

# Effect of Topical Mitomycin C as an Adjunct to Dilation Therapy in Esophageal Stricture

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## ABSTRACT

**Background:** The treatment of choice for most esophageal strictures is esophageal dilatation but it has a low success rate. This study was conducted to determine the effect of topical mitomycin C as an adjunct to dilatation therapy in esophageal strictures among children.

**Methods:** This randomized controlled trial was conducted at the Department of Pediatric Gastroenterology, The Children's Hospital and Institute of Child Health, Multan, Pakistan, from July 2022 to October 2023. Children aged 1-12 years and having esophageal strictures were included. A simple random sampling technique was adopted. Children in the Mitomycin C group received topical mitomycin C (2 mg/20 ml saline) during the endoscopy, whereas the placebo group received normal saline. The counts of dilatation sessions necessary in each group and the proportion of patients who were symptom-free after 12 months of therapy were noted (outcome). IBM-SPSS 26 was used for data analysis with  $p < 0.05$  considered significant.

**Results:** In a total of 76 children, 52 (68.4%) were male. Overall, the mean age was  $4.49 \pm 1.96$  years. The mean age in mitomycin C ( $n=38$ ) and placebo group ( $n=38$ ) were  $4.85 \pm 1.67$  years and  $4.25 \pm 2.27$  years, respectively ( $p=0.1934$ ). After 12 months, patients in the mitomycin C group had a considerably greater rate of therapeutic success than placebo patients did at 12 months follow-up (84.2% vs. 47.4%;  $p=0.0007$ ). The average number of dilatation sessions needed was considerably lower in the experimental group than in the control group ( $2.05 \pm 0.78$  vs.  $3.18 \pm 1.54$ ,  $p < 0.0001$ ).

**Conclusion:** : Topical mitomycin C when combined with endoscopic dilatations, resulted in much improved outcomes in children with esophageal strictures.

**Keywords:** Dilation, dysphagia, esophageal strictures, mitomycin C, placebo, topical.

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## INTRODUCTION

Esophageal strictures, including corrosive strictures, anastomotic strictures, congenital strictures, and peptic strictures, may lead to dysphagia<sup>1</sup>. More than 80% of patients with esophageal strictures need medical treatment. The treatment of choice for most esophageal strictures is esophageal dilatation, which has a low success rate but is still the gold standard. Clinicians may have significant difficulties in treating severe stenosis<sup>2</sup>. Dilation alone may not be enough to treat esophageal strictures; sometimes additional treatments, such as intralesional steroid injection or esophageal stenting, are necessary. The creation of strictures slows down as a consequence of its ability to reduce fibroblast growth in the wound's healing zone<sup>3</sup>. Dysphagia develops when the esophagus lumen is completely or almost blocked by stenosis. As a result, endoscopic conservative therapy of esophageal strictures has become first-line care in place of more invasive surgical replacement. Treatment for esophageal strictures begins with endoscopic balloon dilatation, sometimes known as bougies (savary). In managing esophageal strictures and reinstating the patient's esophageal passage, intraluminal stenting emerges as a viable endoscopic solution. Mitomycin C, known for its fibroblast-inhibiting properties, extensively studied in diverse ophthalmologic procedures and laryngeal/tracheal disorders, showcases potential applicability in this context<sup>3,4</sup>.

Caustic consumption is the leading cause of esophageal strictures in children in "Low- and Middle-income Countries (LMIC)". The ubiquitous and uncontrolled availability of such products that may be bought and used without restriction is a key contributor to esophageal strictures. Many victims and caregivers aren't invested in their therapy, leading to low compliance and insufficient care, which in turn breeds complicated and resistant curtailments<sup>5,6</sup>.

Esophageal atresia, radiation treatment, and acid peptic illness are all possible causes of acquired benign strictures. Many of these strictures are recurring and develop resistance with repeated dilations, however, the short-term prognosis is typically good because of dilatation<sup>7</sup>. Several adjuvants, such as steroid injections of each dilation session and mitomycin C, have been explored in addition to dilatation to enhance the result since esophageal strictures are complicated and are linked with morbidity and poor quality of life<sup>8</sup>. Endoscopic topical administration of mitomycin C in conjunction with dilations has been demonstrated to be more effective than dilations alone or in combination with steroids in dilation sessions in several clinical trials<sup>9,10</sup>. Mitomycin C is effective in the management of congenital, post-surgical, and malignant strictures. Treatment with mitomycin C has been the

method of choice for treating corrosive esophageal strictures in recent years<sup>11</sup>. Hence, the current investigation was carried out to determine the effect of topical mitomycin C as an adjunct to dilation therapy in esophageal strictures.

## METHODS

This randomized controlled trial was conducted at the Department of Pediatric Gastroenterology, "The Children's Hospital and Institute of Child Health", Multan, Pakistan, from July 2022 to October 2023. The hospital setting is a tertiary childcare government facility. Approval from the Institutional Ethical Committee was obtained before the commencement of this study. Considering the success rate of mitomycin C in esophageal strictures as 86.7% versus 43.3% with placebo,<sup>12</sup> taking 95% 2-sided significance level, 80% power, the minimum sample size required was 76 (38 in each group). A simple random sampling technique was adopted. Children of either gender, aged 1-12 years, and having esophageal strictures were recruited. Children having a history of esophageal perforation due to caustic ingestion or esophageal surgery, those who had an allergy to mitomycin C, or those who had severe health issues, were excluded. Patients were recruited from the outpatient department (OPD). Written and informed consents were taken from parents/guardians of enrolled children.

Complete blood count evaluation was done in all patients and viral markers were also assessed. Barium studies were performed in all patients to confirm stricture then proceeded with endoscopy. Endoscopy verified a single esophageal stricture more than 11cm in length and with very tight esophageal lumen. All patients were given a thorough clinical evaluation that included a history, physical examination, and endoscopic evaluation. Upon presentation, the severity of dysphagia was measured using the "Validated Dysphagia Rating System".<sup>6</sup> The Dysphagia Severity Rating Scale (DSRS) is a clinician-rated tool developed from the Dysphagia Outcome and Severity Scale (DOSS). It measures the severity of clinical dysphagia by assessing the extent of modifications needed for fluids and diet, as well as the level of supervision required for safe oral intake. The DSRS consists of three subscales that, when combined, yield a total score ranging from 0 (best) to 12 (worst). Each subscale is a five-level ordinal measure evaluating fluid intake, dietary intake, and supervision, with scores ranging from normal (0) to no intake possible (highest severity). Children in the mitomycin C group were given mitomycin C (2 mg/20 ml saline) during the endoscopy, whereas the placebo group received normal saline during the endoscopy.

Post-procedure, patients were prescribed mucaine syrup and proton pump inhibitors (e.g., Omepra-

zole) for 2 weeks. Endoscopic dilatation sessions were performed on all patients at two-week intervals for three consecutive months, monthly for another three months, and then every two months for the remaining six months. The patients were given general anesthesia under strict aseptic measures. Esophageal stenosis was reached during an upper gastrointestinal endoscopy. A guide wire was inserted into the stomach. To apply mitomycin C (2 mg dissolved in 20-mL saline), prepared mitomycin was mixed in lignocaine gel to thicken its consistency and applied thoroughly on Savary dilators which were then introduced in the stenotic region and kept in place for 2-3 minutes. Then dilator was removed and the endoscope was reintroduced to view the dilated esophageal stricture. All patients were given the H2-blocker Ranitidine to reduce the risk of developing a stricture due to acid reflux. At each subsequent visit, the patients were re-evaluated using the "Validated Dysphagia Scoring System", and dilatation was done only if the patient was still experiencing symptoms. The counts of dilatation sessions necessary in each group and the proportion of patients who were symptom-free after 12 months of therapy were noted (outcome). The pre- and

post-evaluations were performed by a gastroenterologist with more than 5 years of post-fellowship experience. Socioeconomic status was labeled based on monthly family income as low, middle, and high, if below 18,000 PKR, between 18,000 to 40,000 PKR, and above 40,000 PKR respectively<sup>13</sup>.

The data analysis was performed utilizing IBM-SPSS Statistics, version 26.0. Qualitative data were represented in frequency and percentages, while quantitative data were depicted as mean and standard deviation. Numeric data were compared using the independent t-test, whereas categorical data were assessed through the chi-square test. Statistical significance was defined as a p-value below 0.05.

## RESULTS

Of a total of 76 children, 52 (68.4%) were male. Overall, the mean age was  $4.49 \pm 1.96$  years. There were 44 (57.9%) children who belonged to rural areas of residence. The mean age in mitomycin C and placebo groups were  $4.85 \pm 1.67$  years and  $4.25 \pm 2.27$  years, respectively ( $p=0.1934$ ). The table shows a comparison of the demographic characteristics of children in both study groups.

**Table 1: Demographic characteristics of children (n=80)**

Characteristics		Groups		p-value
		Mitomycin C (n=38)	Placebo (n=38)	
Gender	Male	26 (68.4%)	24 (63.2%)	0.6287
	Female	12 (31.6%)	14 (36.8%)	
BMI	Normal	34 (89.5%)	33 (86.8%)	0.7226
	Overweight	4 (10.5%)	5 (13.2%)	
Residence	Urban	17 (44.7%)	15 (39.5%)	0.6422
	Rural	21 (55.3%)	23 (60.5%)	
Socio-economic status	Low	26 (68.4%)	30 (78.9)	0.6221
	Middle	6 (15.8)	5 (13.2)	
	High	6 (15.8%)	3 (7.9)	
Causes of esophageal strictures	GERD	16 (42.1%)	17 (44.7%)	0.7362
	Caustic ingestion	14 (36.8%)	11 (28.9%)	
	Benign strictures	8 (21.1%)	10 (26.3%)	

There were 51 (67.1%) cases of short esophageal stricture (less than 11 cm in length) and 25 (32.9%) cases of long esophageal stricture (greater than 11 centimeters in length). After 12 months, patients in the mitomycin C group had a considerably greater rate of therapeutic success than placebo patients did at 12 months follow-up (84.2% vs. 47.4%;  $p=0.0007$ ), as shown in Table 2. After dilatation, topical mitomycin C was applied to all patients, once for the shorter strictures and many times for the longer strictures. The average number of dilatation

sessions required to completely resolve dysphagia in patients with short stricture after mitomycin C application was 2.05 (10 patients required one session, 15 required two sessions, and 13 patients required three sessions). However, the average dilation in the placebo group was 3.18 with the highest frequency observed in five patients with six times dilation sessions. It was observed that after 3 dilatation sessions, 4 long stricture patients improved in the mitomycin C group. Six patients had only partial improvement after 1-2 dilatation sessions. Fifteen

patients had improvement after 3 dilatation sessions. Endoscopy performed following mitomycin C treatment revealed healthy mucosa in the esoph-

agus at the stricture location. There were no complications during or after the procedure in any of the patients.

**Table 2: Comparison of the outcomes after 12 months of treatment in both study groups**

Outcomes		Mitomycin C group	Placebo group	p-value
Successful treatment	Yes	32 (84.2%)	18 (47.4%)	0.0007
	No	6 (15.8%)	20 (52.6%)	
No. of Dilation Sessions		4.05±2.78	6.48±2.54	<0.0001

Treatment outcome was compared concerning causes of esophageal strictures in both study groups and it was found that significant differences existed among patients having GERG (p=0.0138), and

benign strictures (p=0.0147). Treatment outcomes were statistically similar among patients with caustic ingestion (p=0.4090), and the details are shown in Table 3.

**Table 3: Treatment outcome for causes of esophageal strictures in both study groups**

Causes	Treatment Success	Mitomycin C group	Placebo group	p-value
GERD (n=33)	Yes (n=22)	14 (63.6%)	8 (36.4%)	0.0138
	No (n=11)	2 (18.2%)	9 (81.8%)	
Caustic ingestion (n=25)	Yes (n=18)	11 (61.1%)	7 (38.9%)	0.4090
	No (n=7)	3 (42.9%)	4 (57.1%)	
Benign strictures (n=18)	Yes (n=10)	7 (70.0%)	3 (30.0%)	0.0147
	No (n=8)	1 (12.5%)	7 (87.5%)	

In comparison to placebo groups, the number of dilatation sessions required was significantly less in

the Mitomycin group and the details are shown in Table 4.

**Table 4: Number of dilatation sessions concerning causes of esophageal strictures in both study**

Causes of Esophageal Strictures	Dilatation Sessions		p-value
	Mitomycin C group	Placebo group	
GERD	4.18±2.53	6.02±2.14	0.0310
Caustic ingestion	5.03±3.68	8.16±3.05	0.0328
Benign strictures	4.04±2.68	6.78±2.56	0.0420

Figure 1 shows details about a 4-year-old girl who presented with esophageal stricture due to caustic ingestion, and after 4 sessions of dilatations, 3

months apart using mitomycin C, significant improvement was seen.



**Figure 1: Before and after dilatation with mitomycin C.**

## DISCUSSION

Esophageal salvaging is assumed to be the best treatment option, but if restenosis develops, several dilatation procedures may be necessary. This study focused on the effect of topical mitomycin C as an adjunct to dilation therapy in esophageal strictures. In our hospital, esophageal replacement was recommended for patients with lengthy, numerous, and chronic strictures that did not respond to dilatation. Recurrent dilation may cause emotional distress, hospital anxiety, and family strife. Employing steroid injections in localized esophageal strictures aims to curtail the frequency of dilatations and circumvent the necessity for surgery. However, while this approach extends the duration between dilatation sessions, it does not notably diminish the requirement for eventual replacement. Additionally, utilizing stents as an alternative intervention in these cases, despite their utility, presents challenges due to their high failure rate and associated morbidity (like tissue stent migration, tissue overgrowth, perforation, or bleeding)<sup>14</sup>. Results from isolated studies utilizing mitomycin C on localized strictures have been positive, requiring fewer dilatations<sup>7,11,15</sup>. In a randomized pilot trial performed here at our institution, patients with dysphagia showed significant improvement, with fewer dilatations and fewer replacements after adjunct treatment of mitomycin C. Diseases of the esophagus, such as gastroesophageal reflux, esophageal surgery are common causes of benign strictures of the esophagus<sup>5</sup>. All of these patients present with dysphagia, leading to weight loss and a worse quality of life. Two primary challenges in effectively managing such patients revolve around their lack of interest in therapy and poor compliance. These hurdles significantly impede the successful implementation of treatment plans, requiring focused efforts to address and overcome these obstacles for improved patient outcomes<sup>11</sup>. Our findings are consistent with El-Asmar et al, which studied 40 Egyptian patients who had esophageal strictures and found that topical application was more effective with mitomycin C used ( $p=0.001$ ), and the average number of dilation sessions needed was also low ( $p=0.001$ )<sup>16</sup>.

In severe cases of esophageal strictures caused by restenosis, dilatation may be performed many times.<sup>17</sup> Restenosis may be explained by significant fibrogenesis during healing and after the traumatic dilatation treatment, leading to the need for further dilatations along with an increased risk of complications and perforation<sup>17</sup>. In many studies, the researchers first tried injecting steroids in dilation sessions into localized strictures to lengthen the time between dilations, but this strategy was not very effective<sup>18,19</sup>. Treatment with mitomycin C on localized strictures has demonstrated improved outcomes with fewer dilatation sessions. After the initial treatment in a highly resistant instance, in

which the stricture was 11 cm long and the esophageal lumen was quite tight, the dysphagia improved dramatically, and the frequency of dilatations decreased<sup>20</sup>.

Children in this study who developed esophageal stricture as a consequence of unintentional caustic ingestion, which is consistent with the data reported in children, where most instances of esophageal strictures are caused by ingestion of caustic substances, peptic esophagitis<sup>8,11</sup>. We found that just one patient in our research had esophageal stricture due to gastroesophageal reflux disease (GERD) and peptic damage. This is in contrast to the findings of Richer Joel E et al, who concluded that GERD leading to peptic injury is the most common cause of strictures, our study found that atrophic esophagitis was the most common cause of these abnormalities but it may not be reflective of overall population<sup>21</sup>. In this study, children who received mitomycin C through the mucosa reported no adverse effects from the treatment. To account for any confounding factors, we used stringent exclusion criteria. Based on the findings of this research, combining mitomycin C with dilatation provides a higher success rate with fewer dilatation attempts than the standard practice of dilatation alone in patients with esophageal strictures. Our findings are consistent with others<sup>11,12,18</sup>.

Although our findings provide support for implementing the innovative approach into clinical practice, further research is needed to compare the recurrence of stricture in long-term follow-up with possible consequences of the topical administration of mitomycin C. Combinations of mitomycin C and other adjuvants, such as steroid dilation session, should also be evaluated for their effects. Patients with post-caustic ingestion strictures might benefit further from this knowledge when choosing a therapy approach. In light of the importance of this topic, further research should include such a study. Single-center study design and relatively small sample size were some of the inherent limitations of this study.

## CONCLUSION

Topical mitomycin C, when used as an adjunct to dilatation therapy, significantly improved therapeutic success and reduced the number of dilatation sessions required in children with esophageal strictures.

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## ETHICAL APPROVAL

Approval from the Institutional Ethical Research

Committee was acquired.

#### PATIENT CONSENT

Informed and written consents were acquired from parents/guardians of all study participants.

#### AUTHORS CONTRIBUTION

All authors contributed equally.

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