

Topical Mitomycin-C Application in Recurrent Esophageal Strictures After Surgical Repair of Esophageal Atresia

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ABSTRACT

Objectives: The aim of the present study was to evaluate the efficacy and short-term safety of topical mitomycin-C, an antifibrotic agent, in preventing the recurrence of anastomotic strictures after surgical repair of esophageal atresia (EA).

Methods: We retrospectively reviewed the medical records of patients with recurrent anastomotic strictures after EA surgery who underwent at least 3 esophageal dilations. We compared the outcome (ie, resolution of the stricture) of the group that received topical mitomycin-C treatment with endoscopic esophageal dilation with a historical cohort treated by dilations alone.

Results: A total of 11 children received mitomycin-C concurrently with endoscopic dilations. After a median follow-up of 33 months (range 18–72), and a mean number of 5.4 dilations per patient (range 3–11), 8 of 11 patients achieved a resolution of their strictures, 2 patients remained with stenosis, and 1 patient needed a surgical correction. In the control group, 10 patients required an average of 3.7 (range 3–7) total dilations. After a follow-up of 125 months (range 35–266) after the last dilation, strictures in 9 of 10 children disappeared and the remaining patient was symptom free. No dysplasia related to mitomycin-C was demonstrated.

Conclusions: There is no benefit in the resolution of the stricture when adding mitomycin-C treatment compared with repeated esophageal dilations alone in historical controls. Further randomized controlled studies and a short- and long-term evaluation of safety are needed.

Key Words: anastomotic stricture, children, esophageal atresia, mitomycin-C

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Anastomotic esophageal strictures occur in 18% to 50% of patients after surgery for esophageal atresia (EA) (1). Conservative treatment consists of intraluminal dilation using balloon or Savary-Gilliard bougies. Because of the recurrence of anastomotic strictures, some children need further dilations that are associated with significant morbidity and complications (2,3).

Mitomycin-C, an antibiotic used as an antineoplastic and antifibrotic agent, has been previously used in topical applications

to prevent scar formation and recurrence of stricture after ophthalmological surgery (4), in recurrent laryngeal and tracheal stenosis (5), and after dacryocystorhinostomy (6). A few small series (7–9) and case reports (10–14) have also suggested that mitomycin-C could have a prophylactic role in avoiding postoperative fibrosis when used in patients with esophageal strictures of various origins (peptic, caustic, postoperative). In these series, only a few cases of esophageal stricture following surgery for congenital EA have been reported. Indeed, a review (15) about the use of mitomycin C in the therapy of recurrent esophageal strictures found 31 cases published in 11 articles. Only 7 of the 31 patients were treated for recurrent strictures following surgical repair of congenital malformations of the foregut.

In the present study, our aim was to assess whether topical application of mitomycin-C after endoscopic esophageal dilation was better than esophageal dilation alone, in preventing recurrence of esophageal strictures in children with repaired EA.

METHODS

We retrospectively reviewed the medical records of patients with EA, followed at the EA clinic at Sainte-Justine University Hospital Center, Montreal, Canada. We identified children with recurrent anastomotic strictures, defined as patients who underwent at least 3 esophageal dilations. Then, we compared those who received topical application of mitomycin-C at the same time as endoscopic dilations with a historical cohort. To this end, we included consecutively all of the patients who underwent 3 or more dilations: before 2007, the patients did not receive mitomycin-C application and constituted the control group; from 2007, all of the patients who underwent at least 3 dilations received 1 or more application of mitomycin-C and represented the mitomycin-C group.

Endoscopic pneumatic dilation was performed under general anesthesia. We used balloons (Boston Scientific, Natick, MA) inflated for 2 minutes per dilation, with a maximum increase of 3 mm per session. Mitomycin-C was applied in a way that ensured direct delivery to the targeted site: after balloon dilation, the endoscope was removed and, using a biopsy forceps previously introduced in the instrument channel, a pledget held by the forceps was inserted in the esophagus at the level of the dilated stricture. Then, the biopsy forceps were removed, and a 0.1-mg/mL solution (total amount 2–3 mL per session) of mitomycin-C was sprayed on the pledget using a spray catheter through the instrument channel. After removal of the spray catheter, a grasping forceps was introduced through the instrument channel to grasp the soaked pledget and to swab the anastomotic site for 2 minutes. At the end of the procedure, the pledget was removed simultaneously with the endoscope.

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Dysphagia symptoms were evaluated through a self-assessment questionnaire systematically completed by the child's primary caregiver at each visit.

The endpoint of our study was to compare the resolution of the stricture (assessed on radiologic and endoscopic data) between the group treated by mitomycin-C and the group that received esophageal dilations alone.

Throughout the article, data are reported as median and range. The Mann-Whitney test was used for comparisons between the 2 groups. Differences were considered statistically significant when $P < 0.05$.

RESULTS

There were 134 patients studied at our EA clinic. A total of 46 of 134 patients experienced postoperative esophageal strictures. Among 46 patients, 25 patients responded well to 1 or 2 dilations and were excluded from our study. The remaining 21 patients underwent at least 3 dilations. From 2007 to 2013, all of the patients ($n = 11$) who underwent at least 3 dilations received topical application of mitomycin-C. A total of 10 of 21 patients, dilated before 2007, underwent esophageal dilations alone.

Mitomycin-C Group

In the mitomycin-C group (Table 1), 8 patients had a type C EA (with distal tracheoesophageal fistula) and underwent a surgical esophageal repair by open thoracotomy during the first day of life. Three patients had a type A EA, and were operated on in a delayed fashion (gastrostomy at birth and delayed esophageal anastomosis by open surgery at age 3 months). Before the first endoscopic dilation, all of the patients presented with symptoms of esophageal stricture (regurgitations, cough during meal, and/or solid food impactions) at a median age of 4 months (range 1–13). A barium swallow was performed in all of the patients, and confirmed the anastomotic stricture: all of the strictures were < 2 mm in length, and the mean luminal opening was 2.1 mm (range 1–4 mm). The first endoscopic dilation was performed at a median age of 8 months (range 1–87) and the first mitomycin-C application occurred at a median age of 11 months (range 3–183). Five patients received 1 application of mitomycin-C, 5 patients received 2 applications, and 1 patient received 6 applications. All of the patients were receiving proton pump inhibitors throughout the study period

(lansoprazole $1-2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$). Median follow-up after the first mitomycin-C application was 51 months (range 20–73). Three of 11 patients did not need more than a total of 3 dilations. After the third dilation, in 2 of them, mild dysphagia persisted, but a later endoscopic control confirmed the resolution of the stricture. The dysphagia of the third patient dramatically improved, and this patient has been symptom free for 55 months. No radiologic or endoscopic control has been performed on this patient. Five of 11 children needed a median of 7 (range 4–11) total dilations to achieve the resolution of the stricture: all of them eventually exhibited a total or partial improvement in dysphagia, and in 4 patients, repeated radiologic and/or endoscopic studies confirmed the disappearance of the esophageal stricture. Despite mitomycin-C application and a total of 7 endoscopic dilations, 1 (type A EA) of the 11 patients experienced a refractory stricture with a complete obstruction requiring a surgical correction of the stricture at age 15 months. At the end of the follow-up, the remaining 2 children had persistent stenosis as evaluated by endoscopy and needed a fourth or sixth dilation. These data are summarized in Table 1.

Control Group

In the control group (Table 2), which did not receive mitomycin-C, 8 patients with a type C EA and 1 patient with a type D EA underwent surgical correction by open thoracotomy during the first days of life. The remaining patient had a long-gap-type A EA and underwent delayed esophageal anastomosis at 4 months of life. All of them presented with symptoms of esophageal stricture (regurgitations, cough during meal, and/or solid food impactions) before the first endoscopic dilation at a median age 6 months (range 1–70, $P = \text{NS}$ vs mitomycin-C group). Only short anastomotic strictures were observed on radiologic data (measuring < 2 mm in length, with a mean luminal opening between 1 and 4 mm). The first endoscopic dilation was performed at a median age of 10 months (range 2–77, $P = \text{NS}$ vs mitomycin-C group). Seven of 10 patients underwent a total of 3 dilations and the 3 other children needed 4, 5, and 7 dilations (median 3 dilations per patient, range 3–7, $P = \text{NS}$ vs mitomycin-C group). An endoscopic or a radiologic control, performed at a median time of 98 months (range 3–208) after the last dilation, confirmed an absence of stricture in 9 of 10 patients, although 5 patients experienced mild dysphagia or episodic food impactions. The remaining patient had no digestive

TABLE 1. Summary of clinical data—mitomycin-C group

	Sex	EA type	Age at first symptoms	Age at first dilation	Total no. dilations	Mean time between 2 dilations	No. mitomycin-C application	Follow-up after the last dilation	Evolution at the end of follow-up
1	Male	C	7	8	3	6	1	50	NS
2	Female	A	4	4	3	0.5	1	72	NS
3	Female	C	9	11	3	2.6	1	55	Symptom free
4	Male	C-LG	NA	87	4	4.2	2	38	Symptom free
5	Male	C	1	1	6	0.6	2	70	NS
6	Male	C	1	2	7	6.1	2	25	NS
7	Male	C	13	14	7	2	2	18	NS
8	Male	A-LG	4	5	11	1.4	6	39	NS
9	Female	A-LG	3	6	7	1.1	1	19	Surgery
10	Female	C	6	10	4	9	1	26	Stricture
11	Male	C	NA	85	5	9.6	2	28	Stricture
Median			4	8	5	2.6	2	33	

Age, time, follow-up in months. EA = esophageal atresia; LG = long gap; NA = not available; NS = no stricture (endoscopically assessed).

TABLE 2. Summary of clinical data—control group

	Sex	EA type	Age at first symptoms	Age at first dilation	Total no. dilations	Mean time between 2 dilations	Follow-up after the last dilation	Evolution at the end of follow-up
1	Male	C	70	77	3	1.7	62	Symptom free
2	Female	C	NA	12	3	2.7	196	NS
3	Female	C	NA	16	3	1.7	207	NS
4	Female	C	NA	6	3	0.67	266	NS
5	Male	C	12	15	3	6.3	105	NS
6	Male	D	10	13	3	2	69	NS
7	Female	A-LG	5	6	3	1	145	NS
8	Female	C	6	8	4	4.25	70	NS
9	Female	C	1	3	5	19.2	220	NS
10	Male	C	1	2	7	12	35	NS
Median			6	10	3	2	125	

Age, time, follow-up in months. EA = esophageal atresia; LG = long gap; NA = not available; NS = no stricture (endoscopically assessed).

symptoms 62 months after the last dilation. These data are summarized in Table 2.

Adverse Events

No short-term adverse effects were noted after application of mitomycin-C. Eight of 11 patients underwent an endoscopic control with esophageal biopsies after the last application of mitomycin-C that did not show any dysplasia. One patient, who underwent 2 esophageal dilations with mitomycin-C at ages 2 and 4 months, had a recurrent tracheoesophageal fistula at age 10 months that was surgically closed.

DISCUSSION

Our study is the first that compares the outcome of patients treated with or without mitomycin-C. It is also the only one focusing on anastomotic strictures complicating EA. According to our results, we cannot conclude that the outcome is better in the group that received the adjuvant treatment for mitomycin-C compared with the control group. Indeed, our 2 groups are comparable in terms of number of patients, age, type of EA, clinical symptoms, description of anastomotic strictures, and surgical techniques. In the mitomycin-C group, 11 patients received a median number of 5 total dilations, whereas 10 patients underwent a median number of 3 dilations in the control group. The final outcome was similar in the 2 groups, with the stricture disappearing in the majority of children. Therefore, from the present study, we cannot conclude that adjuvant mitomycin-C treatment confers a real benefit compared with repeated dilations alone. Although demographics are comparable in the 2 groups, we are aware that the median number of dilations, although not statistically significant, was smaller in the historical cohort than in the mitomycin-C group. Because the design of our study is based on a strict consecutive inclusion of all of the patients receiving at least 3 dilations, and given that we did not change our medical care, except in the application of mitomycin-C, we believe that we can consider the historical cohort group as an actual control group.

We cannot rule out that the concentration of mitomycin-C used in the present study could have influenced the outcome. Indeed, although most authors have used the same concentration as we did (8,10), others have reported a “success” rate (ie, no need for further dilation after mitomycin-C application) in 3 of 4 patients using applications of 1 mg/mL mitomycin-C (7,11). Although a dose-dependent effect has been reported in a caustic esophageal

burn model in rats (16), further studies should be conducted in humans to clarify this point.

No short-term adverse effects of mitomycin-C application were reported, but 1 patient experienced a recurrent tracheoesophageal fistula after dilations with mitomycin-C. Although the relation between mitomycin-C application and a fistula recurrence is not certain because mitomycin-C modifies and impairs the healing process, one can hypothesize that if a subclinical esophageal perforation occurs following a dilation associated with mitomycin-C application, a tracheoesophageal fistula could easily reopen. In 8 of 11 patients who underwent esophageal biopsies after mitomycin-C application, no esophageal dysplasia was reported. A long-term follow-up with biopsies at the anastomotic site is warranted in these patients because of the theoretical risk of malignancy associated with mitomycin-C application in patients who already have an increased baseline risk of esophageal carcinoma (17–19).

Although we sought to include only patients with esophageal strictures related to EA repair, we are aware that the present work includes a small number of patients that precludes the analysis of the risk factors predicting the efficacy of mitomycin-C in refractory strictures after EA repair. Type of EA, tension of the anastomosis, length of the stricture, and associated reflux are factors that may influence the efficacy of mitomycin-C. Another weakness is the retrospective analysis with a historical control group with a longer follow-up.

In conclusion, with the limitation of historical controls, the efficacy of mitomycin-C application in preventing the recurrence of esophageal anastomotic strictures in patients with repaired EA has yet to be proven. A randomized controlled trial is needed to determine whether dilation with mitomycin offers significant benefit over standard dilation alone. Long-term safety should also be carefully evaluated, notably with anastomotic biopsies.

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