Prognostic factors for success of topical mitomycin c application with endoscopic dilatation on caustic esophageal strictures

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Background
Caustic ingestion is still a difficult medical problem, and the outcome is often unexpected. Caustic esophageal strictures are mainly managed by serial esophageal intraluminal dilation. However, when applied in isolation, it may not reach the necessary diameter for significant symptom improvement, so there is an unmet need to evaluate novel treatments, such as topical mitomycin C (MMC).
Aim
The main aim of this study was to assess the prognostic factors for success of topical MMC application with endoscopic dilatation on caustic esophageal strictures.
Patients and methods
This prospective study was conducted on patients with postcorrosive esophageal stricture with a recent history of corrosive ingestion attending Pediatric Surgery Departments in Ain Shams University and Minia University Pediatric Hospitals in the period between January 2019 and December 2020. Endoscopic dilatation followed by MMC application was done in all patients. Prognostic factors such as age, sex, type of the caustic substance, dysphagia score, site of stricture, length of stricture, need for gastrostomy, need for admission in the ICU in the acute stage, laboratory data abnormalities in the acute stage (complete blood picture and arterial blood gases), number of dilatations needed, and the required numbers of dilatations per month [periodic dilatation index (PDI)] were studied in all patients. The patients were followed up for at least 1 and a half years after the start of dilatation.
Results
During the specified time periods, 24 patients presented to Pediatric Surgery Departments in Ain Shams University and Minia University Pediatric Hospitals. The patients' ages ranged from 2 to 10 years. There were 14 (58.3%) males and 10 (41.7%) females. In 66.7% of cases, the caustic agent was alkaline, whereas it was acidic in 33.3% of cases. The mean dysphagia score improved from 3.54 ± 0.5 to 0.79 ± 0.66. The site of stricture was at the middle esophagus in 20 (83.3%) cases, whereas four (16.7%) cases had stricture in the lower esophagus. The length of stricture was more than or equal to 3 cm in 58.3% of cases, whereas 41.7% of cases had length less than 3 cm. Two (8.3%) patients needed gastrostomy. A total of 17 (70.8%) children were admitted in the ICU toxicology at acute stage, whereas seven (29.2%) children were not. The mean hemoglobin level was 10.27 g/dl, the mean total leukocytic count was 11.78 cell/mm^3, the mean platelets count was 353 235.29 cell/mm^3, the mean pH was 7.464, and the mean PCO_2 was 35.0 mmHg. The mean number of dilatations was 12.63 ± 3.12 and ranged from 7 to 19. The mean PDI in the studied cases was 0.64 ± 0.14 and ranged from 0.4 to 1.0. Overall, we found that 21 (87.5%) cases showed clinical improvement, whereas three (12.5%) cases did not improve. There was a significant correlation between the PDI and the success of MMC application with endoscopic dilatation, whereas there was no significant correlation between success and other prognostic factors.
Conclusion
Low PDI is a good prognostic factor for success of topical MMC application with endoscopic dilatation on caustic esophageal stricture.

Keywords:
caustic esophageal stricture, endoscopic dilatation, prognostic factors, topical mitomycin C application

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Introduction

Chemical burn of the esophagus following the ingestion of corrosives accounts for a significant number of

strictures, which constitute the major indication for esophageal replacement in children [1].

The management of caustic ingestion remains a difficult problem because of a lack of clear relationship between signs and symptoms and the severity of the gastro-esophageal injury [2].

The cornerstone in the treatment of postcaustic strictures is endoscopic dilatation. The success rate of this treatment varies widely among centers, ranging from 25 to 95%. During the last decade, the success rate has improved worldwide with the concomitant use of certain products such as the antineoplastic agent mitomycin C (MMC) and triamcinolone acetonide [3].

The main aim of this study was to assess prognostic factors for success of topical MMC application with endoscopic dilatation on caustic esophageal strictures.

Patients and methods

This study was conducted at Pediatric Surgery Departments in Ain Shams University and Minia University Pediatric Hospitals on infants and children who were suffering from caustic esophageal stricture with a recent history of corrosive ingestion in the period between January 2019 and December 2020. The patients excluded from the study were those who underwent previous dilatation, refused to follow the protocol, underwent any previous esophageal procedure, or with known hypersensitivity to MMC.

This research was performed at the Department of General Surgery, Ain Shams University Hospitals. Ethical Committee approval and written, informed consent were obtained from all participants.

Prognostic factors such as age, sex, type of the caustic substance, dysphagia score, site of stricture, length of stricture, need for gastrostomy, need for admission in the ICU in the acute stage, laboratory data abnormalities in the acute stage (complete blood picture and arterial blood gases), number of dilatations needed, and the required numbers of dilatations per month [periodic dilatation index (PDI)] were studied in all patients.

All patients were studied through a barium contrast study done 3 weeks after ingestion of the corrosive to define the site of the esophageal stricture, the length of esophageal stricture, and the extent of gastric cicatrization.

Endoscopy was performed in each patient to confirm the radiologic findings and to assess the characteristics of the esophageal strictures and the presence or absence of esophagitis and gastric cicatrization.

We started dilatation 6 weeks after corrosive ingestion with a session every 2 weeks for 3 months then every 1 month for 3 months then every 2 months for 6 months and this was guided more with patient symptoms [4].

The procedure was performed under controlled general anesthesia with endotracheal intubation in all cases, flexible endoscope was introduced, and esophageal dilatations were performed initially.

Patients were progressively dilated (rule of three bougies of increasing size per session) at 14-day interval. The stricture was dilated by a wire-guided passage of Savary-Gilliard dilators. The size of child thumb was considered as a reference guide for appropriate size of dilator used. After placement of guide wire to the stomach, a dilatation was initiated.

The length of the stricture was measured after endoscopic dilatation. A length of 3 cm was used as a threshold value for classifying the stricture: less than 3 cm, short stricture, and more than or equal to 3 cm, long stricture.

The technique of mitomycin application is that defined by El Asmar *et al.* [4]. A piece of cotton was sutured to the distal part of the Nelaton catheter. The length of the sponge, which was wrapped to the distal part of the catheter, must be equal to the length of the esophageal stricture. The distal part of the catheter was placed to the inner side of the stricture. Thereafter, 10 mL of MMC 1 mg/ml is put from the proximal part of the Nelaton catheter, so the sponge was made wet with mitomycin solution.

The catheter with the wet sponge was held in the esophagus for 10 min during application. The catheter was removed, and the procedure was terminated. Chest radiograph was done after 6 h, and the patient was discharged on the same day of application.

After the procedure, improvement of dysphagia (Dysphagia Scoring System) (Table 1), the number

Table 1 Dysphagia scoring system [5]

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 liquids only
4	Unable to swallow anything/total dysphagia

of dilatations required to reach adequate luminal size, PDI, and occurrence of complications [anesthetic complications, intraoperative complications (bleeding and perforation of esophagus), and mitomycin application-related complications such as myelosuppression] were studied. The patients were followed up for at least 1 and a half years after the start of dilatation.

Statistical analysis

Data was collected, coded, and then entered as a spreadsheet using Microsoft Excel 2016 for Windows, of the Microsoft Office bundle; 2016 of Microsoft Corporation, United States. Data were analyzed using IBM Statistical Package for Social Sciences software (SPSS) (IBM SPSS Statistics for Windows, version 26.0.; IBM Corp., Armonk, New York, USA). The Kolmogorov–Smirnov test was used to verify the normality of distribution. Continuous data were expressed as mean±SD, median, and IQR, whereas categorical data were expressed as numbers and percentage. Results were considered statistically significant at a *P* value of less than or equal to 0.05 and highly statistically significant at a *P* value of less than or equal to 0.001.

The used tests were χ^2 test (for categorical variables), to compare between different groups; Fisher's exact or Monte–Carlo correction (correction for $\chi^2$when >20% of the cells have expected count <5); Student *t* test (for normally distributed quantitative variables), to compare between two studied groups; and Mann–Whitney test (for abnormally distributed quantitative variables, to compare between two studied groups).

Table 2 Distribution of stricture length among the studied patients

	Studied patients (*N*=24) [*n* (%)]
Length stricture (cm)	
Range	2.0–5.0
Mean±SD	2.75±0.79
Median	3.0
<3 cm	10 (41.7)
≥3 cm	14 (58.3)

Results

This study was conducted on 24 patients with postcorrosive esophageal stricture with recent history of corrosive ingestion attending to Pediatric Surgery Departments in Ain Shams University and Minia University Pediatric Hospitals. Age of the patients ranged from 2 to 10 years (mean, 4.17±1.95years). There were 14 (58.3%) males and 10 (41.7%) females, with a male-to-female ratio of 1.4 : 1. The caustic type was alkaline in 16 (66.7%) patients, whereas it was acidic in eight (33.3%) children. The site of the stricture was at middle esophagus in 20 (83.3%) cases, whereas four (16.7%) cases had stricture in lower esophagus (Table 2).

Of 24 patients, two (8.3%) patients needed gastrostomy. The mean number of dilatations in the studied cases was 12.63±3.12 and ranged from 7 to 19. The mean period of dilatation in the studied cases was 7.52±2.59 and ranged from 2 to 12 months. The mean PDI in the studied cases was 0.64±0.14 and ranged from 0.4 to 1.0. The mean dysphagia score before dilatation in the studied cases was 3.54±0.5 and the mean dysphagia score after 1 year of dilatation was 1.67±0.70, whereas the mean dysphagia score now is 0.79±0.66. There was significant improvement (decrease) in dysphagia score after dilatation compared with before dilatation (*P*<0.001) (Table 3).

Regarding outcome, 87.5% showed clinical improvement, whereas 12.5% of cases did not improved, as shown in Table 4.

There were 17 (70.8%) children admitted at ICU toxicology at acute stage, whereas seven (29.2%) children were not.

Table 3 Distribution of clinical improvement dysphagia score among the studied patients

	Before dilatation [*n* (%)]	After 1 year of dilatation [*n* (%)]	Score now [*n* (%)]	*P* value
Dysphagia score				
Range	3.0–4.0	1.0–3.0	1.0–2.0	<0.001
Mean±SD	3.54±0.51	1.67±0.70	0.79±0.66	*P*1<0.001 *P*2<0.001 *P*3=0.018
Median	4.0	2.0	1.0	
0	0	0	8 (33.3)	<0.001
1	0	11 (45.8)	13 (54.2)	
2	0	10 (41.7)	3 (12.5)	
3	11 (45.8)	3 (12.5)	0	
4	13 (54.2)	0	0	

P value less than or equal to 0.05 is considered statistically significant, *P* value less than or equal to 0.01 is considered high statistically significant. *P*1: *P* value between before and after 1-year dilatation. *P*2: *P* value between before and score now. *P*3: *P* value between score now and after 1-year dilatation – related-samples friedman's two-way analysis of variance.

Laboratory data of the studied children who were admitted to ICU toxicology at acute stage are shown in Table 5.

Relation between improvement and different parameters, as shown in Table 6.

Discussion

Ingestion of caustic products and the development of esophageal strictures are recognized major public health problems in childhood [6]. Esophageal perforation and mortality are potentially serious complications in the acute period, whereas strictures occur in the chronic period [7]. Caustic strictures are considered the most challenging among esophageal strictures, with dilation as a first line of treatment, aiming at preserving the native esophagus [8].

The traditional initial treatment is serial esophageal intraluminal dilation. However, when applied in isolation, it may not reach the necessary diameter for significant improvement of symptoms. Furthermore, the relapse of injuries is common after dilations due to the process of trauma and healing repeatedly caused to the inner mucosa [9].

There is an unmet need to evaluate novel treatments, such as topical or intraregional corticoid application, esophageal stents, surgical resection of stenosed segments, or esophagectomy with complex reconstruction in refractory cases [10].

Several agents have been proposed as an adjuvant therapy to increase the success rate of dilatation of refractory esophageal strictures [11]. MMC has anti-fibroblastic activity and antiproliferative properties, thus decreasing the incidence of stricture recurrence and might give the chance to avoid a surgical procedure [12].

Some recent studies have evaluated the efficacy of using topical MMC within this context [4,6,13–16].

Nonetheless, the use of MMC is still controversial owing to the small number of comparative studies available in the literature and few prospective data evaluating efficacy, indication, dosage, application technique, and safety. Different techniques for MMC have been reported. Cotton pledgets soaked in the MMC solution have generally been used. Other techniques, such as drugeluting stents, have also been used [17].

Our study included 24 patients (14 males and 10 females), with a male-to-female ratio of 1.4 : 1, which was compatible with another study done by Ley *et al.* [18], where they enrolled 39 patients (17 females and 22 males), with a male-to-female ratio of 1.3 : 1.

Regarding the mean PDI in our studied cases, it was 064 ± 0.14 and ranged from 0.4 to 1 (P<0.001), which was compatible with another study done by Divarci *et al.* [19]. The median frequency of dilatation sessions was 4 weeks (range, 3–6 weeks) before topical MMC and it decreased to 0 weeks (range, 0–24 weeks) after intervention. The interval of dilatation sessions was significantly extended after mitomycin application. The median PDI was 1 (range, 0.66–1.34) before application, and it decreased to 0 (range, 0–1.33) after intervention. Topical MMC application had a significant positive effect on PDI (P<0.001).

Moreover, Ghobrial and Eskander [20] reported that the mean±SD number of sessions required for easy passage of 40 F dilator after application of MMC was 3.25 ± 2.78, with a statistically significant difference (P<0.00001). Moreover, Méndez-Nieto *et al.* [21] found that the number of sessions decreased

Table 4 Distribution of outcome among the studied patients

	Studied patients (N=24) [n (%)]
Complication	
No	24 (100.0)
Yes	0
Improvement	
Not improved	3 (12.5)
Improved	21 (87.5)

Table 5 Laboratory data of the studied children who admitted to ICU toxicology at acute stage

Parameters	Studied patients (N=17)		Median	Minimum	Maximum
	Mean	SD			
Laboratory data					
Hemoglobin	10.27	1.28	10.40	8.30	12.30
TLC	11.78	4.01	11.30	6.70	22.90
Platelets	353 235.29	135 404.27	315 000.0	192 000.0	627 000.0
pH	7.464	0.113	7.440	7.340	7.740
PCO_2	35.0	13.27	34.0	10.87	58.0

TLC, total leukocytic count.

Table 6 Relation between improvement and different parameters

	Improvement [*n* (%)]		Test value	*P* value	Significance
	Not improved (*N*=3)	Improved (*N*=21)			
Age (years)					
Mean±SD	2.50±0.50	4.40±1.97	Z_{MWU}=1.903		
Median	2.50	4.0		0.057	NS
Range	2.0–3.0	2.0–10.0			
Sex					
Male	0	14 (66.7)	χ^2=4.80	0.059^{FET}	NS
Female	3 (100.0)	7 (33.3)			
Caustic type					
Acidic	0	8 (38.1)	χ^2=1.714	0.526 ^{FET}	NS
Alkaline	3 (100.0)	13 (61.9)			
Stricture length					
Mean±SD	3.33±0.58	2.67±0.80	$^{Z}_{MWU}$=0.104		
Median	3.0	3.0		0.145	HS
Range	3.0–4.0	2.0–5.0			
<3 cm	0	10 (47.6)	χ^2=2.45	0.239^{FET}	
≥3 cm	3 (100.0)	11 (52.4)			
Site of stricture					
Lower	1 (33.3)	3 (14.3)	χ^2=0.686	0.437	NS
Middle	2 (66.7)	18 (85.7)			
ICU toxicology					
No	0	7 (33.3)	χ^2=1.412	0.530	NS
Yes	3 (100.0)	14 (66.7)			
Need for gastrostomy					
No	2 (66.7)	20 (95.2)	χ^2=2.805	0.239	NS
Yes	1 (33.3)	1 (4.8)			
PDI					
Mean±SD	0.83±0.19	0.61±0.12			
Median	0.88	0.60	$^{Z}_{MWU}$=2.055	0.040	S
Range	0.62–1.0	0.40–0.80			
N dilatation					
Mean±SD	14.33±4.04	12.38±3.01			
Median	15.0	12.0	$^{Z}_{MWU}$= 0.379	0.401	NS
Range	10.0–18.0	7.0–19.0			
Period of dilatation (months)					
Mean±SD	18.0±1.20	21.26±4.41			
Median	18.0	20.40	$^{Z}_{MWU}$=1.145	0.252	NS
Range	16.80–19.20	15.60–30.0			

PDI, periodic dilatation index. *P* value less than or equal to 0.05 is considered statistically significant, *P* value less than or equal to 0.01 is considered high statistically significant. Comparison between groups done by Mann–Whitney Test and χ^2 test.

significantly with MMC. However, Wishahy *et al.* [22] found that the median PDI decreased from 1 before MMC to 0.75 after MMC; however, the decrease was not statistically significant (*P*=0.052). This may be owing to the median duration between caustic ingestion and the first MMC application, which was 7 months in their study but in our study it was 6 weeks.

In the present study, the mean dysphagia score before dilatation in the studied cases was 3.54±0.5, the mean dysphagia score after 1 year of dilatation was 1.67±0.70, whereas the mean dysphagia score now is 0.79±0.66. There was significant improvement (decrease) in dysphagia score after dilatation compared with before dilatation. It was compatible with what was found by Divarci *et al.* [19], where the median dysphagia score was 2 (range, 1–3) before application and it decreased to 0 (range: 0–3) after intervention. So, dysphagia significantly resolved after application (*P*<0.001).

Our study revealed that the length of the stricture was short in 10 patients and long in 14 patients. The efficacy of mitomycin application was compared in short-segment and long-segment strictures by radiologic studies, endoscopic examinations, and clinical symptoms. Dysphagia was resolved in nine of 10 patients with short-segment strictures after TMC application (90%). In long-segment strictures, 12 of 14 patients were treated successfully after mitomycin application (85.7%). The study by Divarci *et al.* [19]

reported that the length of the stricture did not affect the success rate significantly. They also found that the length of the previous dilatation period before mitomycin application was seen as an important factor in the success rate of mitomycin application.

In our study, no complications were detected among the studied cases. However, Ley *et al.* [18] reported that one patient developed transient *Enterobacter cloacae* bacteremia after application of MC and dilatation, but antibiotic therapy rapidly improved outcome.

Herein, we found that 21 (87.5%) cases showed clinical improvement, whereas three (12.5%) cases did not improve. From literature, we can observe that the least response rate was found by Ley *et al.* [18], with 33% success rate, and the best success rate was found in the study by Zaidi *et al.* [23], who reported 86.7% success rate. Our results showed that 87.5% had clinical improvement. The variation in success rate may be attributed to the differences in sample size and inclusion criteria.

This study was compatible with what was found by Chen *et al.* [24], who concluded that white blood cell counts could not accurately predict severity of esophageal injury or esophageal stricture.

Havanond and Havanondin had considered that total leukocytic count (TLC) more than or equal to 20 000 cell/mm^3 at admission is an independent predictor of mortality and explained the increase in TLC by the pathophysiology of corrosive injury in the first few hours such as edema, eosinophilic necrosis, and mobilization of leukocyte as inflammatory reaction to corrosive injury occurrence [25].

Moreover, Otçu *et al.* [26] concluded that blood pH values had no role in predicting the severity of injury in corrosive intoxicated patients. However, it was not compatible with Rigo *et al.* [27] who concluded that increased TLC more than or equal to 20 000 cells/mm^3 was a predictive factor for failure of improvement and for mortality following corrosive ingestion, and also Cheng and Kao [28] reported that arterial pH less than 7.22 may indicate severe injury in the gastrointestinal tract that may require immediate surgical management. Moreover, Mahmoud *et al.* [29] concluded that the presence of leukocytosis more than or equal to 20 000 cell/mm^3 was a good predictor for stricture formation and the mortality in corrosive intoxicated patients, and there was a significant relation between blood pH less than 7.2 and the morality. Quingking *et al.* [30] concluded that increasing TLC more than or equal to 20 000 was the only significant risk factor of severe gastrointestinal injury and can predict the incidence of stricture formation, whereas clinical manifestations such as dysphagia were found to be a weak factor.

Conclusion

Low PDI is a good prognostic factor for success of topical MMC application with endoscopic dilatation on caustic esophageal stricture. However, age, sex, site of the stricture, length of the stricture, caustic type, hemoglobin, pH, and TLC did not have a strong correlation with success of topical MMC application with endoscopic dilatation on caustic esophageal stricture.

Conflicts of interest

There are no conflicts of interest.

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