Mitomycin C application in resistant caustic esophageal stricture

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Background/purpose **Caustic esophageal strictures still represent a catastrophic problem in children of our country. Management protocol is usually started by regular esophageal dilatation in which multiple sessions may be needed until the resolution of dysphagia; however, in many cases endoscopic dilatation fails and therefore esophageal replacement is eventually required. Our aim is to assess the role of mitomycin C application in the management of caustic esophageal stricture refractory to regular endoscopic dilatation.**

Patients and methods **Patients with resistant caustic esophageal stricture were subjected to topical mitomycin C application on stricture site after endoscopic dilatation. Patients were followed up clinically using validated dysphagia score to assess the improvement of dysphagia, radiologically by contrast esophagogram and endoscopically to confirm resolution of the stricture. Results were analyzed and compared with results of a control group managed at the institution by a regular dilatation protocol.**

Results **During the period January 2008 to June 2010, 12 patients with resistant caustic esophageal stricture were followed at our unit of whom six had a short esophageal stricture (<3 cm) and six had a long stricture (>3 cm). Topical mitomycin C application resulted in clinical and radiological resolution of dysphagia and strictures in 83% and 66% respectively, compared with 44 (eight out of 18 patients with short stricture) and 25% (two out of eight patients with long stricture) in the control group.**

Conclusion **Mitomycin C application can markedly improve the outcome of patients with caustic esophageal stricture, reducing the number of required sessions for endoscopic dilatation. However, double-blinded randomized controlled trial is needed to prove its effectiveness.** *Ann Pediatr Surg* **7:49–54 © 2011 Annals of Pediatric Surgery**

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Introduction

Although the incidence of caustic esophageal strictures has declined in developed countries because of improvement in product packaging and health education, many children in developing countries continue to sustain caustic esophageal injuries from accidental ingestion of alkaline or acidic products, resulting in coagulative or liquifactive necrosis of varied length and depth of the esophagus [1,2].

These esophageal injuries eventually lead to stricture formation in approximately 6 weeks. These strictures require repeated esophageal dilatations, or in severe cases, esophageal replacement. Although a number of agents have been tried experimentally to prevent stricture formation, few have gained clinical application [3].

Mitomycin C (MMC) is an antineoplastic agent that inhibits fibroblast proliferation and reduces collagen cross-linking, which has been proven to be effective in reducing scar formation in animal experiments [2]. In rats, MMC proved to be effective in preventing strictures following experimental caustic esophageal injury, in a dose-dependent manner [3].

MMC has been used successfully with no complications as an adjuvant treatment in several ophthalmological procedures and in laryngotracheal stenosis [4]. Topical application of MMC after dilatation is a new technique that has been recently used for management of esophageal stricture in children, and a few case reports were published; however, no planned studies have been reported yet [2,4–8].

The purpose of this study was to evaluate the effect of MMC topical application after dilatation of caustic esophageal stricture resistant on regular endoscopic dilatation.

Patients and methods

Children presented to the pediatric surgery department, Ain Shams University, with resistant caustic esophageal strictures (who failed to improve after at least 6 months of regular endoscopic esophageal dilatation) were included in this study. Patients with previous esophageal surgery and patients known to have hypersensitivity or contraindication for MMC were excluded from the study.

A detailed history was taken, including time and type of corrosive ingestion, duration and number of previous sessions of endoscopic dilatation, and the degree of dysphagia before and after the previous dilatation

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Table 1 Dysphagia score (Knyrim *et al.* [9])

Dysphagia score	
0	Able to eat normal diet/no dysphagia
1	Able to swallow some solid foods
2	Able to swallow only semisolid foods
3	Able to swallow only liquids
4	Unable to swallow anything/total dysphagia

period. Degree of dysphagia was evaluated according to a validated dysphagia scoring system [9] (Table 1), and a new barium swallow study was conducted before application of MMC.

Informed consent was taken from the parents after an explanation of the endoscopic technique and the possible associated complications including iatrogenic perforation and failure.

MMC solution (Mitomycin C Kyowa, Biochem Pharmaceutical Industries Ltd, India) was prepared by diluting 10 mg of its commercial powder form in 25 ml of distilled water to reach a concentration of 0.4 mg/ml, to be applied on the stricture site for 5 min estimated using a stopwatch.

Technique

Our technique starts by esophageal dilatation using flexible endoscopy and a wire-guided Savary Gilliard dilator under the fluoroscopy. The size of the child's thumb was considered as a rough measure of esophageal lumen and for the appropriate size of the dilator used. After the dilatation, we accurately assessed the stricture site and length by visualizing it endoscopically. Then, application of MMC was followed using a rigid esophagoscope with a piece of cotton soaked in diluted MMC solution that was delivered to the stricture site by a grasper. The soaked cotton piece was kept applied on the esophageal wall at stricture site for 5 minutes. Postendoscopy chest radiograph was a must for exclusion of iatrogenic esophageal perforation.

Follow-up

Patients were followed monthly by the dysphagia score (DS), by the barium swallow study 3 and 6 months after MMC application, and endoscopically 1-month after the session of MMC application for assessment of integrity and continuity of esophageal mucosa over the stricture site.

Our primary endpoint was the number of dilatations required to make the child free of dysphagia.

The results were compared with a control group of patients with caustic esophageal stricture, managed at the same institute in the previous 2 years, who were on a regular dilatation protocol.

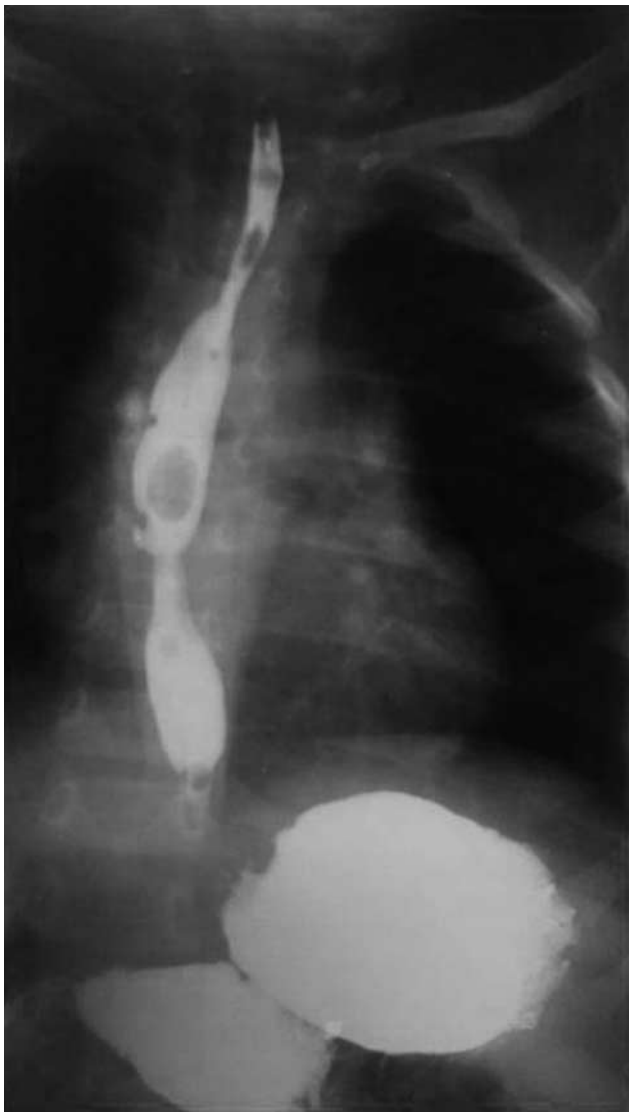
Results

From the period January 2008 to June 2010, 12 patients were followed at our unit with resistant caustic esophageal stricture of whom seven were boys and five were girls. Their age at presentation was ranging from 1.75 to 4.5 years (mean: 2.8 years), and all injuries were caused by alkali corrosive ingestion, except one, which was caused by ingestion of an acidic product. Six of them had a short esophageal stricture (< 3 cm in length) and the other six had a long stricture (> 3 cm in length). These patients underwent multiple sessions of regular endoscopic dilatation with no improvement of their dysphagia; they underwent a mean number of 9.3 dilatation sessions (ranging from 6 to 18 times) within a mean period of 9.5 months (ranging from 6 to 24 months).

All 12 patients were subjected to topical MMC application after dilatation, once for the short strictures and in multiple sessions for the long ones. Patients were followed for a period ranging from 6 to 28 months (mean: 13.6 months).

In the control regular dilatation group, we had 26 patients of which 17 were boys and nine were girls, with age ranging from 1.5 to 5 years (mean: 2.9 years). All had alkali-induced strictures. Eighteen of them had a short stricture, whereas the other eight had a long one.

Fig. 1

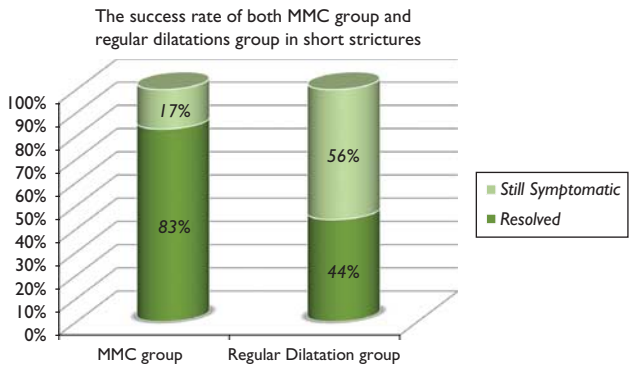


Esophagogram before mitomycin C application for a patient with resistant localized esophageal stricture, dysphagia score = 2.

Fig. 2

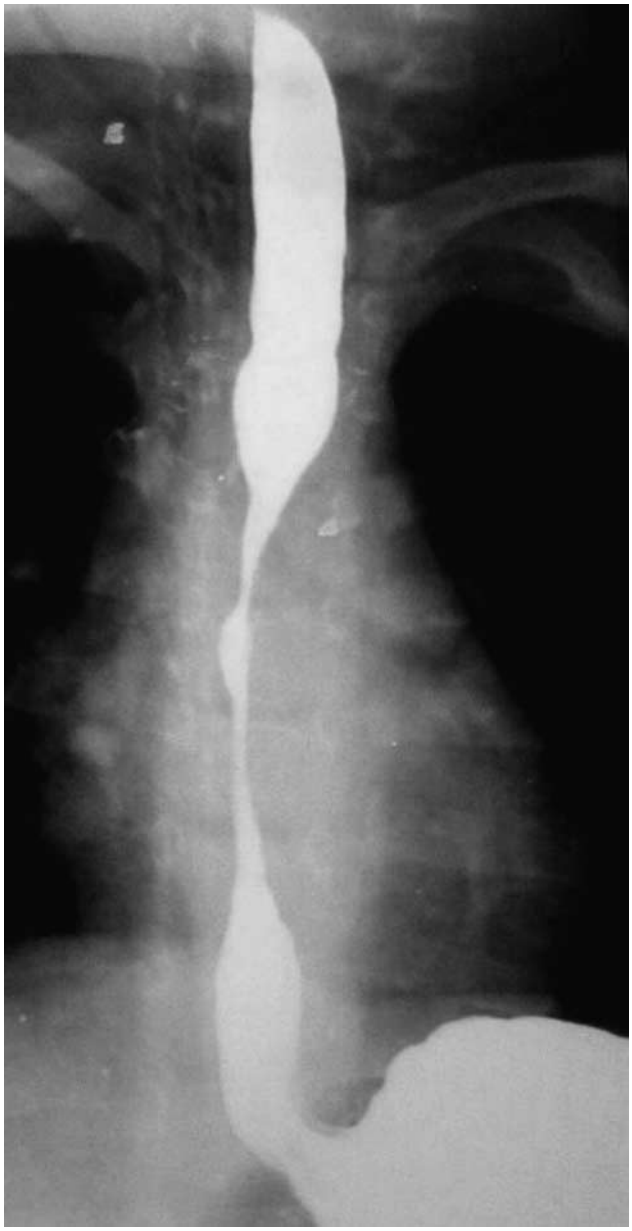
Markedly improved esophagogram of the same patient after mitomycin C application once, dysphagia score = 0.

Fig. 3



The success rate of both mitomycin C (MMC) group and regular dilatations group in short strictures.

Fig. 4



Esophagogram before mitomycin C application for a patient with 6-cm esophageal stricture, dysphagia score = 2.

Patients with short stricture and who had MMC application needed an average of 2.3 dilatation sessions (three patients needed one session, two patients needed two sessions, and the sixth nonresponding patient needed seven sessions till date) to obtain five out of six patients who were completely free of dysphagia, reaching DS = 0 (Figs 1 and 2), whereas the sixth patient had only partial improvement with DS = 1. In contrast, in the regular dilatation group, we needed an average of 8.3 dilatation sessions (ranging from five to 12 sessions) to obtain only eight out of 18 patients who were completely free of dysphagia (Fig. 3).

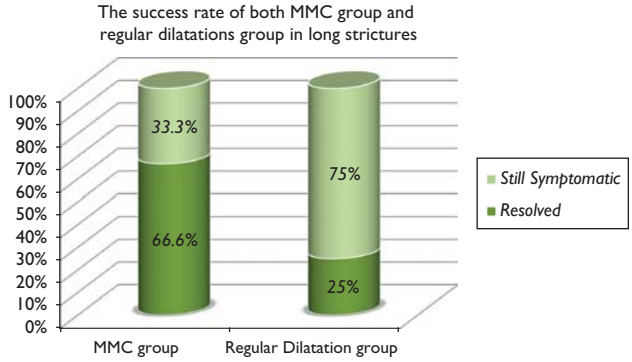
Patients with long stricture and who had MMC application needed an average of 5.5 dilatation sessions (ranging from four to 11 sessions) to obtain four out of six patients

Fig. 5

Markedly improved esophagogram of the same patient after MMC application (four times), dysphagia score = 0.

who were completely free of dysphagia, reaching DS = 0 (Figs 4 and 5), whereas the fifth patient had only partial improvement (from DS = 2 to DS = 1) and the sixth one had not improved at all (DS = 2). In contrast, in the regular dilatation group, we needed an average of 11.5 dilatation sessions (ranging from nine to 15 sessions) to obtain only two out of eight patients who were completely free of dysphagia, with no improvement in the rest of the cases (Fig. 6).

Fig. 6



The success rate of both mitomycin C (MMC) group and regular dilatations group in long strictures.

It is to be noted that long strictures needed multiple sessions of MMC application; in our patients, we applied it two to five times (mean: 3.8 times) for stricture length ranging from 4 to 7 cm (mean: 5.3 cm).

It is worthy to be mentioned that follow-up endoscopy after MMC application showed healthy esophageal mucosa over the stricture site. No intraoperative or postoperative complications were encountered in both groups of patients (Table 2).

Discussion

The ideal management of caustic esophageal stricture still represents a great challenge for pediatric surgeons. Serial endoscopic dilatations and esophageal replacement have been used with varying levels of success [1,10]. Esophageal salvage is preferable when possible, but repeated sessions of dilatation may be required because of occurrence of restenosis. The cause of recurrent stricture is unknown, but intense fibrogenesis during healing and after the traumatic dilatation procedure may be the cause, making repeated dilatations necessary, but with an increased risk of complications and perforation [11,12].

In our institution, failure of dilatation of long, multiple, and persistent strictures was an indication of esophageal replacement. The drawbacks of repeated dilatation include psychological problems, withdrawal from school, hospital fears, and familial problems [1,13]. Trials to decrease the number of dilatations, to avoid surgery, and to revert strictures included the use of steroid injection in localized strictures, which increased the intervals between dilatation but did not decrease the need for replacement [1], stents with its high incidence of failure and morbidity [5], and many other inapplicable experimental studies [3,14,15]. Sporadic trials using MMC application on localized strictures have shown better outcome with less number of dilatations [2,5,7,8]. A pilot study conducted at our institute showed marked improvement of the dysphagia with a decrease in the number of dilatations and in the number of replacements.

MMC has an antiproliferative effect on fibroblasts. By bonding to DNA, it inhibits DNA-dependent RNA synthesis and reduces fibroblastic proliferation and

Table 2 Summary of cases with resistant esophageal stricture subjected to mitomycin C application

Patient number	Age (years)	Sex	Stricture length (cm)	Number of dilatation before MMC	Duration of earlier dilatation (ms)	Number of dilatation after MMC	Follow-up (months)	DS before MMC	Number of MMC application	DS after MMC
Short stricture										
1	4.5	M	1.5	7	12	1	28	2	Once	0
2	3.0	F	1.0	18	24	2	20	3	Once	0
3	3.0	M	2.0	9	6	1	6	2	Once	0
4	2.0	M	2.0	9	6	2	11	3	Once	0
5	2.0	F	2.0	10	6	1	7	2	Once	0
6	4.5	M	2.0	9	16	7	23	3	Once	1
Long stricture										
7	2.25	F	5.0	11	12	4	23	2	2	0
8	2.25	M	6.0	7	6	4	8	3	4	0
9	4.0	F	5.0	6	6	4	10	2	4	0
10	2.0	F	5.0	10	9	6	6	3	5	0
11	1.75	M	4.0	7	6	4	7	2	4	2
12	2.0	M	7.0	9	6	11	15	2	4	1

DS, dysphagia score; F, female; M, male; MMC, mitomycin C.

collagen bonding [16]. The healthy mucosa that was observed endoscopically after the application of MMC suggested that MMC, by reducing the fibrogenesis process in submucosa, gives the mucosa enough time to creep and to cover the stricture site, which prevents restenosis again; however, biopsy for histopathological examination is required to prove this effect.

No data exist that indicate the most effective concentration, duration, or frequency of application of MMC. We used a solution of 0.4 mg/ml MMC and applied it to the stricture site for 5 min. Other investigators reported usage of 1 mg/ml concentration to be applied for 2 min on a small number of patients with no related complications [5,16]. However, double-blinded randomized trial is needed to justify which concentration and duration is more effective and safer.

In this study, we had six patients with a short esophageal stricture, this group had an excellent response to MMC application with a success rate of 83%. The responding five patients needed only one or two sessions of dilatation and now they are able to eat solid food freely with medium-term follow-up of 6–28 months till date. This represents a much better outcome than that achieved by the other groups of regular dilatation with a lower success rate of 44%, in addition to the need for more numbers of dilatations. Our results were consistent with the other published case reports where they stated the marked response of resistant esophageal stricture, either caustic or anastomotic site strictures, to MMC application [2,5,7,8]. Kumar and Bhatnagar [7] reported a 90% success rate of MMC application on 10 patients with esophageal stricture, of which six of them had post-anastomotic stricture and the other four were fresh caustic stricture cases; these patients needed a mean number of 3.4 dilatations.

In the literature, there is no reported trial of MMC application or any other local chemical substance on long caustic esophageal stricture, and no available accurate data about the success rate of regular dilatation on long esophageal stricture, but it is reported that most of them eventually end by esophageal replacement [1]. In our study, the six patients with long esophageal stricture who were subjected to multiple sessions of MMC application obtained a success rate of 66.6% compared with only 25% in the regular dilatation group. The stricture length of 5–6 cm in four patients showed good response to MMC multiple (two–five times) application sessions; these patients can now eat everything with no need for more sessions of dilatation or surgical intervention for 6–23 months of follow-up till date.

Although the success rate of MMC application in long stricture is less than being achieved in short ones with the need for multiple applications, it is worthy to be tried before the decision of esophageal replacement is taken in these patients because, to date, there is no better substitute for the native esophagus; the ideal graft does not exist [1].

Conclusion

MMC topical application can markedly improve the outcome of patients with caustic esophageal stricture, reducing the number of required sessions for endoscopic dilatation. It should be considered as an adjunct new modality and a potential alternative to repeated dilatations, stent placement, or surgery for the management of resistant caustic esophageal strictures, either short or long.

However, prospective double-blinded randomized controlled trial with long-term assessment of outcomes is required to prove the efficacy of MMC in these patients.

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