

Role of Topical Mitomycin-C in the Treatment of Esophageal Strictures caused by Caustic Injury; Prospective Study from a Developing Country

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ABSTRACT

Aim: To compare the outcome of treatment in patients with post-caustic esophageal strictures treated with endoscopic dilatations with versus without topical Mitomycin-C.

Design: The present study was a randomized controlled trial.

Study settings: It was conducted at the Department of Gastroenterology, Mayo Hospital Lahore over 2 years from January 2019 to December 2020.

Methods: Sixty consecutive patients of both genders aged between 18-60 years presenting with esophageal strictures resulting from caustic injury were included after written informed consent. These patients were randomly allocated into 2 treatment groups. Patients in Group-M underwent application of topical Mitomycin-C and dilatations while those in Group-P underwent topical application of placebo and dilatations. Outcome was measured in terms of successful resolution of dysphagia and total no. of endoscopic-dilatation sessions required in each group.

Results: In the present study, the mean age of the study participants was 32.5±11.4 years. There were 34(56.7%) female and 26 (43.3%) male patients with a female to male ratio of 1.3:1. The combined treatment of topical Mitomycin-C and dilatations was associated with significantly higher success rate (86.7% vs. 43.3%; p-value<0.001) and lesser mean no. of dilatation sessions (3.40±1.04 vs. 6.73±2.29; p-value<0.001) regardless of patient's age and gender.

Conclusion: Combining topical Mitomycin-C with endoscopic dilatations was found to improve early outcome among patients with esophageal strictures resulting from caustic injury which advocates the preferred use of this novel approach in future surgical practice.

Keywords: Esophageal Strictures, Caustic Injury, Mitomycin-C, Dilatations

INTRODUCTION

A common rather persistent problem encountered in gastroenterology outdoors is dysphagia caused by esophageal strictures which can be either benign or malignant¹. Benign strictures may be congenital or acquired which in turn may be sequel of some previous surgery like congenital esophageal atresia, radiation therapy or acid peptic disease^{1,2}. Although dilatation frequently resolves the complaint in short term, the long term outcome is usually poor as many of these strictures are recurrent and become resistant with repeated dilatations¹⁻⁴. Due to this complex nature of esophageal strictures and associated morbidity and poor quality of life^{5,6} multiple adjuvants have been tried in addition to dilatation to improve the outcome like steroids and Mitomycin-C⁵⁻⁷. A number of trials have shown that endoscopic topical application of Mitomycin-C along with dilatations is superior to conventional practice of dilatations alone or in combination with steroids⁸⁻¹². However, majority of these studies have been conducted in children with congenital strictures or those resulting from surgery for atresia¹⁰⁻¹².

In developing countries including Pakistan, the most frequent cause of esophageal strictures in adults is caustic intake and sadly instead of being accidental, this caustic intake is most frequently intentional for suicidal tendencies¹³. A major contributor in this whole scenario is the widespread and unlicensed availability of such materials which can be purchased and consumed without any restriction^{13,14}. The situation gets worse as many of these victims and their attendants are not interested in their treatment so poor compliance and incomplete treatment leads to complex and resistant strictures^{13,14}. Although, studies conducted on congenital, post-surgical and malignant strictures have shown beneficial effect of Mitomycin-C⁸⁻¹² yet to date only a single study¹⁵ assessed the effect of Mitomycin-C in the management of strictures caused by caustic agents which are more serious concern in our setup as compared to developed countries. The present study was therefore conducted with a hope that if topical application of Mitomycin-C also improves the outcome of post-caustic strictures, it will enable better management of such cases in future surgical practice.

PATIENT AND METHODS

The present study was a randomized controlled trial (RCT) carried out at the Department of Gastroenterology, Mayo

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Hospital Lahore over 2 years from January 2019 to December 2020. Sample size of 60 cases was calculated with 95% confidence level and 80% power of test while taking expected frequency of successful treatment to be 80.0% with dilatations and Mitomycin-C and 35.0% with dilatations alone.¹⁵ Non-probability, consecutive sampling was done and 60 patients of both genders aged between 18-60 years were included into this study after taking written informed consent. Patients were considered if they had single esophageal stricture ≤ 3 cm in length confirmed upon endoscopy. Those with hypersensitivity to Mitomycin-C, multiple strictures, stricture length > 3 cm, esophageal perforation secondary to caustic ingestion or previous esophageal surgery were excluded. All patients underwent complete clinical assessment consisting of history, clinical and endoscopic examination. Validated Dysphagia Scoring System (Table 1) was used to assess the severity of dysphagia at presentation. A barium swallow was also acquired. The patients were divided in two groups using lottery method. Endoscopy was performed and patients in the experimental Group-M were applied Mitomycin-C (0.4 mg/ml) while normal saline was applied in patients in placebo Group-P. All patients were followed thereafter for endoscopic dilatation sessions every 2 weeks for 3 consecutive months followed by monthly for another 3 months and then after every 2 months for the next 6 months; protocol originally described by El-Asmar et al (2013)¹⁶. An H₂-blocker (Ranitidine) was prescribed to all the patients to prevent reflux-induced stricture. Upon each follow-up, patient was re-assessed by Validated Dysphagia Scoring System and dilatation was performed only if the patient was symptomatic. The outcome variables were proportion of patients who were asymptomatic at the end of 12 months treatment and the total number of dilatation sessions required in each group. Demographic details of the patient along with outcome measures were recorded in a predesigned proforma. All the procedures and patient's pre and post-operative assessments were made by a single consultant gastroenterologist (15 years' experience) to minimize bias while confounders were controlled by exclusion.

Table 1: Validated Dysphagia Scoring System (DS)

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

RESULTS

The age of the patients ranged from 18 years to 60 years with a mean of 32.5 ± 11.4 years. Majority 42(70%) of the patients was young; aged between 18-39 years. There were 34(56.7%) female and 26(43.3%) male patients with a female to male ratio of 1.3:1. There was no statistically significant difference in the study groups in terms of age and gender as shown in Table 2.

At 12 months follow-up, the frequency of successful treatment was significantly higher in patients treated with Mitomycin-C as compared to placebo (86.7% vs. 43.3%; p-value <0.001). The mean no. of dilatation sessions required were also significantly lesser (3.40 ± 1.04 vs. 6.73 ± 2.29 ; p-

value <0.001) in the experimental group as compared to control group as shown in Table 3. Similar difference was observed between the groups across various subgroups based on patient's age and gender.

Table 2: Demographic features of study groups

Characteristic	Mitomycin-C n=30	Placebo n=30	P value
Age (years)	32.23±10.85	32.73±12.11	0.867
• 18-39 years	22 (73.3%)	20 (66.7%)	0.573
• 40-60 years	8 (26.7%)	10 (33.3%)	
Gender			
• Male	14 (46.7%)	12 (40.0%)	0.602
• Female	16 (53.3%)	18 (60.0%)	

Independent sample t-test and chi-square test, observed difference was statistically insignificant

Table 3: Comparison of treatment outcome

Outcome	Mitomycin-C n=30	Placebo n=30	P value
Successful Treatment			
• Yes	26 (86.7%)	13 (43.3%)	$<0.001^*$
• No	4 (13.3%)	17 (56.7%)	
No. of Dilatation Sessions	3.40 ± 1.04	6.73 ± 2.29	$<0.001^*$

Independent sample t-test and chi-square test, * observed difference was statistically significant

DISCUSSION

Benign strictures of the esophagus usually result from gastroesophageal reflux disease, esophageal surgery or ingestion of caustic agents.¹ The common presenting feature in all of these cases is dysphagia and subsequent loss of weight and poor quality of life.¹⁻³ As many of the cases with caustic injury are secondary to suicidal attempt, lack of interest in the treatment and poor compliance are main hurdles in the successful management of such cases.^{13,14} Usually, these patients present late with history of multiple, incomplete and unsuccessful attempts which make the management of these cases complex.¹³ Although Mitomycin-C has been successfully tried in the management of other benign esophageal strictures⁸⁻¹² evidence on its role in post-caustic strictures was limited owing to the hard fact that this caustic injury is the problem of developing countries where there is no restriction on the over the counter sale and use of such chemicals.¹³ In the present study, we investigated the role of Mitomycin-C in the management of esophageal strictures from caustic injury.

In the present study, we observed a relatively younger mean age of 32.5 ± 11.4 years with 70% of patients aged between 18-39 years. We also observed a female predominance among such patients. This younger mean age and female predominance is in line with the suicidal mechanism of injury attributable to emotional instability in this age and gender. Our observation is backed by other similar studies where Qureshi et al¹⁷ (2010) reported similar mean age of 33.4 ± 18.2 years with a female to male ratio of 1.4:1. In a similar Indian study, Shah et al¹⁸ (2019) observed similar female predominance (1.3:1) with a mean age of 31.0 years among patients presenting with caustic induced esophageal strictures. In another similar study, Joshi et al.¹⁹ (2019) observed mean age of 28.8 years

among Indian patients presenting with caustic injury with similar female to male ratio of 1.5:1.

We observed that Mitomycin-C application not only increased the frequency of successful resolution of dysphagia but also decreased the mean no. of dilatation sessions required in these patients. Our observation is in line with a previous study where El-Asmar et al¹⁵ (2013) studied 40 Egyptian patients with esophageal strictures resulting from caustic injury and reported that topical application of Mitomycin-C significantly increased the frequency of successful treatment (80% vs. 35%; p-value<0.001) as well as reduced the mean no. of dilation sessions (3.85 ± 2.08 vs. 6.9 ± 2.12 ; p-value<0.001) as compared to placebo.

The present study is first of its kind in local population and adds to the limited already published research evidence on the topic. The strengths of the present study were its large sample size of 60 cases and randomized study design. We also followed strict exclusion criteria and stratified results for age and gender to address effect modifiers. In the light of results of the present study, this combined approach consisting of Mitomycin-C and dilatation offers better success rate and is associated with lesser dilatation attempts as compared to conventional practice of dilatation alone in patients with post-caustic esophageal strictures. Though these results favor the use of this novel approach in future practice, there is need for future studies comparing recurrence of stricture in long term follow-up and potential complications of this topical application of Mitomycin-C. Also there is need to assess the outcome of Mitomycin-C in combination with other adjuvants like steroids. This information would further help in the selection of more appropriate treatment plan in patients with post-caustic ingestion strictures. Such a study is highly recommended in future research.

CONCLUSION

Combining topical Mitomycin-C with endoscopic dilatations was found to improve early outcome among patients with esophageal strictures resulting from caustic injury which advocates the preferred use of this novel approach in future surgical practice.

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