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Prospective study of the effect of topical application of Mitomycin C in refractory pediatric caustic esophageal strictures

Carolyne Morcos Ghobrial[1] · **A. E. Eskander**[1]

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Abstract

Background Esophageal strictures resulting from caustic ingestion in children are usually difficult to be managed, and surgical replacement is usually required for cases refractory to frequent dilatation sessions. Topical Mitomycin C (MMC) has been recently used in the management of resistant strictures. We evaluated the efficacy of MMC application in treatment of long refractory caustic esophageal strictures.

Methods This prospective study included 120 patients of both sexes with refractory caustic long esophageal strictures (> 3 cm in length). All patients were randomly divided into two equal groups using the research randomizer program (1:1 randomization), group I underwent endoscopic dilatation therapy only and group II underwent dilatation with topical application of MMC. Follow-up was done regularly by assessing the dysphagia score and patients were evaluated after 6 months of management. The procedure was repeated four times with 2-week intervals. Complete relieve of symptoms (dysphagia score = 0) was assessed after the follow-up period.

Results The complete cure was detected in 81.6% of patients in the MMC group compared to only 40% in the first group, p-value < 0.0001. During the follow-up, the average sessions of dilatation needed in group II were 3.25 ± 2.78 compared to 6.25 ± 1.74 sessions in group I ($p < 0.001$). The mean cost of sessions in patients who showed symptomatic and endoscopic improvement was significantly lower in group II (272.2 ± 51 US$) when compared to group I (404 ± SD 55.7 US$).

Conclusions Cure rate was double in the MMC group. MMC application significantly improved symptoms and reduced both the number and frequency of dilatations to alleviate dysphagia in patients with refractory caustic esophageal strictures and hence reduced the cost of treatment.

Keywords Children · Caustic · Long esophageal stricture · Endoscopic dilatation · Mitomycin C

Abbreviations

F	French
MMC	Mitomycin C
SD	Standard deviation
$	Dollar

Caustic ingestion and the development of esophageal strictures remain a major health problem in the pediatric age group, especially in developing countries [1]. Caustic esophageal strictures affect the children's quality of life negatively because of the higher incidence of dysphagia, in addition to aspiration and recurrent chest infection [2]. This also reflects on their behavioral and educational status because of repeated absence from school [3].

Caustic esophageal strictures that are difficult to be dilated, usually related to the extent and depth of fibrotic reaction within the esophageal wall. In many cases, the management is challenging and dilatation is unsatisfactory as restenosis following scar formation remains the main problem [4, 5]. Repeated dilatation procedures may cause repeated trauma to the mucosa leading to increase fibroblast proliferation and collagen deposition, thus worsening of the stricture [6].

Several agents have been proposed as an adjuvant therapy to increase the success rate of dilatation of refractory esophageal strictures [7]. Mitomycin C (MMC) has antifibroblastic activity and antiproliferative properties, thus

✉ Carolyne Morcos Ghobrial
cmiga82@yahoo.com

A. E. Eskander
dr.aymanemil@yahoo.com; emileskander71@yahoo.com

[1] Department of Pediatrics, Kasr Alainy School of Medicine, Cairo University, 115 Elmanial Street, Cairo 11451, Egypt

decreasing the incidence of stricture recurrence and might give the chance to avoid a surgical procedure [8].

Two patients with caustic esophageal stricture, who were treated with dilatation plus MMC, had showed good outcome. In a review of 11 papers with 31 children with esophageal stricture, MMC resulted in complete symptom relief for 21 children (67.7%), partial relief in 6 (19.4%) children, and no improvement in 4 children (12.9%) [9]. In a recent study, the authors reported significant effectiveness of MMC in improving dysphagia in 18/30 patient with caustic stricture [10]. In addition, two papers by ElAsmar et al., showed that the same results with no adverse effects were reported in any series [11, 12].

While the authors of one study reported that similar result was found in both groups, those treated with dilatation only and the group treated with dilatation plus MMC [13].

Different techniques for the topical application of MMC application have been reported. Cotton pledgets soaked in the MMC solution have generally been used. Other techniques, such as drugeluting stents or the local instillation of a MMC solution at the stricture level with a cotton swab, have produced an accurate solution aspiration and lavage after 4–5 min [14].

Therefore, we aimed to evaluate the efficacy and safety of topical application of MMC in benign refractory long caustic esophageal strictures.

Materials and methods

Study design

The present study was carried out in the Pediatric Endoscopy Unit, Cairo University, Egypt, from the beginning of January 2015 to the end of December 2016. All patients were enrolled in the study after an informed consent was obtained from the parent/guardian. The study was approved by the Research Ethics Committee of Pediatric Department, Faculty of Medicine, Cairo University, Egypt. The research was carried out in accordance with the Helsinki Declaration.

The total number of patients with caustic strictures during the study period was 420 patients, from whom 120 patients with complex, long, refractory strictures were included in the study with established caustic esophageal stricture after accidental ingestion of caustic potash (potassium hydroxide). They were initially evaluated, including a detailed history with age, gender, time, and type of corrosive ingestion, and the degree of dysphagia. The degree of dysphagia was evaluated according to a dysphagia scoring system (Table 1), and an initial barium swallow was performed 6 weeks after the initial insult. Six weeks after caustic ingestion, the length of the strictures was measured by the endoscopy after initial dilatation with wire-guided malleable semirigid Savary–Gilliard dilators® (Wilson-Cook Medical, Inc., Winston-Salem, NC, USA). Only those with refractory long (strictures > 3 cm in length) esophageal strictures (inability to dilate up to 14 mm diameter over 5 sessions at a 2-week interval) were included in the study.

Table 1 Dysphagia scoring system [11]

Dysphagia scores	Degree of dysphagia
0	Able to eat normal diet/no dysphagia
1	Able to swallow some solid foods
2	Able to swallow only semi-solid foods
3	Able to swallow liquids only
4	Unable to swallow anything/total dysphagia

Exclusion criteria included patients with short strictures (< 3 cm in length), patients underwent previous esophageal surgery, congenital esophageal stricture, stricture associated to eosinophilic esophagitis and patients known to have a hypersensitivity or contraindication for MMC.

Patients were randomly divided into two groups using the research randomizer program (http://www.randomizer.org/form.htm), using 1:1 randomization; group I included 60 patients who underwent standard dilation using semirigid Savary–Gilliard bougies only without topical mitomycin and group II included 60 patients who underwent esophageal dilation session with topical MMC applied over the esophageal mucosa after dilation. The endoscopist and investigator who assessed the outcome were not be the same.

The drug was prepared to use a concentration of 0.4 mg/ml. MMC was delivered to the stricture site using the rigid esophagoscope (Karl Storz Gmbh & Co. KG, Tuttlingen, Germany). The number of sessions of application of MMC was protocols in our center to be repeated four times with 2-week intervals. Regular follow-up and re-evaluation were done after 6 months of management.

Patients were followed up regularly and the intervals between dilatations before treatment, according to our dilatation protocol (every 2 weeks into the first 3 months, then monthly in the next 9 months, then every 2 months in the next year; however, this depends more on the patient's symptoms). A dysphagia score was used for close follow-up of improving symptoms clinically. The number of dilatations sessions required to achieve maximum dilator size (14 mm) after 6 months of follow-up, was analyzed. All patients were treated with an H2 blocker (Ranitidine) throughout the study to eliminate the effect of acid reflux on the healing process of the stricture. We included children with refractory strictures which is the inability to dilate up to 14 mm diameter over more than 5 sessions at a 2-week interval. Intervals between dilatations after treatment, as for group II (endoscopic dilatation with MMC): dilatation with MMC was done every 2 weeks for 4 sessions (= 2 months). Then

assessed monthly according to the dysphagia score (Fig. 1). As for group I (endoscopic dilatation only), they follow the same protocol, according to our dilatation protocol (after the first 3 months, dilatation is monthly in the next 9 months, then every 2 months in the next year).

Mitomycin C application technique

Our technique started by esophageal dilatation using the upper gastrointestinal endoscopy (Silver Karl Storz Endoscope 13821 PKS, SPIES Technology Storz Professional Image Enhancement System), HD system and 100 W xenon light source, Tuttlingen, Germany and the wire-guided Savary–Gilliard dilator. The size of the child's thumb is considered as a rough measure to the targeted esophageal lumen and for the appropriate size of the dilator used [15].

After dilatation, we assessed the stricture site and length by visualizing it through the reintroduction of the endoscopy. Then MMC was topically applied. The application of MMC was performed by introduction of the endoscope till the beginning of the stricture site, and then the multi-porous spray catheter was introduced through the endoscope. Injection of the prepared MMC solution 0.4 mg/ml inside the catheter to spray MMC solution to the mucosa at the level of the stricture and the procedure will be repeated four times with 2-week interval thereafter, until the maximum dilatable size was achieved or there was marked clinical and endoscopic improvement. It is given in the same dose in all patients.

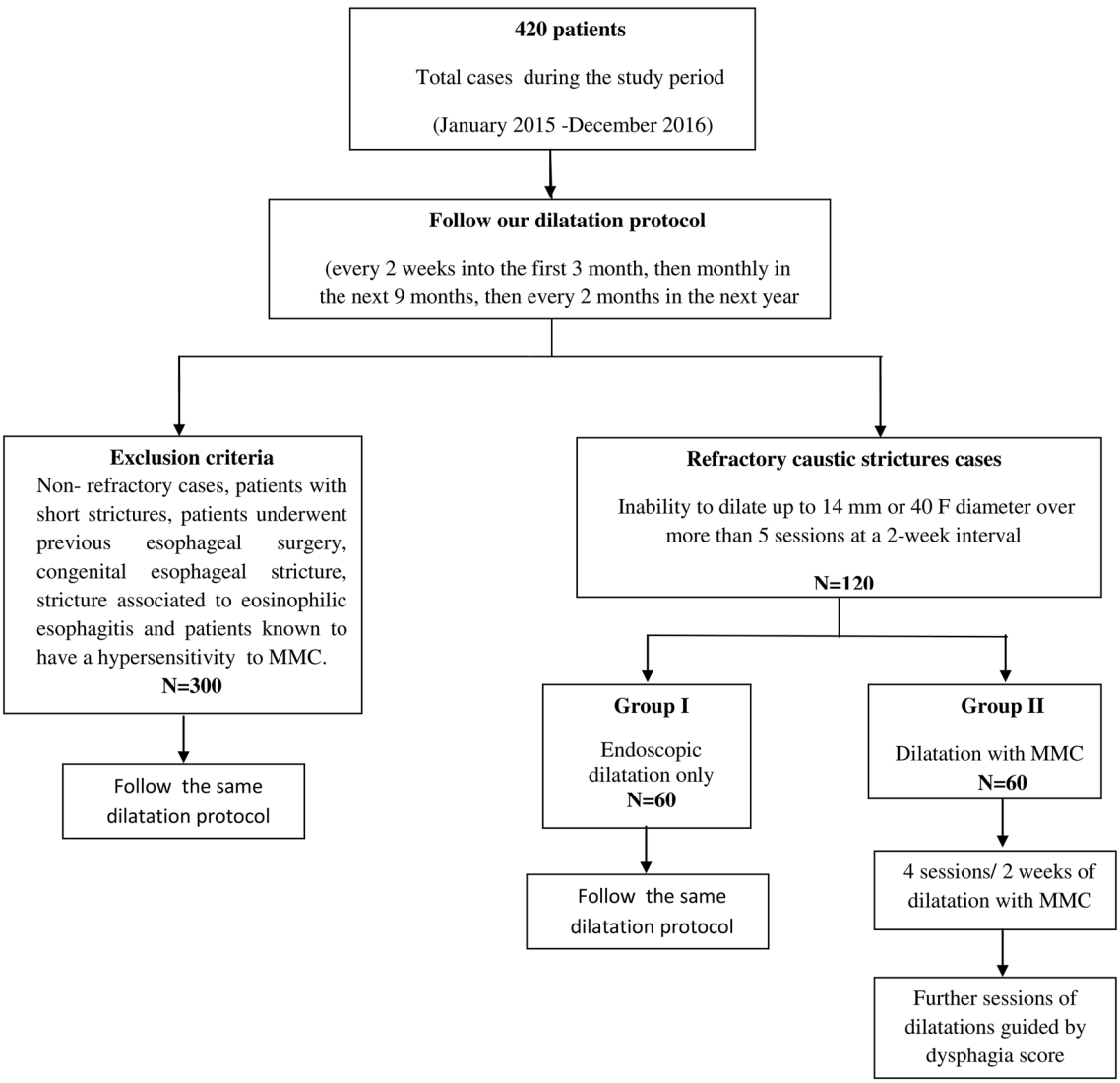

Fig. 1 Flow chart of the treatment protocol

Follow-up

Patients were followed up clinically using the previously mentioned dysphagia score before every session and monthly after resolution of dysphagia for 6 months after the last dilatation session. Endoscopic evaluation of the esophagus was performed for the assessment of the integrity and continuity of esophageal mucosa at the stricture site.

Outcome measures

The primary outcome was the percentage of patients with complete resolution of dysphagia in both groups. The patient is considered cured if he/she is dysphagia-free (dysphagia score = 0) with no need for dilatation after the last dilatation session. Secondary outcome measures were the number of dilatation sessions needed for easy passage of 40 F (French) dilator. In addition, the costs of the sessions were calculated within the treatment period in both groups of patients who showed symptomatic and endoscopic improvement.

Statistical methods

Statistical analyses were performed using SPSS software (SPSS, version 23.0; SPSS, Chicago, IL, USA). Data were statistically described in terms of mean ± standard deviation (± SD), median and range or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t*-test for two independent samples in comparing normally distributed data and Mann–Whitney *U* test for independent samples for comparing quantitative data. For comparing categorical data, Chi-square (χ^2) test was performed. A two-sided *p* value < 0.05 was considered statistically significant.

Results

Our study included 120 children with established esophageal strictures. The underlying cause of the stricture was caustic ingestion in all cases. The age ranged from 1.5 to 8 years with a mean of 3.33 ± 1.47 years old at the time of dilatation and MMC application.

Group I included 60 children who underwent dilatation therapy only, 50% were males with their ages ranged from 1.5 to 7 years with a mean of 3.09 ± 1.39 years. While group II, who underwent dilatation plus MMC therapy was 60 cases, 60% were males and their age ranged from 1.5 to 8 years with a mean of 3.5 ± 1.5 years (Table 2).

The initial dysphagia score of these patients was ranging from 2 to 4 (median = 3). They had long strictures ranging in length from 3.5 to 10 cm (median = 7). Outcome parameters 49/60 patient were symptom-free with dysphagia score = 0 for 6 months after the last dilatation session, representing 81.6% of group II, while 40% in group I, with *p*-value < 0.0001.

Table 2 Comparison of the presenting data between the studied groups

	Group I (*n* = 60) (Dilatation only)	Group II (*n* = 60) (Mitomycin C + dilatation)	*p*-values
Age (years, mean ± SD)	3.09 ± 1.39	3.15 ± 1.5	0.142
Gender *n* (%)			
Female	30 (50)	24 (40)	–
Male	30 (50)	36 (60)	
Corrosive type	Caustic	Caustic	–
Stricture length (mean ± SD)	6.71 ± 1.97	6.866 ± 2.04	0.342
Number of dilations before study (mean ± SD)	9.26 ± 2.48	9.85 ± 3.7	0.158

n number, *SD* standard deviation

**p*-value is significant

During the period of follow-up in the study, the MMC group showed 1 patient who required no further sessions of dilatation, 26 patients requiring 1 session each (43%), 22 (36%) patients required 2–3 sessions each (once per month) and the rest 11 patients (18.33%) required from 4 to 10 sessions until complete cure (dysphagia score = 0).

The average number of sessions required for complete cure (dysphagia score = 0) and for easy passage of 40 F dilator in group II after application of MMC locally was mean ± SD = 3.25 ± 2.78, while in group I mean of 6.25 ± 1.74 dilatation sessions (Fig. 2; Table 3). MMC treatment failed in 18.33%. The pain was observed in all patients of both groups, no other adverse effects were reported such as anaphylaxis, perforations, and fever.

Follow-up endoscopy of the cured patients revealed intact healthy mucosa at the site of the previous stricture with easy passage of the endoscope into the stomach. Follow-up endoscopy was done after four sessions of the topical MMC application, showing resolution of esophageal stricture in cases with dysphagia score = 0 (Fig. 3).

There was a significant difference in the cost of sessions from the start of the study till the follow-up period in patients with complete improvement. The cost of one session of dilatation has only been 50 US$, and that of dilatation with MMC application costed 60 US$. So the calculated cost of sessions in patients who showed symptomatic and endoscopic improvement in the MMC group ranged from 180 to 380 US$ with a mean of 272.2 ± 51 US$, while in group I ranged from 300 to 550 US$ with mean 404 ± 55.7 US$, with *p*-value < 0.00001 (Table 3).

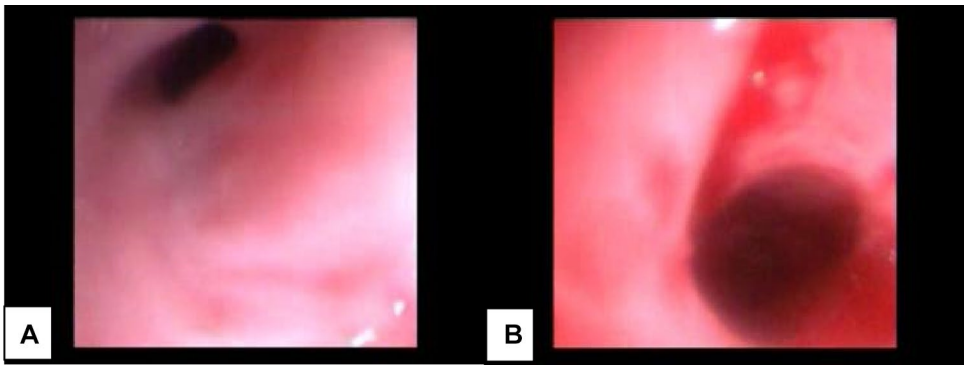

Fig. 2 Endoscopic images of the esophagus showing **A** esophageal caustic stricture before dilation and **B** esophagus after dilation with wire-guided Savary–Gilliard dilator only without MMC

Table 3 Comparison between outcome measures of both groups

	Group I ($n=60$) (Dilatation only)	Group II ($n=60$) (Mitomycin C + dilatation)	p-values
Symptom-free with dysphagia score = 0	24 (40%)	49 (81.6%)	< 0.0001*
Number of dilatations performed in cured patients within 6 months of management (mean ± SD)	6.25 ± 1.74	3.25 ± 2.78	< 0.00001*
Cost of sessions in patients who showed symptomatic and endoscopic improvement (mean ± SD)	404 ± 55.7 US$	272.2 ± 51 US$	< 0.00001*

n number, *SD* standard deviation

*p-value is significant

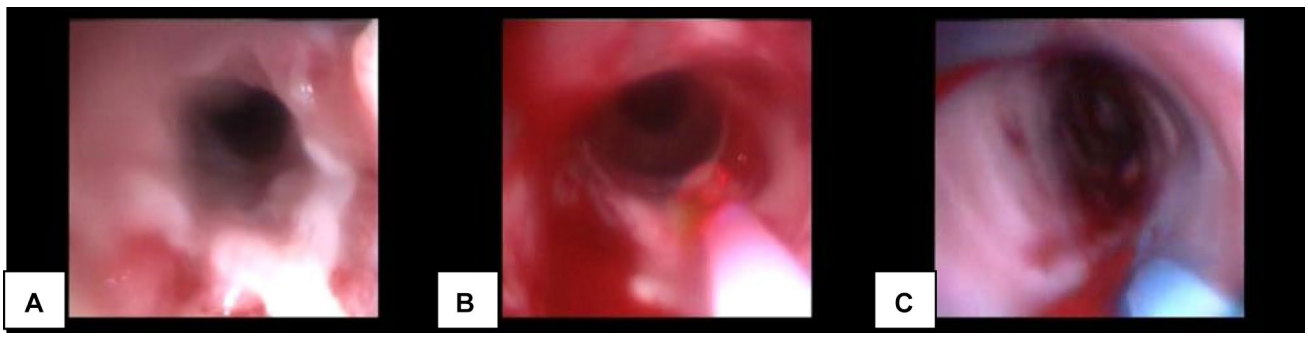

Fig. 3 Endoscopic images of the esophagus showing **A** esophageal caustic stricture before dilation, **B** esophagus after dilation with wire-guided Savary–Gilliard dilator and **C** a session after topical Mitomycin C application

Discussion

Accidental ingestion of corrosives represents a major childhood problem, especially in developing countries. Long caustic esophageal strictures are one of the most difficult problems facing pediatric surgeons all over the world. Endoscopic management is the first line of treatment which usually requires several repeated sessions of dilatation for a long period up to 2–3 years [5, 15]. The rate of restenosis is very high, so replacement of the native esophagus is done in most cases [16]. The postoperative scarring in different ophthalmological and trachea-laryngeal pathologies were successfully decreased by topical application of MMC [17–19]. In the last decade, MMC has been used topically with dilatation as an adjuvant therapeutic agent in resistant esophageal strictures, by preventing new collagen formation and thus decreasing the incidence of stricture recurrence [11, 20].

In this study, the patients who showed complete cure in MMC group was double the number of patients in the group treated with dilatation alone (81.6 vs. 40%). Berger et al. [9] published a systematic review on treatment of refractory esophageal strictures by topical application of

MMC, it constituted 31 cases from 11 publications showing complete cure of symptoms in 67.7% of cases and partial relief for 19.4% patients [9]. This effect was confirmed by a randomized, double-blind, placebo-controlled trial done on localized caustic esophageal stricture done by El-Asmar et al. [11]. A few case reports were published on refractory esophageal strictures showed a promising response to topical application of MMC [21, 22]. Kumar and Bhatnagar reported a 90% success rate in their 10 cases series of MMC application on caustic esophageal stricture [23].

Topical MMC application was effective in the treated group II, allowing the passage of large sized dilators easily and there was early symptomatic relief. We also did not observe any adverse effect of MMC treatment as well as in other studies [7, 22].

The mean number of sessions required for easy passage of 40 F dilator after application of MMC locally was $3.25 \pm$ SD 2.78, with statistically significant difference ($p < 0.00001$) in comparison to the first group as shown in Table 3. Also, Kumar and Bhatnagar, reported a 3.4 mean number of dilatation sessions with the application of MMC in each session [23].

In this study, the mean cost of sessions within the treatment period in the MMC group was almost half that of the dilatation only group. So the early introduction of MMC could save these patients a lot of stress and money and decrease the number of sessions and duration till complete improvement in children with caustic esophageal strictures.

We concluded that topical application of MMC is a promising agent in the management of long-segment refractory caustic esophageal strictures. The cure rate in our study was double in MMC group when compared with the group treated with dilatation alone. MMC application significantly improved symptoms and reduced both the number and frequency of dilatations in patients with refractory caustic esophageal strictures and hence reduced the cost. The adjuvant effects that were observed in our patients, made us recommended the topical application of MMC with endoscopic dilatation of benign refractory caustic oesophageal strictures, as it would augment the efficacy of endoscopic dilatation.

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Author contribution Dr. Carolyne Morcos Ibrahim Ghobrial carried out data collection and the initial analyses, statistical analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Ayman Emil Eskander designed the data collection, and coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

Compliance with ethical standards

Disclosures Dr. Carolyne Ghobrial and Prof. Ayman Eskander have indicated that they have no conflicts of interest to disclose and have no financial relationships relevant to this article to disclose.

Ethical approval This study was approved by the Ethics Committee of the Departments of Pediatrics, Kasr Alainy School of Medicine, Cairo University, Cairo, Egypt

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