07$), or concurrent use of advanced endoscopic therapies ($P = 0.92$). The median ΔD was significantly greater in the ISI+ group: 1 mm (IQR 0, 3) versus 0 mm (IQR −1, 1.5) ($P < 0.0001$) (Table 1, Fig. 1).

Analysis of ΔD between ISI+ (n = 373) and ISI− (n = 445) groups showed a greater percentage of improved ΔD 229 (61%) versus 188 (42%) ($P < 0.0001$) and lesser percentages of unchanged ΔD 70 (19%) versus 128 (29%) ($P = 0.0009$) and decreased ΔD, 74 (20%) versus 129 (29%) ($P = 0.003$) at subsequent endoscopy in the ISI+ when compared to the ISI− group (Supplemental Figure, Supplemental Digital content, *http://links.lww.com/MPG/B741*).

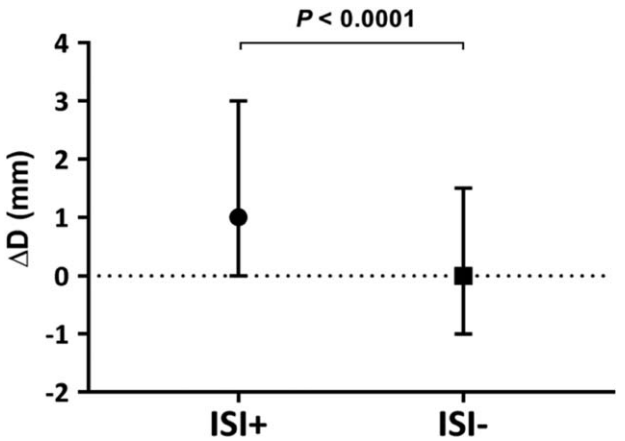

FIGURE 1. The group receiving dilation with intralesional steroid injection (ISI+) demonstrated a greater change in anastomotic diameter (ΔD) in comparison to the group receiving dilation alone (ISI−) ($P < 0.0001$). ISI = intralesional steroid injection; ISI− = dilation procedure without steroid injection; ISI+ = dilation procedure with steroid injection.

Our study population included 120 nonrefractory and 48 refractory anastomotic strictures. The nonrefractory stricture group had a greater proportion of ISI+ procedures performed than the refractory group: 0.5 (IQR 0.3, 0.7) versus 0.4 (IQR 0.3, 0.7) ($P = 0.0003$). Thirty-three anastomoses required subsequent stricture resection. We did not identify a significant difference in the proportion of ISI+ procedures between the groups that required versus did not require stricture resection ($P = 0.76$).

Analysis was performed comparing the first 3 ISI+ and the first 3 ISI− treatments on each anastomosis with subsequent (fourth or more) procedures of that same type: 287 of the 373 ISI+ ΔDs (77%) and 314 of the 445 ISI− ΔDs (71%) were one of the first 3 procedures of that type on each anastomosis. Median ΔD for the first 3 ISI+ procedures was greater than for the first 3 ISI− procedures: 1 mm (IQR 0, 3) versus 0 mm (IQR −1, 1.5) ($P < 0.0001$). In addition, within the ISI+ group, ΔD for the first 3 procedures was greater than ΔD for >3 procedures: 1 mm (IQR 0, 3) versus 0.5 mm (IQR −1.25, 2) ($P = 0.001$). There was no significant difference between ISI+ ΔD for the group of >3 and ISI− ΔD for either the group of 1 to 3 or >3 procedures (Fig. 2).

The significant difference in ΔD between ISI+ and ISI− groups was maintained after exclusion of 20 ΔDs in the ISI+ group and 33 ΔDs in the ISI− group with time intervals between dilation >26 weeks to limit the effect of advancing age on the change in stricture diameter ($P < 0.0001$), and 52 ΔDs in the ISI+ group and 64 ΔDs in the ISI− group with concurrent advanced endoscopic therapy ($P < 0.0001$).

Multivariable regression analysis demonstrated 2 independent predictors of stricture diameter improvement, including ISI+ versus ISI− (adjusted odds ratio = 3.24; 95% CI: 2.15–4.8) ($P < 0.001$), and initial anastomotic diameter ≤7 mm (adjusted odds ratio = 3.31; 95% CI: 2.00–5.5) ($P < 0.001$). Interval from prior dilation, age at procedure, presence of fundoplication, and advanced endoscopic therapy were not significant predictors of stricture diameter improvement (Table 2).

Adverse Events

Adverse events directly attributable to steroid injection were not identified at the time of ISI or immediately after the procedure. Post-dilation intraoperative contrast studies were performed after balloon dilations to assess for perforation. Post-dilation perforations were identified in 15 of the total 1055 (1.4%) dilation procedures. There was no significant difference in perforation incidence between ISI+ (6/452, 1.3%) and ISI− (9/603, 1.5%) groups ($P = 0.82$). After exclusion of all procedures that included advanced endoscopic therapies, there remained no significant difference between ISI+ and ISI− groups.

There was a single case in which a potential central adrenal suppression was identified that may have been attributable to ISI.

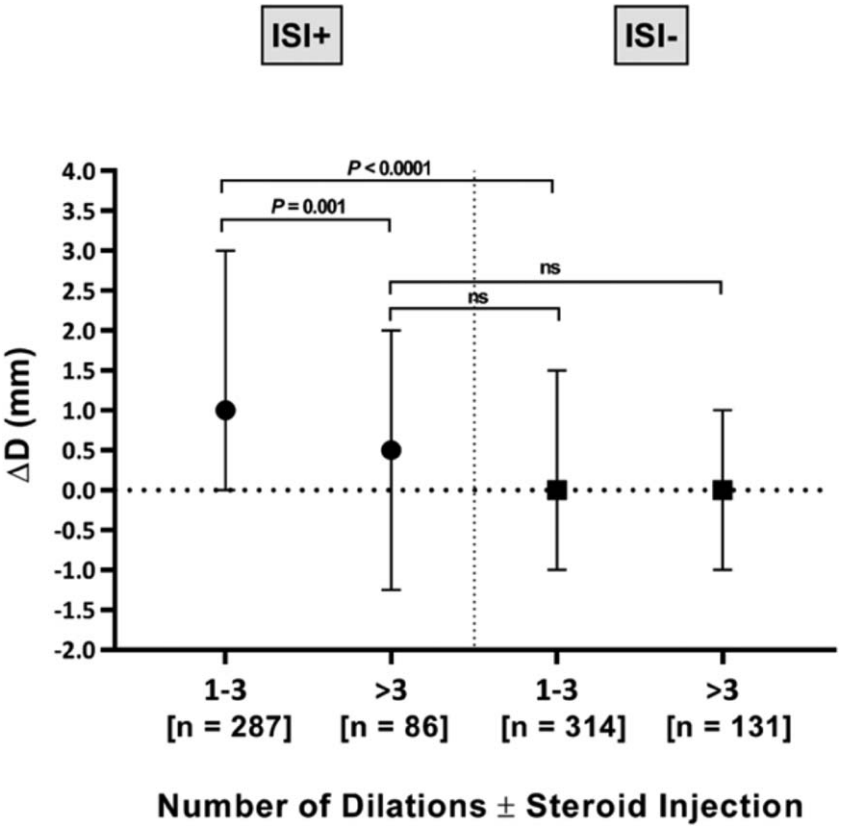

FIGURE 2. The group receiving dilation with intralesional steroid injection (ISI+) demonstrated a greater change in anastomotic diameter (ΔD) for the first 3 procedures than the group receiving dilation alone (ISI−) ($P < 0.0001$). In addition, within the ISI+ group, the ΔD for the first 3 procedures was greater than the ΔD for >3 procedures ($P = 0.001$). ISI = intralesional steroid injection; ISI− = dilation procedure without steroid injection; ISI+ = dilation procedure with steroid injection.

A 5-month-old girl (6 kg) who received 2 ISI at 2-week intervals with a cumulative dose of 3.1 mg/kg over 14 days had transient hypotension and adrenal insufficiency was identified on adrenocorticotropic hormone stimulation testing after a cumulative dose of 5.6 mg/kg over 5 weeks. Repeat adrenocorticotropic hormone stimulation testing was normal 18 months later. No other patients with suspected clinical adrenal suppression were identified.

DISCUSSION

In this study, we report the largest experience with ISI for anastomotic stricture in an adult or pediatric population. Our study is the first controlled study on ISI that evaluates only esophago-esophageal anastomoses as other controlled studies have involved mixed etiologies, esophago-gastric anastomoses, or caustic strictures (26,27). Our study is also the first to evaluate for loss of efficacy of ISI with repeated procedures. Assessment of the efficacy of therapeutic endoscopic interventions for esophageal strictures has traditionally been difficult with most well controlled studies involving relatively small populations. To increase study population numbers, often strictures of mixed etiologies have been grouped together which is problematic as their response to therapies may differ (26,27).

In most controlled studies that evaluate ISI efficacy, the total number of repeat dilations and/or dysphagia score has been used to assess efficacy (20,21,24). The largest randomized controlled ISI study to date with a total of 60 subjects did not identify a significant difference in frequency of repeat dilations or length of dysphagia free period (21). In a number of retrospective studies with a crossover design, a periodic dilation index (PDI) has been used to compare the frequency of dilation performed (dilations/month) in the period before and after ISI intervention (22,23,33,34). While the use of a PDI would have been feasible in our study, a pre and post-intervention comparison of PDI is an inherently problematic measure of efficacy. Prior ISI studies using a PDI have claimed that the decrease in PDI from the time period before ISI to after ISI measures efficacy but this assumes that PDI would remain constant over time without intervention. This measure can also be susceptible to bias as the decision on the need and timing of repeat dilation can be subjective to both providers and patients. In our study each

TABLE 2. Multivariable logistic regression model—significant independent predictors of stricture diameter improvement ≥1 mm

Variable	Adjusted odds ratio	95% CI	*P*
ISI+	3.24	2.15–4.88	<0.001*
Initial anastomotic diameter ≤7 mm	3.31	2.00–5.50	<0.001*
Interval from prior dilation, wk	1.00	0.99–1.02	0.429
Age at procedure, wk	1.01	0.78–1.30	0.973
Presence of fundoplication	0.94	0.62–1.43	0.781
Advanced endoscopic therapy	1.50	0.73–3.08	0.273

CI = confidence interval; ISI = intralesional steroid injection; ISI+ = dilation procedure with steroid injection.
*Statistically significant.

stricture served as its own control and change in stricture diameter was the primary outcome.

Our study demonstrates that ISI therapy in addition to stricture dilation improves anastomotic diameter greater than stricture dilation alone. The identified diameter increase with each individual ISI+ dilation procedure was 1 mm greater than ISI− procedures with balloon dilation alone. Given that the initial stricture diameter in the ISI+ group was 6 mm, the 1 mm change in diameter represents a 17% increase in diameter over the ISI− group. It is also important to recognize the greater cumulative effect when patients undergo multiple ISI procedures. For each of the categorical groups (improved, unchanged, and decreased ΔD), the group receiving steroid injections had a significantly improved clinical outcome at follow-up endoscopy. Multivariable analysis also confirmed the efficacy of ISI as an independent predictor of improvement in anastomotic diameter. The only other identified predictor was a smaller initial diameter at the time of dilation. It is possible that these tighter strictures were treated with a relatively larger balloon size compared to their stricture diameter to facilitate more rapid improvement.

The strictures that went on to become nonrefractory were more likely to have received ISI therapy than refractory strictures. The decision to proceed with stricture resection may have been affected by a prior history of refractory nature to endoscopic therapy at other institutions. These strictures frequently received only 1 or 2 ISI+ procedures before confirming their refractory nature and proceeding to surgery. This may explain why we did not identify a decreased proportion of ISI therapy before stricture resection.

In addition to ISI efficacy, our study also identifies a limitation of the benefits of continued ISI therapy past 3 injections. The first 3 steroid injections improved anastomotic diameter greater than further injections; and the improvement obtained after the third injection was not significantly different than balloon dilation alone. Although prior study authors have chosen to limit ISI to a total of 3 injections, our study is the first to evaluate for and identify a loss in ISI efficacy with repeated procedures (22). ISI was well tolerated in our study population. Our study demonstrated no difference between perforation rate in ISI+ and ISI− dilation groups, and these rates fell below reported rates for anastomotic stricture dilations in pediatric EA populations despite our use of a broad definition of perforation (35).

It is known that patients with EA have abnormal esophageal motility and higher risk of abnormal gastroesophageal reflux and it has been postulated that patients with EA with refractory anastomotic strictures have uncontrolled acid reflux as a contributor to the stricturing process (36–38). For this reason, fundoplication may be performed in these patients despite a lack of rigorous data (39). We did not identify a difference in the presence of a fundoplication in our study groups that could account for the observed ISI efficacy. In addition, our multivariable analysis did not identify the presence of fundoplication as an independent predictor of improvement in stricture diameter.

The collection of initial anastomotic diameter before intervention with every endoscopy performed in our EAT center allowed for assessment of ΔD. Our center practice has been to record these data not only with dilation procedures but also with follow-up endoscopic evaluations in which dilation is not performed. This routine data collection not only helps guide therapeutic decision making at the time of procedure, such as dilation size, but also allows for evaluation of changing anastomotic diameter over time. The data also allow for systematic evaluation of practice patterns, complication risks, and efficacy of therapeutic interventions. Our group recommends the routine documentation of these data with all evaluations of esophageal anastomoses at the time of endoscopic evaluation. Although our study does not assess the accuracy of the initial anastomotic diameters recorded, the 2 endoscopists in this study recorded the diameters at the time of each procedure regardless of the therapeutic intervention performed so there is little reason to suspect any inaccuracy in measurement would be biased to benefit one specific therapeutic intervention, such as ISI.

Our study is limited by its retrospective and nonrandomized design. Although the use of anastomoses as their own control helps eliminate the effect of multiple factors on stricture formation, it limited our ability to use final clinical outcomes as the main measure of clinical efficacy. We did not assess functional outcomes of therapy such as feeding behavior and tolerance in this study. Although the same method was used to record anastomotic diameters, the precision and reproducibility of this technique has not been separately validated. The retrospective nature of this study also limited the ability to assess for any minor adverse events. Although the majority of ISI- dilations resulted in improved anastomotic diameters, the median ΔD in our ISI− group might be lower than expected for mechanical dilation alone. This might be explained by the characteristics of our patient population. Our referral center performs a large number of LGEA repairs and stricture resections which have a higher propensity for stricture development than routine primary anastomoses. Thus, our findings may not be generalizable to all centers and it may be best to reserve steroid injections for refractory or high-risk strictures.

In conclusion, ISI was well tolerated and improved anastomotic stricture diameter greater than dilation alone. The benefit of ISI over dilation alone was limited to the first 3 interventions, and ISI did not increase risk of adverse events. Large-scale prospective randomized studies are needed to confirm these findings.

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