REVIEW

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Efficacy of endoscopic topical mitomycin C application in caustic esophageal strictures in the pediatric population: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT – **Background** – Caustic ingestion and development of esophageal strictures are recognized major public health problems in childhood. Different therapeutic methods have been proposed in the management of such strictures. **Objective** – To evaluate efficacy and risk of endoscopic topical application of mitomycin C in the treatment of caustic esophageal strictures. **Methods** – We searched MEDLINE, EMBASE, Central Cochrane, and LILACS databases. The outcomes evaluated were dysphagia resolution rate, number of dilations performed in resolved cases, and the number of dilations performed in all patients. **Results** – Three randomized clinical trials were included for final analysis with a total of 190 patients. Topical mitomycin C application group showed a significant increase in dysphagia resolution rate, corresponding to a 42% higher dysphagia resolution as compared to endoscopic dilation alone, with statistical significance between the two groups (RD: 0.42 – [CI: 0.29–0.56]; *P*-value <0.00001). The mean number of dilations performed in resolved cases were significantly less in the topical mitomycin C application group, compared to endoscopic dilations alone, with statistical significance between the two groups (MD: 2.84 [CI: 1.98–3.69]; *P*-value <0.00001). When comparing the number of dilations in all patients, there was no statistical difference between the two groups (MD: 1.46 [CI: -1.53–4.44]; *P*-value =0.34). **Conclusion** – Application of topical mitomycin C with endoscopic dilations in caustic esophageal strictures was more effective in dysphagia resolution than endoscopic therapy alone in the pediatric population. Moreover, topical mitomycin C application also reduced the number of dilation sessions needed to alleviate dysphagia without rising morbidity.

Keywords – Mitomycin C; esophageal stricture; pediatric; endoscopy; meta-analysis.

INTRODUCTION

Ingestion of caustic products and the development of esophageal strictures are recognized major public health problems in childhood[1,2]. Esophageal perforation and mortality are potentially serious complications in the acute period, while strictures and cancer may occur in the chronic period[3,4]. Caustic strictures are considered the most challenging among esophageal strictures, with dilation as first-line treatment, aiming at preserving the native esophagus[5,6].

The traditional initial treatment is serial esophageal intraluminal dilation. However, when applied in isolation, it may not reach the necessary diameter for significant symptoms improvement. Furthermore, the relapse of injuries is common after dilations due to the process of trauma and healing repeatedly caused to the inner mucosa[7].

There is an unmet need to evaluate novel treatments, such as topical or intralesional corticoid application, esophageal stents, surgical resection of stenosed segments, or esophagectomy with complex reconstruction in refractory cases[2,4,8,9].

Some recent studies have evaluated the efficacy of using a topical or intralesional application of mitomycin C within this context[10,11].

Nonetheless, the use of mitomycin C is still controversial due to a small number of comparative studies available in the current literature and few prospective data evaluating efficacy, indication, dosage, application technique, and safety. This is the first systematic review with meta-analysis using only randomized clinical trials to assess the efficacy of endoscopic topical application of mitomycin C associated with dilation in caustic esophageal strictures in the pediatric population.

The goal of this study is to compare the endoscopic topical application of mitomycin C associated with esophageal dilation using semiflexible thermoplastic bougies to esophageal dilation only as approaches to caustic esophageal strictures in the pediatric population. Efficacy and risk were evaluated, comparing randomized clinical trials available in the current literature, by means of a systematic review and meta-analysis, to demonstrate the real impact of such a method.

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METHODS

Protocol and registration

This systematic review was designed according to the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The study was registered in The International Prospective Register of Systematic Reviews (PROSPERO) – available in https://www.crd.york.ac.uk/prospero – maintained by the Centre for Reviews and Dissemination, University of York (England), under the code CRD42020137676. The study was approved by the local institutional review board.

Eligibility criteria

Types of studies: randomized clinical trials comparing the endoscopic topical application of mitomycin C associated with esophageal dilation to esophageal dilation only in caustic strictures in children, irrespective of language or date of publication. Exclusion criteria were stricture related to other etiologies, non-esophageal caustic strictures, non-pediatric population, non-explicit study design, studies that did not provide sufficient data for outcome analysis, studies that did not provide a complete text, and non-comparative studies

Types of participants: a pediatric population with esophageal strictures of caustic etiology submitted to therapeutic methods.

Types of interventions: endoscopic topical application of mitomycin C associated with either esophageal dilation (intervention) and esophageal dilation only or to endoscopic topical application of saline/placebo (comparison).

Outcomes: primary outcomes included dysphagia resolution rate, the mean number of dilations performed in cases of a complete resolution of dysphagia, and mean number of dilations performed in all patients. As secondary outcomes, we evaluated complications inherent to therapeutic methods and treatment costs.

Information sources and search

We searched the following electronic databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and LILACS. We also performed a manual search and a gray literature search by means of reviewing the references about the topic. The last search was performed in November 2020. The following search strategy was used for all databases:

– MEDLINE; EMBASE; Central Cochrane e LILACS: ((esophageal OR esophagus)) AND (stricture OR stenosis) AND mitomycin C + ((esophageal OR esophagus)) AND (mitomycin C).

Study selection and data collection process

Two independent investigators extracted the data according to the pre-defined data extraction form. After the initial evaluation of titles and abstracts, some studies were selected for a full reading. Duplicated studies were removed. Any disagreements were resolved by consulting a third reviewer. The researchers used Excel sheets to extract the data and relevant results.

Data items

After selecting the studies for final analysis, we collected the following data: author, country, publication year, study type, total number of patients, gender, age-range, stricture etiology, stricture length, stricture diameter, number of necessary dilations to resolve dysphagia, mitomycin C application techniques, applied dosage, esophageal dilation technique, adverse effects, complications, dysphagia score before and after treatment, cost of method and follow-up.

Risk of bias in individual studies

Risk of bias in the individual studies was assessed by the Revised Cochrane Risk-of-Bias tool for randomized clinical trials (RoB-2). We performed a full analysis using RoB-2 for each outcome of every included study. Aiming at simplifying the analysis, we also assessed the global risk of bias for each study using the same domains suggested by RoB-2.

Summary measures, synthesis of results and data analysis

We calculated the risk difference (RD) using the Mantel-Haenszel method with the fixed-effect model for dichotomous variables. Mean difference (MD) was calculated by random effect with inverse variance for continuous variables. Both parameters were assessed using a confidence interval (CI) of 95%. The quantitative values were described by weighted arithmetic mean using the number of patients in each study, along with the standard deviation. All data were processed with an intention-to-treat analysis. Heterogeneity values (I^2) were qualified according to the Chi-squared test (x^2) and the Higgins method.

Heterogeneity values above 50% were considered high, with the application of the random effects model in this case. For heterogeneity values under 50%, we used the fixed-effect model. Absolute numbers, mean and standard deviations were used in data analysis. For studies that lacked mean and standard deviation determination, data standardization was estimated using mathematical formulae (S. P. Hozo, B. Djulbegovic, I. Hozo).

We used the RevMan 5 software (Review Manager version 5.3.5 – Cochrane Collaboration, Oxford, United Kingdom) to perform the meta-analysis and forest plot and to calculate confidence intervals.

Risk of bias across studies and quality of evidence (GRADE)

We assessed the clinical randomized trials using the criteria from Cochrane Collaboration's tool for assessing the risk of bias – RoB2 – (Higgins, 2019). The tool analyzes the risk of bias by classifying it into five different domains: randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The risk of bias for each specific domain is assessed as "low risk", "some concerns", and "high risk", for each outcome, according to the criteria described in detail in the Cochrane Handbook.

Quality of evidence was assessed using the objective criteria of GRADE (Grading of Recommendations Assessment, Development and Evaluation) for each outcome, and result by means of GRADEpro – Guideline Development Tool Software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada). The items considered in quality of evidence assessment are based on criteria that involve evaluation of the risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The evaluation of the risk of bias and study quality was performed under the supervision of our statistical analysis team (TABLE 1).

TABLE 1. Assessment of quality (certainty) of evidence using GRADE-pro. 'Mitomycin C + Dilation' compared to 'Dilation Only' for caustic esophageal stenosis in children.

Outcomes	N of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with dilation only	Risk difference with mitomycin C + dilation
Resolution of dysphagia (%) assessed with: (%) follow up: mean 6 months	160 (2 RCTs)	⨁⨁⨁⨁ HIGH	not estimable	388 per 1.000	388 fewer per 1.000 (388 fewer to 388 fewer)
Number of dilations performed in resolved cases only assessed with: mean ±SD follow up: mean 6 months	96 (2 RCTs)	⨁⨁⨁⨁ HIGH	–	The mean number of dilations performed in resolved cases only was 0	0 (0 to 0)
Number of dilations performed in all patients assessed with: mean ±SD follow up: mean 6 months	70 (2 RCTs)	⨁⨁⨁⨁ LOW	–	The mean number of dilations performed in all patients was 0	0 (0 to 0)

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval.

RESULTS

Study selection

At first, a total of 534 records were identified through a database search, manual search, and gray literature search. After adjusting for duplicates, 337 studies were selected. Of these, 89 studies were screened based on the abstract evaluation. After applying exclusion criteria, 29 entries were eligible for full-text assessment, of which 26 were then excluded. Therefore, we included three randomized clinical trials for quantitative analysis and meta-analysis (FIGURE 1). Selected studies were published between 2013 and 2018.

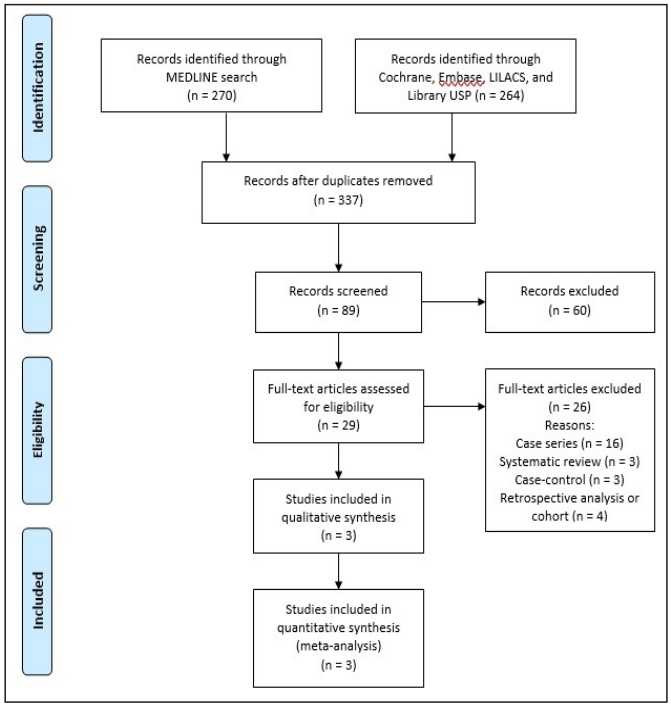

FIGURE 1. Flow diagram of included and excluded clinical trial.

Definitions

In the included studies, we used two distinct score metrics (equivalent to each other) to assess the degree of dysphagia after interventions. Sweed et al.[12] – used the score suggested by Earlam and Cunha-Melo (1981)[13]. El-Asmar et al.[14] – and Ghobrial et al.[15] – used the Dysphagia Scoring system. In the present study, complete resolution of dysphagia is referred to as the capacity to ingest any type of food (grade 1 – Earlam and Cunha-Melo; grade 0 – Dysphagia scoring system) – FIGURE 2.

Earlam and Cunha-Melo (1981)

Grade	Degree of dysphagia
1	Able to eat everything but with difficulty
2	Dysphagia to solids
3	Dysphagia to semi-solids
4	Dysphagia to fluids
5	Absolute dysphagia

Dysphagia scoring system

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

FIGURE 2. Grading of dysphagia.

The number of dilations performed both on resolved cases only and on all participating patients was reported as the mean and the standard deviation. The cost of treatment was assessed only in the study by Ghobrial et al.[15] - who used mean and standard deviation in American dollars (US$), only for patients that presented with some degree of clinical or endoscopic improvement. Regarding complications, the authors assessed: local pain after the procedure, bleeding, and esophageal perforation.

Study characteristics

Three randomized clinical trials, with a total of 190 patients were included of which 98 were treated with esophageal dilations associated with endoscopic topical application of mitomycin C. A total of 92 were treated only with esophageal dilations using semi-flexible thermoplastic bougies. All studies were conducted in Egypt between 2013 and 2018. Concerning mitomycin C concentration, all included studies used the same dosage of 0.4 mg/mL, applied to all patients in the intervention group. All patients included in the study were treated with H2 blockers (ranitidine) to eliminate the effect of acid reflux in the evolution of strictures. Population characteristics of each study are summarized in TABLE 2.

Description of interventions

Ghobrial et al.[15] – topical application through a multi-porous spray catheter placed on the injury under direct visualization using a concentration of 0.4 mg/mL after an initial dilation. The initial schedule was for four applications within 2 weeks between them. Subsequent dilations depended on clinical evaluation and symptomatology during follow-up. The same dosage was used for all patients.

Sweed et al.[12] – topical application through the placement of cotton soaked in mitomycin C on the injured region using a concentration of 0.4 mg/mL and maintaining contact for 5 minutes. The application of mitomycin C was initiated 2 weeks after the first dilation session. Subsequent dilatations were performed at intervals of 2 weeks during follow-up. The same dosage was used for all patients.

El Asmar et al.[14] – the application was executed through the placement of cotton soaked in mitomycin C on the region of injury using a concentration of 0.4 mg/mL and maintaining contact for 5 minutes. The application of mitomycin C was initiated 2 weeks after the first dilation session. Subsequent dilatations were performed with intervals of 2 weeks during follow-up. The same dosage was used for all patients.

All endoscopic dilations were performed using semiflexible thermoplastic bougies (Savary-Gilliard, for instance) according to the diameter of each stricture. The assessed results were divided into descriptive and meta-analyzed results.

Risk of bias in the included studies

The risk of bias for each study was assessed by the Revised Cochrane Risk-of-Bias Tool for randomized clinical trials (RoB-2). The complete risk of bias for each outcome in each study is detailed in FIGURE 3. The high risk of bias in cost assessment

TABLE 2. Characteristics of the patient samples in the included studies.

Author	Publication year	Country	Study type	Patients (n)	MMC + Dilation (n)	Dilation only (n)	Age range – MMC (mean ±SD)	Age range – dilation (mean ± SD)	Stenosis length – MMC (cm)	Stenosis length – dilation (cm)	Gender	Concentration – MMC	Follow-up (months)	Primary outcome
Ghobrial, CM	2018	Egypt	RCT	120	60	60	3.50±1.50 (y-o)	3.09±1.39 (y-o)	6.88 ±2.04 cm	6.71±1.97 cm	66M 54F	0.4 mg/mL	6	% of complete cure
Sweed, AS	2014	Egypt	RCT	30	18	12	3.57±0.82 (y-o)	2.50 ±0.35 (y-o)	3.12±0.62 cm	3.25±0.38 cm	13M 17F	0.4 mg/mL	9.1	Improvement of dysphagia grade
El-Asmar, KM	2013	Egypt	RCT	40	20	20	2.80±0.92 (y-o)	2.77±1.04 (y-o)	1.85±0.65 cm	1.92±0.91 cm	23M 17F	0.4 md/mL	6	Number of dilation sessions for resolution of dysphagia

MMC: mitomycin C.

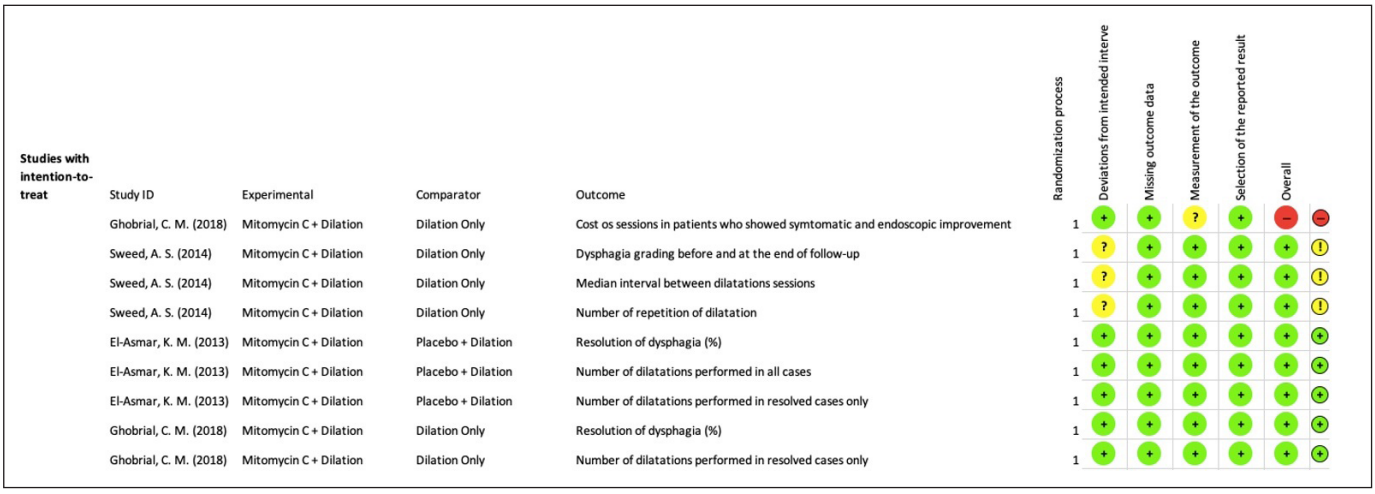

FIGURE 3. Risk of bias by outcome of individual studies assessed by the RoB-2 tool.

took into account the analysis of data only for patients who presented with some degree of clinical or endoscopic improvement. Sweed et al.[12] – showed "some concerns" in all their outcomes: the randomization process was not described in a clear and objective manner.

DESCRIPTIVE RESULTS

Complications

Ghobrial et al.[15] reported the presence of local pain in all patients from both groups. There were no reports of other adverse effects such as anaphylaxis, perforations, nausea, vomiting, or fever. A follow-up endoscopy visualized a healthy-looking mucosa in the site of the previous stricture. No biopsies were performed.

El-Asmar et al.[14] reported the occurrence of three perforations (in different patients) during 215 dilation sessions, configuring at a rate of 1.39%. One occurred in the group of mitomycin C and the other two in the group of dilation only (P=1.0). The perforation that occurred in the mitomycin C group received conservative treatment, while the other two needed surgical treatment (one with the performing of esophagostomy + gastrostomy and the other with a surgical suture of the abdominal esophageal perforation). None of these perforations occurred during the sessions of the application of mitomycin C or placebo. Adverse effects or other complications were not reported during follow-up.

Sweed et al.[12] report that there were not any complications or adverse effects in the patients included in the study during follow-up.

Costs

Only one study assessed the costs of therapeutic methods. Ghobrial et al.[15] evaluated the cost of sessions only in patients that presented with any degree of symptomatic or endoscopic improvement. The cost of a single dilation session was 50 US$ (American dollars), while the cost of the session of dilation + mitomycin C application was 60 US$. The mean cost of performed sessions was 272.2±51 US$ and 404±55.7 US$ (P<0.00001) for the mitomycin C and dilation only groups, respectively.

META-ANALYZED RESULTS

Resolution of dysphagia

Two studies reported the dysphagia resolution rate (Ghobrial et al.[15]; El-Asmar et al.[14]) with a total of 80 patients in the mitomycin C group and 80 patients in the dilation only group. A 42% increase was observed in dysphagia resolution rate with mitomycin C combined with esophageal dilation with statistical significance between the two groups - RD: 0.42 (95%CI: 0.29–0.56); P<0.00001, as displayed in FIGURE 4. According to GRADE criteria, this outcome has high-quality evidence.

Number of dilations performed in resolved cases only

Two studies reported the number of dilations performed in cases with complete resolution of dysphagia, including a total of 65 patients in the mitomycin C group and 31 patients in the dilation only group (Ghobrial et al.[15]; El-Asmar et al.[14] A decrease of 2.84 dilations was shown when associating mitomycin C to dilations with statistical significance between the two groups – MD: 2.84 (95%CI: 1.98–3.69); P<0.00001, as shown in FIGURE 5. According to the GRADE criteria, this outcome has high-quality evidence.

Number of dilations performed in all patients

Two studies reported the number of dilations performed on all patients, globally, submitted to two techniques, including 38 patients in the mitomycin C group and 32 patients in the dilation group (Sweed et al.[12]; El-Asmar et al.[14]). There was not any statistical difference between the two groups - MD: 1.46 (95%CI: -1.53–4.44); P=0.34, FIGURE 6. High heterogeneity was established between

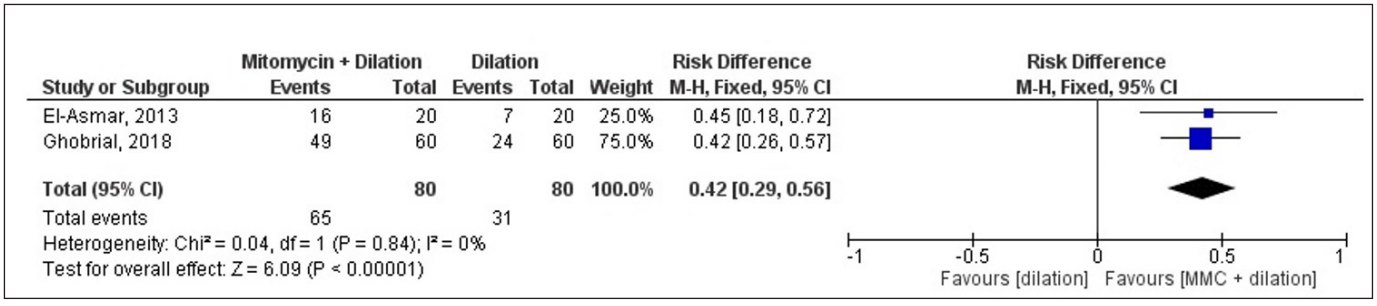

FIGURE 4. Forest plot for the outcome of resolution of dysphagia (n) using fixed-effects with the Mantel-Haenszel method (M-H).
CI: confidence interval; MMC: mitomycin C.

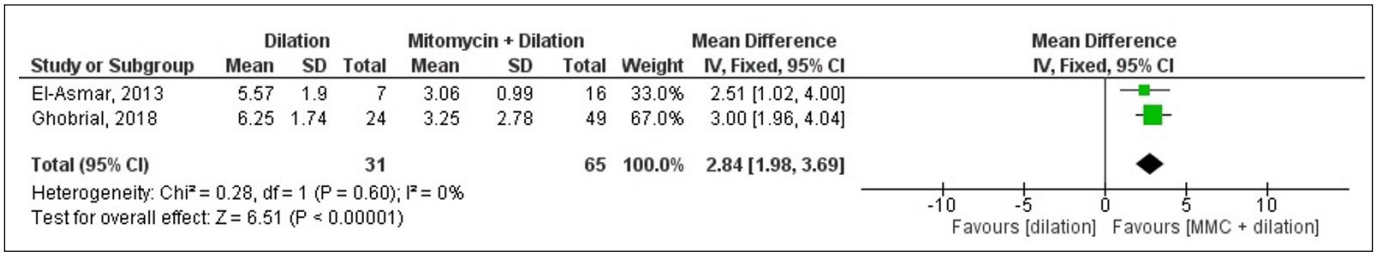

FIGURE 5. Forest plot for the outcome of number of dilations performed in resolved cases only (mean ±SD) using the fixed-effects model with the inverse variance test.
CI: confidence interval; IV: inverse variance test; MMC: mitomycin C.

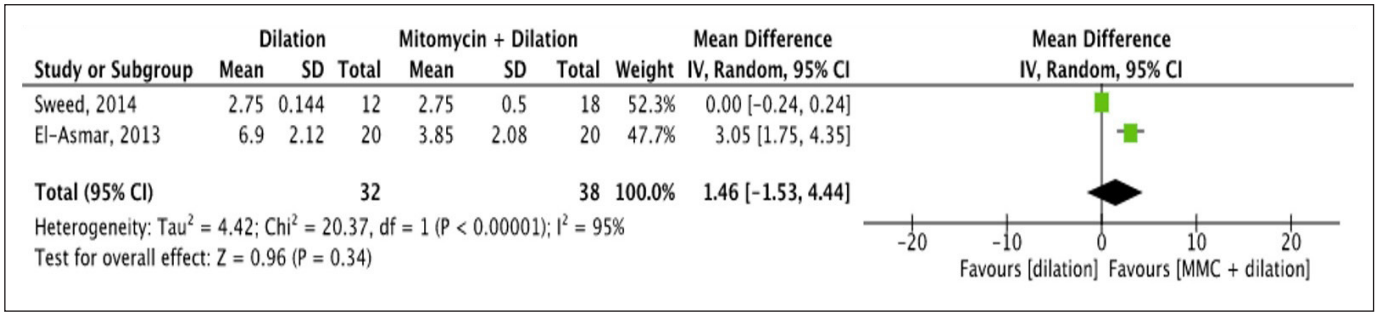

FIGURE 6. Forest plot for the outcome of number of dilations performed on all patients (mean ±SD) using a random-effects model with the inverse variance test.
CI: confidence interval; IV: inverse variance test; MMC: mitomycin C.

the studies (I^2=95%). For this reason, the random-effects model was applied in the analysis. According to the GRADE criteria, this outcome has low-quality evidence.

DISCUSSION

Summary of evidence

This is the first systematic review with a meta-analysis assessing the efficacy of endoscopic topical application of mitomycin C in caustic esophageal strictures in the pediatric population.

Esophageal strictures are categorized as congenital, acquired, or functional. Among the acquired ones, caustic strictures are the main reason for complex and difficult-to-handle strictures[16-19]. These strictures predominantly affect the proximal and middle esophagus[20]. Caustic substances are present in many products of domestic use, which makes children a group that is particularly vulnerable to these accidents[21]. The age group that is subject to greater risk comprises children under the age of 5, since they already present autonomous capacity for mobility, but lack the cognitive capacity to recognize danger[22]. Each year, approximately 5,000 accidents with corrosive substances occur in children under the age of 5 in the United States[3].

The involved type of product varies according to geographic region, but the most frequent ones include sodium hypochlorite (present in bleaches and disinfectants) and sodium hydroxide (caustic soda)[23-24]. The physiopathology of the harm caused by caustic substances involves deep penetration (able to reach the muscularis propria), causing liquefactive necrosis of the mucosa, following damage to the submucosa. When in contact with lipids, they cause saponification and higher dissemination through tissues. The most common symptoms that occur after ingestion of corrosive substances include vomiting, dysphagia, sialorrhea, epigastric pain, and refusal to eat[25].

Endoscopic examination between 12–24 hours after the accident is useful to assess injury degree and generate information regarding the possible complications in the short and long term, according to the findings of the examination[3].

In the literature, some systematic reviews have suggested benefit in the utilization of mitomycin C associated with esophageal dilation in the treatment of caustic strictures[1,26,27]. The initial therapeutic method for such cases is the esophageal intraluminal dilation with semiflexible thermoplastic bougies and balloon dilators[28]. As an alternative method, the intralesional or systemic application of corticoids combined with esophageal dilation has been effective in children, especially in complex structures[10]. A large variety of surgical procedures, such as esophagectomy and gastric tube reconstruction, and jejunal or colonic interposition, may also be applied in the resolution of such injuries[29]. Despite technical advances, such procedures still have high morbidity and mortality. Each therapeutic method has its advantages and disadvantages[30,31]. Berger et al.[1] in their systematic review assessed the topical application of mitomycin C in a dosage that varies from 0.1 to 1.0 mg/mL in pediatric patients only, exhibiting safety in the application of such dosages.

Mitomycin C, isolated from *Streptomyces caespitosus*, is an antimetabolite that acts at the cellular level blocking DNA and RNA replication and inhibiting protein synthesis and cell proliferation mainly during G1 and S phases. It has anti-fibroblastic activity and antiproliferative properties that decrease the incidence of stenoses and that may avoid or retard a more invasive surgical procedure, which implicates in high morbidity, mortality, and potential risk of anastomosis strictures[8,21,32].

The physiopathology of caustic stricture formation involves fibroblast proliferation and collagen deposition, secondary to the injury promoted during the contact between caustic agent and mucosa, depending on concentration, quantity, and exposure time[33]. In general, fibroblast deposition and formation of scar retractions begin around 3 weeks after ingestion and are potentiated by acid reflux in the affected area[20]. Commonly, the ideal period to initiate dilations is after acute period healing, often between the third and sixth week. Late initiation of dilations is also associated with a greater number of necessary sessions since there will be more fibrosis and collagen deposition.

Only one of the randomized clinical trials included patients carrying strictures considered refractory alone, which were defined as the incapacity of dilation up to 14 mm of diameter or 40 Fr after five sessions of dilations with an interval of 2 weeks[15]. There are several definitions in the literature to consider esophageal stricture as refractory, which hinders standardization in the selection of such patients[34].

We consider as therapeutic failure factors with serial dilations: small diameter during the first dilation; diameter inferior to 28 Fr after three months of dilations; strictures larger than 3 cm and the presence of multiple strictures[20].

In our meta-analysis, there was a benefit in favor of the mitomycin C group regarding improvement of dysphagia and a decrease in the number of necessary dilations to resolve dysphagia in the resolved patients. When compared to the number of dilations performed in all patients, globally, there was not any statistical significance. A critique of the included studies is the limited follow-up

that lasted, on average, only 6 months. This period is considered short and may be insufficient to adequately assess for relapse of symptoms, strictures, or evolution of complex structures. These children will still go through different growth phases and esophageal remodeling over the years. Remodeling time, that is, the period necessary for stricture stabilization varies between 6 months and 3 years. However, the progression may be very long due to ischemic injury as a result of microvascular involvement, which corroborates the necessity for longer follow-up.

Topical application of mitomycin C to the esophageal mucosa alters cellular turnover, which can lead to dysplasia in the application areas, mainly after repeated sessions. Other collateral effects described are myelosuppression, nausea, vomiting, dementia, alopecia, and even pulmonary toxicity[35,36]. The included studies did not report in detail the presence or absence of such collateral effects. This is one more reason that justifies a longer follow-up of these patients.

If possible, performing biopsies in the region subjected to contact with mitomycin C in subsequent exams, whether by evaluation of the application of mitomycin C in the long term or by assessing the risk of developing an esophageal carcinoma inherent to caustic ingestion is warranted. Esophageal carcinomas occur in 1–2% of patients with a history of caustic ingestion. In regards to squamous cell carcinomas, 1% are associated with a previous accident with a caustic substance, representing a risk 1.0 times higher when compared to the general population[1,20,21].

The major complication associated with esophageal dilations are bleeding and perforation[16]. The perforation rate reported by El-Asmar et al.[14] was 1.39%. In the literature, the perforation rate in caustic esophageal strictures varies from 0.4 to 17.4%, which is higher than that seen in congenital strictures, associated with gastroesophageal reflux, or with anastomoses strictures[20].

In regards to application technique, the number of applications, dosage, and application interval, there is still no sufficient evidence in the literature to standardize such parameters. Nevertheless, all techniques described in the included studies had benefits in favor of the mitomycin C group, which supports the efficacy of its utilization. There are not in the literature studies that compare the effectiveness of different concentrations, dosages, and topical or intralesional application of mitomycin C[37]. The most commonly used concentration is 0.4 mg/mL. Length of application in the studies varies from 1 to 5 minutes, which is a duration that is considered safe.

Thus, endoscopic topical application of mitomycin C proves to be a safe and effective therapeutic method for the treatment of caustic esophageal strictures in the pediatric population. Although the results of this study are encouraging, there is still the necessity for a larger number of prospective studies with a longer follow-up and a greater number of included patients to better define the technique to be applied, the most effective and safe dosage and concentration, optimal indications, and the best moment to start mitomycin C application. It is important to highlight that implementation of preventive measures is one of the most effective solutions in the long term.

Limitations

This study has several limitations. First, different definitions of refractory strictures, technical non-standardization, indications, dosage, and the number of applications may interfere in the obtained results, in addition to the short follow-up in each study. Second, the small number of randomized clinical trials with few included patients is the greatest limitation, which supports the necessity of more prospective studies about the topic. In this systematic review, only 1% (3/337) of the eligible studies were used in the meta-analysis, which demonstrates the small number of randomized clinical trials on this topic. It is known that the small number of randomized clinical trials can exclude or mitigate possible adverse outcomes. However, using only this study design, we obtained a better quality of evidence. Therefore, it is necessary to prepare new studies to assess new outcomes, whether these are favorable or not. Future studies may contradict the herein obtained results.

CONCLUSION

Endoscopic topical application of mitomycin C in caustic esophageal strictures in the pediatric population is safe and effective, reducing the number of necessary dilations to reach complete resolution of dysphagia, and increasing the complete dysphagia resolution rate without increasing morbidity. These results support the applicability of this therapeutic method in this patient population.

Authors' contribution

Flor MM: acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval. Ribeiro IB: analysis and interpretation of data, revising the article. de Moura DTH: acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval. Marques SB: analysis and interpretation of data, drafting the article, final approval. Bernardo WM: analysis and interpretation of data, drafting the article, final approval. de Moura EGH: analysis and interpretation of data, drafting the article, revising the article, final approval.

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Flor MM, Ribeiro IB, de Moura DTH, Marques SB, Bernardo WM, de Moura EGH. Eficácia da aplicação endoscópica tópica de mitomicina C em estenoses esofágicas cáusticas na população pediátrica: uma revisão sistemática e meta-análise de ensaios clínicos randomizados. Arq Gastroenterol. 2021;58(2):253-61.

RESUMO – **Contexto** – A ingestão de soda cáustica e o desenvolvimento de estenoses esofágicas são reconhecidos como importantes problemas de saúde pública na infância. Diferentes métodos terapêuticos têm sido propostos no manejo dessas estenoses. **Objetivo** – Avaliar a eficácia e o risco da aplicação endoscópica tópica de mitomicina C no tratamento de estenoses esofágicas cáusticas. **Métodos** – Buscamos as bases de dados MEDLINE, EMBASE, Central Cochrane e LILACS. Os desfechos avaliados foram taxa de resolução da disfagia, número de dilatações realizadas nos casos resolvidos e número de dilatações realizadas em todos os pacientes. **Resultados** – Três ensaios clínicos randomizados foram incluídos para análise final com um total de 190 pacientes. O grupo de aplicação de mitomicina C tópica apresentou aumento significativo na taxa de resolução da disfagia, correspondendo a uma resolução da disfagia 42% maior em comparação à dilatação endoscópica isolada, com significância estatística entre os dois grupos (RD: 0,42 - [IC: 0,29–0,56]; *P*-valor <0,00001). O número médio de dilatações realizadas em casos resolvidos foi significativamente menor no grupo de aplicação tópica de mitomicina C, em comparação com as dilatações endoscópicas isoladas, com significância estatística entre os dois grupos (MD: 2,84 [IC: 1,98–3,69]; *P*-valor <0,00001). Ao comparar o número de dilatações em todos os pacientes, não houve diferença estatística entre os dois grupos (MD: 1,46 [IC: -1,53–4,44]; valor de *P*=0,34). **Conclusão** – A aplicação de mitomicina C tópica com dilatações endoscópicas em estenoses esofágicas cáusticas foi mais eficaz na resolução da disfagia do que a terapia endoscópica isolada na população pediátrica. Além disso, a aplicação tópica de mitomicina C também reduziu o número de sessões de dilatação necessárias para aliviar a disfagia sem aumentar a morbidade.

Palavras-chave – Mitomicina C; estenose esofágica; pediatria; endoscopia; meta-análise.

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