Endoscopic dilatation with and without mitomycin C local application in esophageal strictures in pediatric patients

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Received: 28 December 2019
Accepted: 7 January 2020
Published: 27 April 2020

The Egyptian Journal of Surgery 2020, 39:437–442

Background
Esophageal stricture is an important health problem in pediatrics. It affects the patient health and quality of life negatively. The aim was to compare between endoscopic dilatation followed by mitomycin C local application and conventional endoscopic dilatation alone in outcome of treatment of pediatric patients with esophageal strictures.
Patients and methods
This prospective randomized controlled study was performed on 42 pediatric patients presented with dysphagia resulting from esophageal strictures. The patients were classified into two groups (21 patients in each): group A, where endoscopic dilatation was followed with local application of mitomycin C, and group B, where endoscopic dilatation alone was done.
Results
There was no significant difference between both groups in age, sex, etiology, and weight before dilatation. Weight after dilatation and weight gain showed significant increase in group A than B. There was significant decrease in number and duration of sessions with significant increase in the intervals between sessions in group A than B. There were no detected complications related to mitomycin C.
Conclusion
Mitomycin C local application following endoscopic dilatation in esophageal stricture improves the outcome in pediatric patients by decreasing the number of dilatation sessions and shortens the treatment period thus reaching earlier cure.

Keywords:
endoscopic dilatation, esophageal stricture, mitomycin C, pediatrics

Egyptian J Surgery 39:437–442

1110-1121

Background

Esophageal stricture is an important health problem in pediatrics. It affects the patient health and quality of life negatively owing to the resultant dysphagia and its complications such as aspiration, recurrent chest infection, and failure to thrive [1].

Anastomotic strictures following surgery for congenital foregut anomalies such as tracheoesophageal fistula, ingestion of caustic agents, and severe gastroesophageal reflux disease (GERD) are the main etiological factors. The traditional initial treatment of esophageal strictures is endoscopic dilatation, which is usually repeated many times according to patient condition [2].

In many cases, the management of esophageal strictures is difficult and challenging, and conventional endoscopic dilatation results are unsatisfactory, as restenosis and eventually recurrence of the symptoms remains the main problem. Also, Some cases with GERD related esophageal stenosis surgical interference in the form of nissen fundoplication may be required, [11] in some cases repeated dilatation procedures may cause repeated trauma to the esophageal mucosa leading to fibrosis and worsening of the condition [1].

Several agents have been proposed to be used as an adjuvant following the endoscopic dilatation to sustain and prolong the dilatation effect and prevent restenosis, thus decreasing the need for further dilatation sessions and reaching faster cure, especially in refractory esophageal strictures [1].

Recently, mitomycin C, owing to its antifibroblastic activity and antiproliferative properties, is described as an adjuvant therapeutic option for recurrent esophageal stricture, and favorable early results have been perceived [2].

The aim of this study was to compare between endoscopic dilatation followed by mitomycin C local application and conventional endoscopic dilatation

 DOI: 10.4103/ejs.ejs_236_19

alone in outcome of treatment of pediatric patients with esophageal strictures.

Patients and methods

In this prospective randomized controlled study, 42 pediatric patients who presented to the Outpatient Clinic of Pediatric Surgery in Benha Children Hospital and Menofia University Hospital with dysphagia resulting from esophageal strictures due to anastomotic strictures, post-tracheoesophageal repair, postcorrosive esophageal stenosis, and erosive strictures from GERD were included after approval from Institutional Ethical Committee.

Exclusion criteria were patients with dysphagia after colon bypass or gastric pull-up esophageal replacement, malignant dysphagia, associated debilitating disease (liver, cardiac and respiratory), and/or severe congenital anomalies (that may affect the outcome), as well as known hypersensitivity to mitomycin C.

There was a code number for every patient's file, and the results of our research were only used for academic interest. Fully informed consent was obtained from the parents regarding the endoscopic dilatation, mitomycin C local application, and the potential intraoperative or postoperative complications.

History was taken from the parents regarding the possible etiological factors (e.g. ingestion of corrosive, previous esophageal surgery, or GERD), the symptoms of esophageal stenosis (in the form of dysphagia and regurgitation of food, fluids, or saliva), aspiration, recurrent chest infections, loss of weight and failure to thrive, the onset of these symptom/symptoms following the possible etiological factor, and history of any associated medical diseases, surgeries, hospital admissions, or previous investigations and treatment if any.

Full examination was done including weight measurement and chest examination looking for signs of failure to thrive or chest infection. Complete blood picture was done to assess hemoglobin level to exclude anemia resulting from malnutrition and to assess white blood cell count. Contrast swallow was done to assess the esophageal condition and reveal presence/absence of esophageal stricture (Fig. 1).

The patients were classified randomly into two groups (21 patients in each group): group A, where endoscopic dilatation was followed with local application of mitomycin C, and group B, where endoscopic dilatation was done without mitomycin C. A computer-generated randomization was done, and numbers were concealed in sealed envelopes showing the group of the assignment.

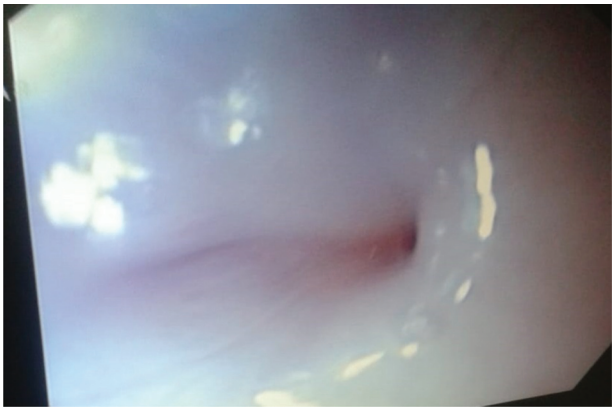
Operative steps

General anesthesia with endotracheal intubation was used in all patients. Endoscopy was done, the stricture site localized, and guide wire passed through the stenotic segment into the stomach, and then its position was checked by fluoroscopy. Savary–Gilliard dilators were passed over the guide wire in sequence (Figs. 2 and 3). In group A, after dilatation, mitomycin C solution was formed by adding 25 ml of distilled water to the mitomycin C 10 mg vial to form a 0.4 mg/ml solution. A gauze was soaked in the solution and then a grasper was used to introduce it to the stricture

Figure 1

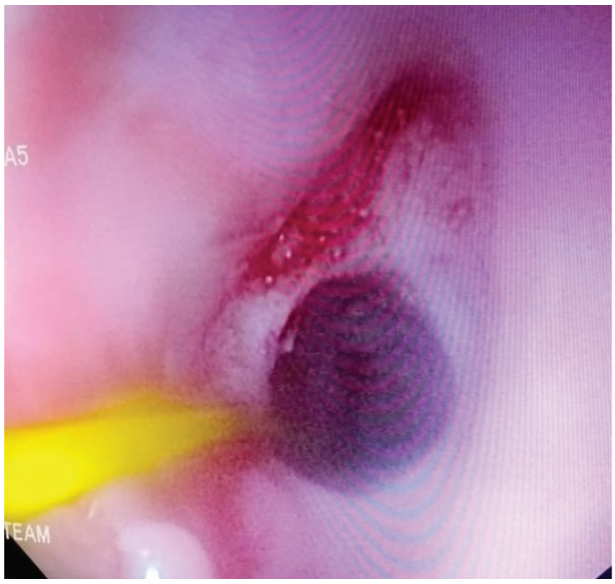
Contrast swallow showing anastomotic stricture in an infant following repair of esophageal atresia with tracheoesophageal fistula type C.

Figure 2



Endoscopic view of tight esophageal stenosis due to anastomotic stricture after esophageal atresia with tracheoesophageal fistula repair.

Figure 3



Endoscopic view of guide wire bypassing the stenotic segment.

site under vision using rigid esophagoscope. The soaked gauze was left in place for 5 min before removal.

After dilatation, the patients were kept under observation and nothing was allowed per month for 2 h. Then plain chest radiograph was done (to rule out iatrogenic esophageal perforation), and then fluids and soft diet were permitted. The patients were discharged with prescription of H_2 blocker (ranitidine 5–10 mg/kg/day in two divided doses) for 1 week.

Follow-up

Follow-up for the swallowing of fluids, solids, dysphagia-free interval, and recurrence of dysphagia and its degree was done every 2 weeks. Weight (and complete blood count for group A) was done every 2 months. On recurrence of significant dysphagia, another dilatation session was arranged. After 6 months, the two groups of patients were reassessed regarding dysphagia if present and its degree (dysphagia to solids, semisolids, and liquids). Follow-up was done for at least 6 months.

Dysphagia-free interval, weight gain, number of total dilatations done, the intervals between dilatation sessions, and endoscopic finding during dilatation (the degree of stenosis, the length of stenotic segment, and inflammation of esophagus) were recorded.

Statistical analysis

The collected data were analyzed using Statistical Package for the Social Sciences (IBM, USA) version 25 (statistical analysis was done using IBM SPSS statistics for windows, version 23.0, Armonk, NY: IBM Corp). Normality test was done using Shapiro–Wilk test, and the following data did not follow the normal distribution (nonparametric): weight gain and number, as well as duration and interval of dilatation session. Quantitative parametric data were presented as mean and SD and were compared by Student's *t*-test. Nonparametric data were presented as median and range and were compared by Mann–Whitney (*U*) test. Categorical data were presented as frequency and percentage and were compared by χ^2-test. The level of significance was adopted at *P* value less than 0.05.

Results

In this study, 61 patients were assessed for eligibility; 12 patients did not meet the inclusion criteria and seven patients refused to participate in the study. Therefore, 42 patients were randomized into two groups, and all patients were included in the followâ up and analysis (Fig. 4).

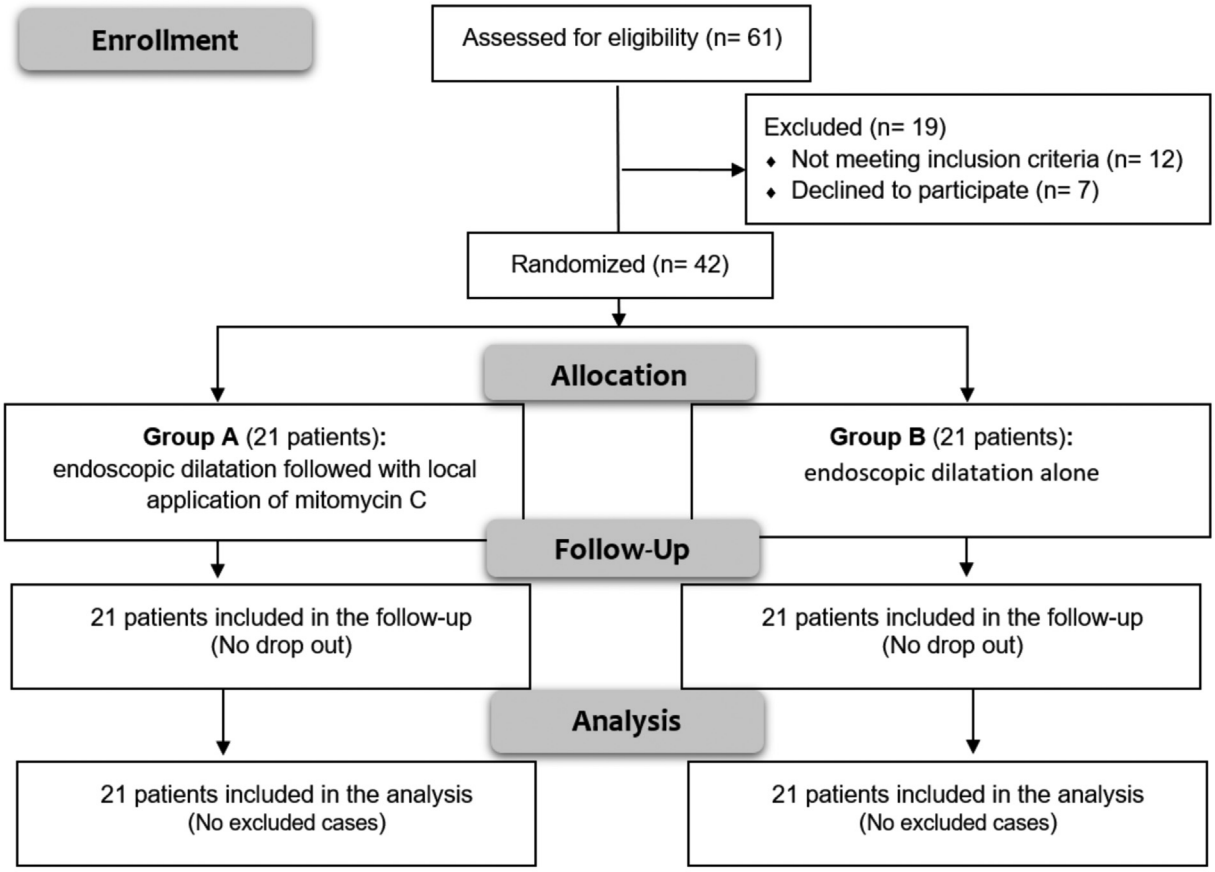
Patients' characteristics are shown in Table 1. There was no significant difference between both groups regarding age, sex, and etiology (Table 1). Regarding the etiology of the esophageal stenosis, group A included 21 patients: 11 (52.4%) patients with postcorrosive esophageal stenosis, six (28.6%) patients with anastomotic stricture following surgical repair of tracheoesophageal fistula type C, and four (19%) patients with erosive due to GERD. Group B included 21 patients: 18 (85.7%) patients with postcorrosive esophageal stenosis, two (9.5%) patients with anastomotic stricture following tracheoesophageal fistula type C repair and one (4.8%) patient with erosive due to GERD.

Mean follow-up period was 9.90±3.08 months (ranged from 6 to 18 months) in group A and 11.33±3.93 months (ranged from 6 to 18 months) in group B, with no significant difference between both groups.

Regarding weight before dilatation, there was no significant difference between both groups. Regarding weight after dilatation and weight gain, there was a significant increase in group A as compared with group B (Tables 2 and 3).

Regarding the number and duration of sessions, there was a significant decrease, and the intervals between sessions were increased in group A as compared with group B (Table 2). The median number of dilatation sessions for group A was 8 and median for group B was 10 sessions.

Figure 4



CONSORT flowchart of the patients.

Table 1 Patients' characteristics in the studied groups

	Group A (*n*=21)	Group B (*n*=21)	*P* value
Age (years)			
Mean±SD	1.86±0.95	2.41±0.89	0.064^{+}
Range	3 months to 4 years	2 months to 4 years	
Sex			
Male	11 (52.4)	13 (61.9)	0.755^{++}
Female	10 (47.6)	8 (38.1)	
Etiology			
TOF	6 (28.6)	2 (9.5)	0.064^{++}
PCOS	11 (52.4)	18 (85.7)	
GERD	4 (19)	1 (4.8)	

PCOS, post corrosive esophageal stenosis; TOF, tracheo esophageal fistula. Data are presented as mean±SD and range or as frequency (and percentage)$^{+}$compared by *t*-test $^{++}$ compared by χ^2-test. GERD, gastroesophageal reflux disease.

There were no detected complications related to mitomycin C local application in this study.

Discussion

Esophageal strictures in children may occur as a complication of caustic ingestion or severe GERD or as a sequela of esophageal surgery and other fibrosing conditions [3].

The first line of treatment for these strictures is endoscopic dilatation. However, because of the extensive fibrosis faced in caustic esophageal strictures, they may be refractory to repeated dilatation. These cases usually require multiple dilatation sessions over a prolonged period of time to achieve a complete resolution of dysphagia. A recently described adjunct in the treatment of refractory esophageal strictures, with good promising

Table 2 Weight in both groups

	Group A (*n*=21)	Group B (*n*=21)	*P* value
Weight before dilatation (kg)			
Mean±SD	10.09±2.79	8.76±3.07	0.157[+]
Range	3–13	2.5–15	
Weight after dilatation (kg)			
Mean±SD	12.64±3.08	10.46±3.37	0.038*[++]
Range	3.5–16	3–18	
Weight gain (kg)			
Median	2	1	0.004*++
Range	0.5–4	0–4.5	

Data are presented as mean±SD and range or as median and range [+] compared by *t*-test [++] compared by Mann–Whitney (*U*) test. *Significant as $P<0.05$

Table 3 Dilatation sessions in both groups

	Group A (*n*=21)	Group B (*n*=21)	*P* value
Number			
Median	8	10	0.016*
Range	2–20	2–22	
Duration (months)			
Median	6	8	0.040*
Range	1–15	1–16	
Intervals between sessions (months)			
Median	1	1	0.023*
Range	0.5–4	0.5–1.25	

Data are presented as median and range and compared by Mann–Whitney *U*-test. *Significant as $P<0.05$.

results, is the topical application of mitomycin C on the stricture site after dilating it endoscopically [4].

Etiology

In the study by Divarci *et al.* [5], there were 20 patients (14 patients were due to postcorrosive esophageal stricture, five patients with anastomotic stricture, and one patient with congenital esophageal stenosis).

The study by El-Asmar *et al.* [6] included 40 patients with esophageal stricture due to corrosive ingestion only, although this may make the assessment of the response more accurate owing to the same nature of the pathology, but it excluded other pathological types from the study.

Total number of dilatation sessions required to reach satisfactory and sustained relief of dysphagia

Moreover, in the study done by El-Asmar *et al.* [7], the results confirmed less dilatation sessions needed with mitomycin C application.

This is supported by another study done by Divarci *et al.* [5] which concluded that after mitomycin C application in 20 patients with esophageal stricture, the median number of dilatation sessions decreased from 5 to 1 after mitomycin C application in those patients and that regular esophageal dilatation was no longer needed in 80% of cases.

Another aspect regarding topical application of mitomycin C is shortening of the total period of treatment. In our study in group A where Mitomycin C was used, the median number of total period of dilatation sessions needed to achieve cure was 6 months compared with 8 months in group B.

In the series by El-Asmar *et al.* [6], it was concluded that during specified follow-up period of 6 months, 80% of strictures in mitomycin C got completely resolved compared with 35% in placebo group; thus, the mitomycin C use decreased the treatment period and achieved earlier cure.

On the contrary, the study by Madadi-Sanjani *et al.* [8] failed to confirm the high success rate for mitomycin C local application following endoscopic dilatation in the study conducted on 11 patients with esophageal stenosis. Their results showed that 6 of 11 patients (66%) included had resolution and five patients had no resolution, of whom, two needed redoesophageal surgery to resect the stenosed segment.

This conflict may be attributed to the nature of the pathology in the patients included in their study, which was performed on 11 patients with resistant and recurrent esophageal stricture, and nine of them were owing to anastomotic strictures in patients operated for type C and type A esophageal atresia (82% of patients), with only two patients with postcorrosive esophageal stenosis (18% of patients) as an etiology for esophageal stricture, which may explain the poor outcome in this study [8].

The concentration of mitomycin C solution to be locally applied represents a controversial point. In our study, we used concentration of 0.4 mg/ml, and also El-Asmar *et al.* [7] used the same concentration, which proved to be effective.

Lower concentration of mitomycin C solution was used in other studies. Rosseneu *et al.* [9] in their series concluded that mitomycin C concentration of 0.1 mg/ml was effective in their study to reach improvement in 13 of 16 patients included in the study.

In our study, no complications were detected related to mitomycin C local application with the solution concentration of 0.4 mg/ml.

Moreover, in the studies done by Divarci *et al*. [5], Rosseneu *et al*. [9], and El-Asmar [6], no complications resulted from the mitomycin C local application.

Mitomycin C thus seems safe and effective as an adjuvant therapy in esophageal strictures, but the dose, number of times of application, and intervals in-between remain controversial.

Further studies are needed to define a protocol for mitomycin C use regarding number of application and concentration to be used.In this study, patients with different pathological causes were included, which widened the scope of the study, but it also did not consider the variable response of different pathological types to dilatation and mitomycin C, and also no patients with congenital esophageal stenosis were included.

The results of mitomycin C local application should be compared with new studies using mitomycin C local injection into the stricture to estimate the possible benefits and potential risk of such intervention. A study done in 13 patients with pharyngoesophageal stenosis refractory to endoscopic treatment in patients treated with head and neck cancer concluded that short-term injection of mitomycin C is not recommended owing to the high incidence of adverse effects in all included patients [10].

Mitomycin C local application results are inspiring for its use in similar conditions with stenosis, for example, urethral stenosis.

The result of our study recommends the use of mitomycin C topically as an adjuvant to endoscopic dilatation to decrease the treatment period and total number of dilatation sessions and achieve earlier cure in the pediatric patients with esophageal stenosis. No complication was detected attributed to the use of mitomycin C with the solution of 0.4 mg/ml concentration, which seems to be safe and effective.

Conclusion

Mitomycin C local application following endoscopic dilatation in esophageal stricture improves the outcome in pediatric patients by decreasing the number of dilatation sessions and shortens the treatment period, thus reaching earlier cure.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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