Intralesional steroid injections in addition to endoscopic dilation in benign refractory esophageal strictures : a systematic review

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Abstract

Background and study aims **: Benign esophageal strictures are primarily treated with dilation therapy, but strictures can recur or can be unresponsive, requiring additional or repeated treatment. This study investigates the efficacy and safety of intralesional steroid injections in addition to dilation in comparison to dilation alone in patients with benign refractory or recurrent esophageal strictures.**

Methods **: A systematic search was carried out in PubMed, using the search terms "Esophageal Stenosis"[Mesh] AND "Injections, Intralesional"[Mesh]. In addition, the reference list of all selected articles was searched manually for other relevant articles. All clinical trials and case series were considered.**

Results **: This systematic review included four randomized controlled trials, six case series and two cohort studies, comprising 341 patients with benign esophageal strictures of different etiologies. A benefit of adding intralesional steroid injections to dilation in reducing the need for repeat dilation was seen in the subgroups of peptic, radiation-induced and corrosive strictures. Results were inconsistent for anastomotic strictures and too limited for strictures due to eosinophilic esophagitis, sclerotherapy or pill esophagitis. Complications were rare and of limited severity.**

Conclusion **: Endoscopic dilation remains the first-line treatment, since its efficacy and safety are mostly satisfactory. In recurrent or refractory strictures, intralesional steroid injections are advised in peptic strictures and can be considered in radiation-induced, corrosive strictures and anastomotic strictures. It is recommended to restrict the steroid use to a maximum of three sessions and to consider alternative treatment if treatment effects remain insufficient.** (Acta gastroenterol. belg., **2020**, 83, **432-440**).

Keywords : dysphagia, bougie dilation, balloon dilation, corticosteroid injections, esophageal stricture, esophageal stenosis

Introduction

Benign and malignant esophageal strictures are a common problem in clinical practice, causing symptoms of organic dysphagia. Since the management differs between the two groups, this review will only focus on the benign esophageal strictures. This group can be further subdivided by cause, including peptic strictures, rings and webs, anastomotic strictures, radiation-induced strictures, caustic strictures, strictures after endoscopic resection of lesions and eosinophilic esophagitis. Peptic strictures are responsible for 60-70% of all cases (1).

The first-line treatment for benign esophageal strictures consists of dilation therapy to relieve symptoms of dysphagia. However, the stricture and associated symptoms can recur or can be unresponsive to the initial dilation, requiring additional or repeated treatment. A widely accepted definition of refractory and recurrent esophageal stricture is an anatomic restriction because of cicatricial compromised lumen or fibrosis that results in the clinical symptom of dysphagia in the absence of endoscopic evidence of inflammation, which may occur as the result of either an inability to successfully remediate the anatomic problem to a diameter of 14 mm over 5 sessions at 2-week intervals (refractory) or as a result of an inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent) (2).

The complexity of a stricture is an important predictor of its response to dilation. Strictures that are short, focal, straight and allow passage of a normal diameter endoscope are called simple strictures and are rarely refractory to dilation therapy. On the other hand, strictures that are long (> 2 cm), irregular, angulated or have a severely narrowed diameter are considered complex strictures and are often refractory. These two groups have an etiological correlate: Schatzki ring, esophageal webs and peptic strictures mostly result in simple strictures, whereas radiation therapy, caustic ingestion and anastomotic strictures give rise to complex strictures (3).

Dysphagia caused by simple strictures can mostly be resolved by at most 3-5 dilations (4). Dilation can be performed with either a through-the-scope balloon dilator or a bougie dilator (5). The 'rule of three' is often followed, stating that the incremental dilation diameter in a single session should be no more than 3 mm to minimize the risk of perforation, although the validity of this rule has recently been questioned (6). For more complex strictures, dilation alone is often insufficient and supplementary treatment modalities can be used, including topical injections with steroids or mitomycin C, incisional therapy, stent placement, repetitive self-dilation and surgery. However, evidence on these different techniques is limited or even contradictory and the optimal order of the different modalities is yet to be determined. Especially the indication and modalities of intralesional steroid injections remain highly controversial (4).

The use of intralesional steroid injections is well established in keloid and burn-induced scars, where it

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avoids collagen deposition and enhances its breakdown, diminishing scar formation (7,8). Their use in benign esophageal strictures was first tested in a canine model in 1969, which showed a significant improvement of the stricture after triamcinolone injection, compared to saline injection or no treatment (9). Based on these results, the authors suggested that steroid injections are not only able to inhibit collagen synthesis, but can also suppress fibrosis and chronic scarring, thereby impeding stricture formation. However, the effects of intralesional steroid injection for refractory strictures in humans are still unclear and controversial.

This systematic review aims to investigate the efficacy and safety of intralesional steroid injections in addition to dilation in comparison to dilation alone in patients with benign refractory esophageal strictures. Based on the collected evidence a possible treatment algorithm for benign strictures is presented.

Methods

Search method

A systematic search was carried out in PubMed to identify all relevant articles. The language was restricted to English, but no time limitation was used since dilation and steroid injection techniques have not significantly evolved over time. The used search terms were "Esophageal Stenosis"[Mesh] AND "Injections, Intralesional"[Mesh]. The search was conducted on June 11, 2019. In addition, the reference list of all selected articles was searched manually for other relevant articles. The articles were consecutively screened by title, abstract and full-text for relevance and eligibility.

Eligibility criteria

This systematic review included studies on benign esophageal strictures, regardless of their etiology, that were treated with intralesional steroid injections in addition to dilation. Preclinical studies and articles considering only children and preventive intralesional injections after endoscopic procedures were excluded. The latter were considered a different treatment approach since these are prophylactic injections in contrast to injections before or after dilatations in an existing stricture which is the focus of the current systematic review. All clinical trials and case series were considered, but case reports were excluded because of their limited, merely anecdotal value.

Data extraction

The data extracted from the selected articles were: first author, year of publication, study design, inclusion and exclusion criteria, number of patients, stricture etiology, modalities of dilation and steroid injections, modalities of the control group if applicable, any additional treatments and outcome data on efficacy and safety.

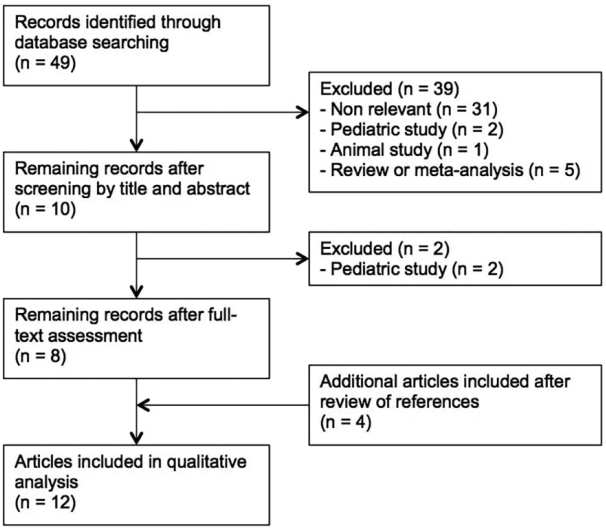

Figure 1. — Flowchart of literature search

Assessment of risk of bias in the included studies

The risk of bias was assessed in all included randomized controlled trials, using the Cochrane Collaboration's tool, as a judgment (low, high or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other) (10).

Since case series and cohort studies carry an inherently high risk of bias, this was not further elaborated with a specific tool.

Results

Results of literature search

The PubMed search revealed 49 articles, eight of which met the inclusion criteria, as detailed in the flow diagram presented in figure 1. In addition, a hand search of the reference list of the selected articles led to the selection of four more articles, leading to a total of 12 articles included in this systematic review.

Characteristics of included studies

Four randomized controlled trials, six case series and two cohort studies were included. The randomized controlled trials all compared a study group of patients receiving both dilation and intralesional steroid injections to a control group receiving either dilation alone or dilation in combination with sham injections. The case series compared the outcome of intralesional steroid injections and dilation to their status before additional intralesional steroid injections, with each patient serving as their own control. In the cohort studies, a study group of patients receiving both dilation and intralesional steroid injections was compared to a historical control group of patients undergoing dilation alone.

The 12 selected articles comprise a total of 341 patients with benign esophageal strictures of different

Table 1. — **Assessment of risk of bias using the Cochrane Collaboration's tool**

Article	Domain							Overall judgment
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	
Altintas et al, 2004(12)	Unclear	Unclear	High risk	High risk	Unclear	Low risk	High risk	High risk
Hirdes et al, 2013(13)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pereira-Lima et al, 2015(14)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ramage et al, 2005(15)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

etiologies: anastomotic (148), corrosive (67), eosinophilic esophagitis (3), peptic (97), pill esophagitis (1), radiation induced (24) and sclerotherapy induced (1). One article also included two cases of pyloric stenosis, but these fall outside the scope of this review.

To answer the research question whether dilation in combination with intralesional steroid injections is superior to dilation alone, various outcome parameters were used to assess treatment efficacy. The most commonly used parameter is the total number of dilations. In 1999, the periodic dilation index (PDI) was introduced, defined as the total number of dilations divided by the duration of time in months (11). This parameter allows a more uniform assessment of the frequency of dilation, since follow-up time can differ greatly from study to study. Many other parameters were used in the different studies, like the maximal achieved diameter, dysphagia score with different scoring systems and the time to the first repeat dilation. To assess the safety of the treatment all minor or major complications as a result of dilation and/or intralesional steroid injections were recorded.

Randomized controlled trials

Table 1 represents the risk of bias in the included randomized controlled trials. The study by Altintas et al. carries a high risk of bias, since the method of randomization was not described, blinding was absent, notion of completeness of outcome data was missing and no subgroup analysis was conducted despite heterogeneous stricture etiology (12). On the other hand, Hirdes et al., Pereira-Lima et al. and Ramage et al. clearly described the randomization protocol, blinded the patients and investigators, had limited dropout and only focused on one etiological subgroup, generating a low risk of bias in their studies (13-15). However, all included randomized controlled studies have a limited sample size, which should be taken into account.

Table 2 and 3 represent the characteristics and outcome of the included RCT. Altintas et al. included 21 patients with strictures of different causes (12). Patients in the study group had a lower PDI, corresponding to a longer interval between dilations, and a longer symptom-free period compared to patients in the control group. There was also a difference in total number of dilations and PDI within the study group, when comparing the outcome of these patients before and after the addition of intralesional steroid injections to dilation. Two patients with caustic strictures developed perforations, one in the control group and one in the study group. These findings led to the conclusion that intralesional steroid injections increased the efficacy of bougie dilation and decreased the requirement for repeated bougie dilation. No subgroup analysis was performed according to the different stricture etiologies.

Two randomized controlled trials focused on the subgroup of anastomotic strictures, but reached opposite conclusions (13,14). Hirdes et al. included 60 patients with dysphagia resulting from an anastomotic stricture after esophagectomy with a gastric conduit and cervical anastomosis, who did not undergo previous dilations (13). They found no significant difference in number of dysphagia-free patients after 6 months, median time to repeat dilation, median number of dilations, dysphagia score, quality of life or patient satisfaction between study and control group. In addition, there were more complications in the study group, including four patients who developed candida esophagitis, which was interpreted as a direct consequence of the steroid injections. Pereira-Lima et al. used the same inclusion criteria but added the condition that the stricture could not be passed with a 0.98 cm endoscope (14). In this smaller study comprising 19 patients, there were significantly more patients who were free of dysphagia after 1 and 6 months and there was a lower dysphagia score at 6 months in the study group. However, there was no reduction in the number of dilations.

Ramage et al. studied 30 patients with peptic strictures with a history of stricture dilation within the preceding 18 months (15). They observed a significant reduction in the need for repeat dilation and an increase in time to repeat dilation in the study group. On the other hand, when comparing dysphagia frequency and dietary consistency intolerance at baseline and at the time of the first repeat dilation or at 6 months (whichever came first), no significant difference was found. This was interpreted

Table 2. — **Characteristics of the included studies**

Article	Patients			Intervention		Control
	No of patients (SG/CG or no of cases)	Stricture etiology (SG/CG or no of cases)	Previous dilation	Dilation modalities	Steroid injection modalities	Control group if applicable
Altintas et al, 2004(12) RCT	10/11	Anastomotic: 1/3 Corrosive: 2/1 Peptic: 6/4 Radiation induced: 1/3	Yes	SGBD	8 mg triamcinolone into each quadrant. After dilation. Only first time.	SGBD alone
Hirdes et al, 2013(13) RCT	29/31	Anastomotic: 29/31	No	SGBD	20 mg triamcinolone into each quadrant. Before dilation. Repeated up to 3 times.	SGBD and sham injection
Pereira-Lima et al, 2015(14) RCT	10/9	Anastomotic: 10/9	No	SGBD	40 mg triamcinolone at the border of the mucosal tears caused by dilation. After dilation. With each dilation.	SGBD and sham injection
Ramage et al, 2005(15) RCT	15/15	Peptic: 15/15	Yes	TTS-CRE	20 mg triamcinolone into each quadrant of the narrowest region of the stricture. Before dilation. With each dilation.	TTS-CRE and sham injection
Ahn et al, 2015(18) CS	25	Anastomotic: 1 Eosinophilic esophagitis: 3 Peptic: 17 Radiation induced: 4	Yes	SGBD or TTS-CRE	10 mg triamcinolone into each quadrant at the proximal margin of the stricture and into the strictured segment. After dilation. With each dilation.	
Kirsch et al, 1991(16) CS	2	Peptic: 2	Yes	SGBD	5 mg triamcinolone into each quadrant of the narrowest region of the stricture. After dilation. In initial dilations.	
Kochhar et al, 1999(11) CS	17	Corrosive: 17	Yes	SGBD	4 to 6 injections of 2.5 mg triamcinolone at the proximal margin and 4 to 6 injections into the strictured segment. Before dilation in 13 patients and after dilation in 4 patients. Injections repeated if no subjective response at subsequently scheduled session (maximum: 3).	
Kochhar et al, 2002(19) CS	71	Anastomotic: 19 Corrosive: 29 Peptic: 14 Radiation induced: 9	Yes	SGBD	10 mg triamcinolone into each quadrant at the proximal margin of the stricture and into the strictured segment when possible. Before dilation in 63 patients and after dilation in 8 patients. Injections repeated if no subjective response at subsequently scheduled session (maximum: 4).	
Lee et al, 1995(20) CS	31	Anastomotic: 8 Corrosive: 1 Peptic: 12 Pill esophagitis: 1 Radiation induced: 6 Sclerotherapy: 1 (Pyloric stenosis: 2)	Yes	SGBD or TTS-CRE	28 mg triamcinolone into each quadrant at the narrowest region of the stricture. After dilation. With each dilation.	
Nijhawan et al, 2016(17) CS	11	Corrosive: 11	Yes	SGBD	10 mg triamcinolone into each quadrant of the proximal margin of the stricture and into the strictured segment if long stricture. Before dilation. Weekly during 5 weeks.	
Miyashita et al, 1997(21) Cohort	11/22	Anastomotic: 11/22	No	TTS-CRE	2 mg dexamethasone into each quadrant at the anastomosis. After dilation. Unclear repeating schedule.	SGBD or TTS-CRE alone
Orive-Calzada et al, 2012(22) Cohort	9/14	Anastomotic: 2/2 Corrosive: 4/2 Peptic: 3/9 Radiation induced: 0/1	No	SGBD or TTS-CRE	20 mg triamcinolone into each quadrant. Before dilation. Only first time.	SGBD or TTS-CRE alone

RCT, randomized controlled trial ; CS, case series ; SG, study group ; CG, control group ; SGBD, Savary-Gilliard bougie dilation ; TTS-CRE, through-the-scope controlled radial expansion balloon dilation.

as a consequence of the small sample size and the low event rate of recurrent dysphagia.

Case series

The characteristics and outcome of the included case series are described in table 2 and 3. The oldest included case series by Kirsch et al. involved only two patients, both with peptic strictures (16). The stricture diameter improved in one of the patients after the addition of intralesional steroid injections to dilation. However, there was subjective improvement and amelioration of dysphagia score in both patients after intralesional steroid injections.

Kochhar et al. and Nijhawan et al. focused on corrosive strictures (11,17). Both studies found a significant reduction of PDI, a decrease in number of dilations and an increase in maximum achieved dilation diameter. One

Table 3. — **Outcome of the included studies**

Article	Outcome		
	Efficacy (SG vs. CG for RCT or cohort study; before vs. after intralesional steroid injections for RCT* or CS)		Complications
Altintas et al, 2004(12) RCT	Mean PDI Mean ND Mean symptom-free period Obtainment of sufficient dilation (14 mm) Mean PDI* Mean ND* Obtainment of sufficient dilation (14 mm)*	0.193 vs. 0.597 (P < 0.05) 5.3 vs. 6 (P = 0.86) 24 vs. 5.18 months (P < 0.001) 1 vs. 2 patients (P = 0.28) 0.712 vs. 0.289 (P = 0.03) 5.3 vs. 1.6 (P = 0.03) 4 vs. 1 patients (P = 0.5)	SG: 1 (perforation) CG: 1 (perforation)
Hirdes et al, 2013(13) RCT	Dysphagia-free after 6 months Median time to repeat dilation Median ND DS[a] Quality of life by Short Form 36 Patient satisfaction by Visual Analogue Scale	45% vs. 36% (P = 0.46) 108 vs. 42 days (P = 0.29) 2 vs. 3 (P = 0.36) n/a (P = 0.78) n/a (P = 0.39) n/a (P > 0.05)	SG: 5 (1 submucosal laceration, 4 candida esophagitis) CG: 1 (hemorrhage)
Pereira-Lima et al, 2015(14) RCT	Dysphagia-free after 1 month Dysphagia-free after 6 months Mean ND DS[b]	40% vs. 0% (P = 0.021) 62% vs. 0% (P = 0.009) 3 vs. 4 (P = 0.388) n/a (P = 0.009)	None
Ramage et al, 2005(15) RCT	Need for repeat dilation Time to first repeat dilation Dysphagia frequency Dietary consistency intolerances	13% vs. 60% (P = 0.0209) n/a (P = 0.011) n/a (P > 0.05) n/a (P > 0.05)	None
Ahn et al, 2015(18) CS	Mean PDI Mean ND Mean MD	0.58 vs. 0.28 (P < 0.05) 3.0 vs. 2.28 (P < 0.05) 16.08 vs. 18.88 mm (P = 0.17)	None
Kirsch et al, 1991(16) CS	DS[c] Stricture diameter Subjective improvement	3 vs. 21 in patient 1; 1 vs. 21 in patient 2 3.5 mm vs. 3.5 mm in patient 1; 8 mm vs. 20 mm in patient 2 Improvement in patient 1 and 2	None
Kochhar et al, 1999(11) CS	Median PDI Mean ND MD	1.67 vs. 0.32 (P < 0.01) 27.92 vs. 3.57 n/a	1 (bleb formation with dysphagia)
Kochhar et al, 2002(19) CS	Mean PDI Mean ND Mean MD DS[d]	1.24 vs. 0.51 (P < 0.001) 9.67 vs. 3.88 (P < 0.05) 13.49 vs. 14.82 mm (P < 0.01) n/a (P = 0.001)	None
Lee et al, 1995(20) CS	Mean ND Mean interval between dilations Mean MD	n/a (P < 0.05) n/a (P < 0.05) n/a	None
Nijhawan et al, 2016(17) CS	Mean PDI Mean ND Mean MD DS[e]	2.54 vs. 0.19 (P < 0.001) n/a 9.90 vs. 14.7 mm (P < 0.001) 3.54 vs. 0.45 (P < 0.001)	None
Miyashita et al, 1997(21) Cohort	Mean ND	1.1 vs. 4.7 (P < 0.05)	None
Orive-Calzada et al, 2012(22) Cohort	Mean ND Rate of refractory strictures Grades of DS[f] decreased	3.33 vs. 3 (P = 0.673) 0% vs. 42.85% (P = 0.048) 3.78 vs. 1.69 (P = 0.009)	SG: none CG: 1 (perforation)

RCT, randomized controlled trial ; CS, case series ; SG, study group ; CG, control group ; PDI, periodic dilation index ; ND, number of dilations ; MD, maximum dilation ; DS, dysphagia score ; n/a, no overall data available in article, data is either presented in a figure or table or not specified. [a]DS measured with the MDQ (> 40%, positive for dysphagia ; 15%-40%, indeterminate ; < 15%, negative for dysphagia). [b]DS 1 to 5 (1, unable to swallow certain solid foods ; 2, able to swallow only semisolid soft foods ; 3, able to swallow just liquids ; 4, unable to swallow liquids in adequate amounts or difficulty in swallowing the own saliva). [c]DS 0 to 21 (based on ability to swallow certain foods : 1, water ; 2, applesauce ; 3, banana ; 4, unpeeled apple wedge ; 5, prunes ; 6, white bread with crust – 0, total dysphagia ; 21, absence of dysphagia). [d]DS 0 to 4 (0, no dysphagia ; 1, dysphagia to solid food ; 2, dysphagia to semisolid food ; 3, dysphagia to liquids ; 4, aphagia). [e]DS 0 to 4 (0, able to eat normal food or no dysphagia ; 1, able to swallow some solid food ; 2, able to swallow only semisolid food ; 3, able to swallow liquids only ; 4, unable to swallow anything or total dysphagia). [f]DS 0 to 5 (0, no dysphagia ; 1, dysphagia with ingestion of meat ; 2, dysphagia with ingestion of bread ; 3, dysphagia to soft food ; 4, dysphagia with semisolid food ; 5, dysphagia with liquids).

study also showed a significant amelioration in dysphagia score (17). One patient presented with deterioration of dysphagia for 24 hours after intralesional steroid injections, supposedly due to a superficial injection of triamcinolone creating a submucosal bleb (11)

The remaining three case series comprised a heterogeneous study population (18-20). Ahn et al. observed a significant reduction in PDI and number of dilations, but no significant increase in maximum dilation diameter (18). However, after subgroup analysis, PDI

was significantly enhanced after intralesional steroid injections in all subgroups except eosinophilic esophagitis (3 patients only) and the number of dilations reduced only significantly in the group of peptic strictures. Kochhar et al. found a significant decrease in PDI, number of dilations and dysphagia score and a significant increase in maximum dilation after intralesional steroid injections, for all etiologic categories (19). Finally, Lee et al. observed a significant decrease in number of dilations and increase in interval between dilations in all etiological subgroups (20). The maximal achieved dilation diameter was significantly enhanced in patients with peptic and radiation-induced strictures. Other subgroups showed only a trend toward larger dilation diameter.

Cohort studies

Table 2 and 3 show the characteristics and outcome of the included cohort studies. A first cohort study by Miyashita et al., including 33 patients with refractory anastomotic strictures, found a significantly lower number of dilations in the study group, compared to the historical control group (21). Orive-Calzada et al. included 23 patients with complex strictures of different etiology and observed no significant effect of intralesional steroid injections on the number of dilations (22). However, they did find a lower incidence of refractory strictures and a lower dysphagia score when intralesional steroid injections were added to the dilation. One patient in the control group suffered a perforation. No subgroup analysis was conducted.

Discussion

The causative factor of recurrent and refractory stenosis in benign esophageal strictures is still unknown. It is thought to be a result of intense fibrogenesis during healing and after the dilation-induced trauma (12). However, the underlying pathogenesis varies considerably between the different types of strictures. For example, peptic strictures develop as a result of ulceration and inflammation caused by gastroesophageal reflux, whereas anastomotic strictures are formed as a consequence of relative ischemia of the proximal part of the gastric tube (13). This could have an effect on their response to therapy and more specifically on their response to intralesional steroid injections.

The different pathogenesis and the associated potentially different treatment effect hamper the interpretation of the results since the number of patients per subgroup is often low. One randomized controlled trial and one cohort study studied an etiologically heterogeneous population without performing a subgroup analysis, making interpretation even harder (12,22). Therefor, these two studies will not be discussed in the following summary of results. The need for repeat dilations is considered the most important outcome measure, since reducing dilation sessions is of great importance for the patient's quality of life, the reduction in costs and the minimization of the risk of perforation (14). This can be expressed as periodic dilation index or number of dilations, with the former being more reliable since it has been corrected for the time period.

Anastomotic strictures were included in six of the included studies. Two randomized controlled trials, focusing only on anastomotic strictures, did not find a reduction in the number of dilations in the study group (13,14). However, the study of Pereira-Lima et al. showed a significant increase in the number of patients who were dysphagia-free after six months and an improvement in the dysphagia score, while the study of Hirdes et al. failed to confirm these results. This led the former to argue in favor of intralesional steroid injections, while the latter argued against. The cause of these opposing results is difficult to determine, since the studies differ on various points such as the modalities of steroid injections, the complexity of the included strictures and the sample size. Firstly, Pereira-Lima et al. injected 40 mg triamcinolone after dilation per session whereas Hirdes et al. used 80 mg triamcinolone before dilation. Thus, the dose alone is insufficient to explain the different results, since the positive study used the lowest dose of triamcinolone. The moment of injection may have affected the results. Secondly, the complexity of the included strictures differed between the studies, with Hirdes et al. including all strictures regardless of their anatomy and Pereira-Lima et al. only focusing on strictures that were not passable with a 0.98 cm endoscope and thus complex. If the difference in complexity was responsible for the different outcome, it would mean that the benefit of steroid injections is limited to complex strictures. However, no subgroup analysis is available in the study of Pereira-Lima to support these findings. Thirdly, the sample size of Pereira-Lima et al. was three times smaller, making the study more prone to bias. Yet, it is important to note that there was only a difference in subjective outcome between both studies, without reduction of the number of dilations in either of the studies. On the other hand, three case series and one cohort study showed a significant reduction in need for dilations in the subgroup of anastomotic strictures (18-21). Four patients in the study group of Hirdes et al. developed candida esophagitis, which was interpreted as a direct consequence of the steroid injections (13).

Patients with peptic strictures were studied in five of the included articles. A randomized controlled trial found a reduction in need for repeat dilation after intralesional injections (15). This favorable outcome was confirmed in four case series, after subgroup analysis (16,18-20). None of the studies showed complications as a consequence of addition of intralesional steroid injections to dilation.

Four studies included patients with corrosive strictures. These four case series all found a reduction in need for dilation (11,17,19,20). Only one minor complication occurred as a result of intralesional injections, being the formation of a bleb after submucous injection with temporary increase in dysphagia (11).

Radiation-induced strictures were studied in three case series, which all found a significant reduction in need for dilation in this subgroup (18-20). No complications resulted from intralesional steroid injections.

There were only a limited amount of patients with strictures due to sclerotherapy (1), pill esophagitis (1) and eosinophilic esophagitis (3), which makes it difficult to draw any relevant conclusion. In those first two patients a trend of reduction in number of dilations was observed (20). As for the subgroup of eosinophilic esophagitis, there was no significant reduction in periodic dilation index after intralesional steroid injections (18). None of the patients suffered complications.

An emerging entity are the strictures after endoscopic mucosal resections (EMR) and endoscopic submucosal dissection (ESD) for esophageal lesions (23). In these patients, the focus is on preventing stricture formation by injection of corticosteroids or treatment with a corticosteroid viscous solution immediately after the resection (24-28). Since this is a different treatment approach compared to injections after dilatation of an existing stricture, these studies were not included in the current review.

The main limitations of the included studies are their limited sample size and their heterogeneity. Firstly, two different dilation techniques were used: Savary-Gilliard bougie dilation and through-the-scope controlled radial expansion balloon dilation. Theoretically, bougie dilation would carry a higher perforation risk than balloon dilation, since they exert not only radial forces, but also longitudinal forces as they are passed. However, both

Table 4. — **Inclusion and exclusion criteria of the included studies**

Article	Inclusion criteria	Exclusion criteria
Altintas et al, 2004(12) RCT	- Benign esophageal strictures confirmed by clinical, radiological and endoscopical features	- Esophageal malignancy
Hirdes et al, 2013(13) RCT	- Patients with dysphagia grade 2 or more (grade 0, ability to eat a normal diet; grade 1, ability to eat some solid foods; grade 2, ability to eat semisolid food; grade 3, ability to swallow liquids only; grade 4, complete obstruction) after transhiatal or transthoracic esophagectomy with gastric conduit and cervical anastomosis with a confirmed anastomotic stricture during endoscopy	- Previous dilation or stent placement (after esophagectomy) - Suspicion of recurrent malignancy - R1 or R2 resection - Active anastomotic leak or perforation - Known duodenal or gastric ulcers - Poor candidates for upper endoscopy
Pereira-Lima et al, 2015(14) RCT	- Patients with dysphagia to solids after esophagectomy with gastric pull-up and cervical handsewn esophagogastrostomy, with a confirmed anastomotic stricture that was not passable with a 0.98 cm endoscope	- Suspicion of recurrent malignancy at the diagnosis - Previous dilations or radiotherapy - Active anastomotic leak - Refusal to enter in the protocol
Ramage et al, 2005(15) RCT	- Patients with dysphagia occurring at least once a week with a history of peptic stricture dilation within the preceding 18 months. When the findings of gastroesophageal reflux were absent on endoscopy, patients were required to have had symptoms compatible with gastroesophageal reflux as defined by validated criteria; heartburn at least once a week plus one associated symptom (relief with an antacid, nocturnal awakening, radiation toward the neck) or acid regurgitation occurring at least once a week	- Barrett's esophagus with dysplasia - Prior radiation therapy to the thoracic cavity - Esophageal malignancy - Prior esophageal or gastric resection - Esophageal varices - Clinical history implying that stricture may be secondary to pill-induced esophagitis
Ahn et al, 2015(18) CS	- Refractory esophageal strictures defined as anatomic restriction due to fibrosis requiring more than 3 sessions of dilatation to maintain lumen of at least 14 mm or inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm had been achieved	n/a
Kirsch et al, 1991(16) CS	- Benign peptic strictures of the esophagus	n/a
Kochhar et al, 1999(11) CS	- Corrosive-induced esophageal strictures	- Esophagitis - Pharyngeal stenosis - Tracheoesophageal fistula - Gastric cicatrization preventing safe optimum placement of a guidewire
Kochhar et al, 2002(19) CS	- Benign esophageal strictures of differing etiologies causing significant dysphagia and requirement of esophageal dilation on a regular basis	- Pharyngeal stenosis precluding endoscopic examination and dilation - Tracheoesophageal fistula - Gastric cicatrization precluding safe placement of a guidewire
Lee et al, 1995(20) CS	- Upper gastrointestinal strictures requiring frequent dilations	- Underlying primary motility disorder
Nijhawan et al, 2016(17) CS	- Refractory corrosive esophageal stricture defined as an anatomic fibrotic esophageal restriction with inability to achieve dilatation of ≥14mm or to maintain dilatation for 4 weeks once ≥14mm diameter is achieved - Age 2–80 years	- Failure to pass a guide wire secondary to pharyngeal stenosis or gastric cicatrization - Tracheoesophageal fistula - Those who received triamcinolone injections earlier - Failure to follow the rigorous schedule of triamcinolone injection with dilatation - Failure to follow up for 1 year
Miyashita et al, 1997(21) Cohort	- Anastomotic stricture after esophagogastrostomy	- Stricture caused by tumor recurrence
Orive-Calzada et al, 2012(22) Cohort	- Study group: patients with dysphagia and complex benign eso-phageal strictures of differing etiologies that had never been dilated before and that consecutively had to undergo esophageal dilation - Control group: patients with complex benign esophageal strictures who had consecutively been treated with esophageal dilation	- Barrett esophagus with dysplasia - Esophageal malignancy - Esophageal varices

RCT, randomized controlled trial ; CS, case series.

techniques have been shown to be equally safe and effective in clinical studies (29). Nevertheless, balloon dilators are single-use in contrast to bougie dilators and thus significantly more expensive.

Secondly, there was a wide variation in the modalities of the steroid injections, in terms of dose, schedule of injection and injection site. The dose per session ranged from 20 mg to 112 mg triamcinolone (16,20). In some studies, injections were repeated in the case of redilation (11,13-20), while in others this was not the case (12,22). It is not yet clear what the optimal dose and repeating schedules are, since on the one hand a beneficial effect of injections could already be seen with low doses of triamcinolone in some studies (11,12,16) and on the other hand high doses did not always turn out a success (13,22). In only one study complications related to the steroid injections were encountered, i.e. four cases of candida esophagitis (13). They used 80 mg, a relatively high dose of triamcinolone per session and repeated this up to three times. This suggests that caution is required when using higher doses of triamcinolone. The moment of injection was before dilation in four studies, (13,15,17,22) after dilation in six studies (12,14,16,18,20,21) and mixed in two studies (11,19). Hirdes et al. carried out the steroid injections before dilation, so to avoid injecting in a lacerated wall and thereby possibly causing a perforation (13). Pereira-Lima et al. argued that injections should be performed after dilation, since some of the injected fluid can be lost in the lacerations provoked by dilation before diffusion into the tissue (14). Although both are plausible arguments, no benefit in efficacy or safety of either of these two methods has been demonstrated in clinical studies. The optimal site of injection is also yet to be determined. However, injecting into the four quadrants is widely accepted, as this technique was used in all but two of the included studies (11,14).

Thirdly, some studies used an additional treatment, like antireflux therapy with antacids, proton pump inhibitors or histamine H2-receptor antagonists (12,13,15,16,18-20,22) and preventive antifungal treatment with keto-conazole (11), which might have had an influence on the efficacy and safety. Potent acid suppression with proton pump inhibitors is known to bring down the recurrence rate of strictures to 30% over a period of one year (30).

Fourthly, the inclusion and exclusion criteria differed considerably between studies (Table 4). In some studies it was explicitly stated that the strictures had to be refractory, recurrent or complex, or this was indicated implicitly in characteristics that fit their description (14-20,22). Other studies allowed all benign strictures, regardless of their anatomy or tendency to refractoriness or recurrence (11-13,21). Some studies excluded patients having received previous dilation to rule out the effect of gradual opening of the stricture in response to repeated dilations (13,14,21,22). This was of course impossible in the case series, as they used a cross-over design, in which all patients first received sole dilation in order to serve as their own control afterwards (11,16-20).

Fifthly, the majority, but not all of the patients were adults, which was the target group of this review. Studies concerning only minors were excluded, but the use of pediatric patients as absolute exclusion criteria for studies was not possible, given the limited amount of literature on the subject.

Implications for daily practice

Endoscopic dilation remains the first-line treatment for benign esophageal strictures, since its efficacy and safety are satisfying in the majority of patients (5,31). In strictures that fail to respond adequately to dilation therapy and meet the definition of recurrent or refractory strictures, intralesional steroid injections are recommended to be added to dilation in peptic strictures and should be considered in radiation-induced, corrosive strictures and anastomotic strictures. Even though the evidence in radiation-induced and corrosive strictures is only derived from case series and the evidence in anastomotic strictures is inconsistent, the use of intralesional steroid injections can be defended given the potential benefit and the very limited incidence of complications. Intralesional steroid injections can also be started from the first dilation in complex strictures, because of the high likelihood of evolution to refractoriness. The use of steroid injections is currently not recommended for strictures due to eosinophilic esophagitis.

As there are no studies into the optimal modalities of steroid injections, we propose to follow the protocol of Ramage et al., i.e. 20 mg triamcinolone into each quadrant of the narrowest region of the stricture before dilation, as it has shown to be effective and safe in a randomized controlled trial (15). Taking into account the risk of candida esophagitis, the use of steroids should be restricted to a maximum of three sessions, since this was found to be safe in the majority of the included studies. If a satisfactory result has not been reached by this time, alternative treatment should be considered, like incisional therapy, stent placement and surgery (4).

Conclusion and prospects for future research

The evidence collected in this systematic review suggests a benefit of adding intralesional steroid injections to dilation in reducing the need for repeat dilation in the subgroups of peptic, radiation-induced and corrosive strictures. The effect is less clear in the case of anastomotic strictures, where the study results are inconsistent. The number of patients with strictures due to eosinophilic esophagitis, sclerotherapy or pill esophagitis was too low to come to a relevant conclusion.

Large randomized controlled trials that take into account the etiology and anatomy of the stricture are needed. In addition, further research into the optimal modalities of intralesional steroid injections is necessary.

Conflict of interest

None.

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