Endoscopic Management of Benign Laryngo-Tracheal Stenosis: Balloon vs. Rigid Dilatation

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ABSTRACT **Background:** Management of acquired laryngotracheal stenosis (LTS) is challenging and often requires recurrent procedures.
Objectives: To compare the efficacy and safety of balloon dilatation (BD) versus rigid dilatation (RD) in the treatment of LTS.
Methods: A retrospective study of patients undergoing endoscopic intervention for LTS was performed.
Results: The study included 69 balloon (BD) and 48 rigid dilations (RD). Most cases were grade 3 Cotton-Meyer stenosis. Mean time interval to recurrence after BD and RD were 27.9 and 19.6 weeks, respectively. Remission of over 8 weeks was achieved in 71% of BD compared to 31.2% of RD ($P < 0.05$). In the BD group, dilatation of subglottic stenosis showed higher rates of remission of over 8 weeks compared to upper and mid-tracheal stenosis (92% vs. 62% and 20%, respectively, $P < 0.05$). Complications were encountered in 4.2% of RD and 2.9% of BD.
Conclusions: BD and RD are effective and safe procedures. Overall, BD achieved slightly better long-term results compared to RD.
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KEY WORDS: balloon catheters, dilatation, endoscopic, laryngeal stenosis, tracheal stenosis

Endotracheal intubation and tracheostomy are considered the most common etiologies for benign acquired laryngotracheal stenosis (LTS) [1].Other causes include mainly inflammatory disorders (i.e., granulomatosis with polyangiitis) and idiopathic stenosis. Upper airways stenosis may involve sub-sites of the larynx and trachea including the posterior glottis, the subglottic area, the cricotracheal junction, and the trachea.

Treatment of the variety of pathologies encountered in LTS naturally requires different solutions or interventions and, not infrequently, recurrent procedures.

Segmental resection with end-to-end anastomosis (CTR) yields the highest cure rates in the management of isolated tracheal stenosis [2]. This technique was adopted to include the subglottic area as well, with high rates of success and low rates of morbidity [3,4]. However, patient co-morbidities, previous interventions, and the extent of stenosis may prevent its implication. Other techniques may include tissue grafting (e.g., costal cartilage), laser scar vaporization, stent insertion, and dilatation [2]. The use of endoscopic dilatation for airway stenosis has expanded gradually because of its minimal invasiveness and relative simplicity [2].

Dilatation can be performed by using balloon (BD) or rigid dilators (RD) [2,5-9]. The success rate in gaining a permanent and satisfactory patent airway varies greatly in the range between 40% and 82% [10]. Dilatation procedures became more popular in recent years because they are short in time, can be performed on a day-service, and are considered highly safe compared with open surgery.

The aim of this study was to compare the efficacy and safety of BD and RD in the treatment of benign acquired LTS.

PATIENTS AND METHODS

A retrospective study was conducted of all patients with benign LTS treated with BD or RD, between the years 2011 and 2017 in a tertiary university affiliated medical center. Medical charts were reviewed for patient demographics, etiology, site and severity of stenosis, primary intention of dilatation, surgical parameters, complications, and outcome.

All patients with postoperative follow-up of less than 6 weeks were excluded.

Endoscopic dilatation was selected for patients with a short stenotic segment (< 2 cm in length) and a limited involvement of the tracheal cartilaginous skeleton.

The severity of stenosis was graded by the Myer-Cotton classification [11] and was calculated by the size of the largest endotracheal tube that could pass through it.

The indications for dilatation were divided into three categories:

- Curative intention
- Bridging intention: an alternative for tracheostomy when open procedure (i.e., CTR) was indicated and preferred, but could not be conducted at the time of intervention due to patient's medical status
- Revision dilatation: a corrective procedure for residual stenosis after CTR

The selection between BD and RD was influenced mainly by the time period when the surgery was performed (from 2011until mid 2014 we performed only RD). Other factors include the

procedure's urgency (urgent situations were managed by RD because they are performed faster), etiology of stenosis (inflammatory reaction was more commonly treated by BD because in these cases the stenosis is usually made of a soft and friable tissue which responds well to balloon dilatation), and indication (bridging procedures were usually performed by using RD).

SURGICAL TECHNIQUE

All procedures were performed under general anesthesia with spontaneous ventilation. Topical anesthetic (lidocaine10%, xylocaine) was sprayed on the larynx prior to endoscopy. The degree, length, and structure of the stenosis were assessed via microlaryngobronchoscopy using a 4 mm Hopkins Telescope (Karl Storz™ [KARL STORZ Endoscopy-America, Inc., USA], 0 degree). The natural size of the lumen was estimated in regard to the proximal and distal segments adjacent to the stenosis. Balloon catheters (Boston Scientific [USA], CRE pulmonary™, sizes 8–18 mm) were inserted to the trachea either through rigid bronchoscopes placed proximal to the stenosis or under endoscopic guidance. In tracheotomized patients with middle or lower tracheal stenosis, balloon catheters were directed either through the larynx via rigid bronchoscopy or through the stoma under endoscopic guidance. Balloon catheters were inflated under visualization according to manufacturer's guidelines in the center of the stenotic segment until the desired pressure was reached (Pressure range = 1–4.5 ATM). The pressure was held for 1 minute or until oxygen saturation decreased below 80%. A second attempt was made if the desired airway patency was not attained. In RD, conoid shaped CO2 laser bronchoscope (Richard Wolf GmbH, Knittlingen, Germany™, sizes 4-6-8-9) were directed through the narrowed segment, with gradual sizing up of larger calibers until the natural size of the airway was met.

Recurrence was defined by recurring symptoms combined with endoscopic findings consistent with worsening stenosis. Flexible fiber-optic bronchoscopy was performed under topical anesthesia in the outpatient clinic, performed by senior residents and the authors (EG, AP-F, EC, EA, MW). All images were recorded.

We selected 8 weeks as a cutoff point for prolonged remission, as this time length ensures near total scar healing/maturation.

The study was reviewed and approved by the research ethics committee at the Sheba Medical Center, Tel Hashomer, Israel (application number 2544-15-SMC).

STATISTICAL ANALYSIS

Continuous variables are displayed as mean ± standard deviation and categorical variables are presented as number and percent in each group. The means and standard deviations of each measurement were determined. Student's *t*-test and chi-square test were used to compare categorical and continuous variables between the different patient groups. Univariate and multivariate logistic regression were applied to find factors associated with remission length. All measurements were considered significant at $P < 0.05$ (two tailed).

RESULTS

The study included 69 BD procedures performed in 40 patients (23,10,4,2, and 1 patients underwent 1,2,3,4, and 6 procedures, respectively) and 48 RD performed in 29 patients (18,5,4, and 2 patients underwent 1,2,3, and 4 procedures, respectively). Patient demographics, etiology of stenosis, and co-morbidities are listed in Table 1. In the BD group there was a female predominance, whereas male predominance was noted in the RD group. The most common etiology of stenosis in both groups was previous endotracheal intubation (65% of BD and 100% of RD). In approximately one-third of the remaining BD patients the etiology was idiopathic/inflammatory or related to other etiologies (e.g., thermal, caustic or radiation-induced injury) compared to none of the RD ($P < 0.01$).

Table 1. Patient demographics, co-morbidities, and etiology of airway stenosis

	Balloon dilatation	Rigid dilatation
Number of patients	40	29
Mean age (years)	45.3 (range 12–86)	49.76 (range 18–74)
Gender		
Male	15 (37.5%)*	25 (86%)*
Female	25 (62.5%)	4 (14%)
Co-morbidities		
Essential hypertension	11 (27.5%)	12 (41.3%)
Diabetes mellitus	9 (22.5%)	10 (34.4%)
Ischemic heart disease	7 (17.5%)	7 (24.1%)
Etiology of stenosis		
Intubation	26 (65%)*	29 (100%)*
Idiopathic	9 (22.5%)	0
Other	5 (12.5%)	0
Tracheostomy dependency	7 (17.5%)	8 (27.1%)

*$P < 0.05$

The characteristics of the stenosis and the outcome of treatment are presented in Table 2. Over 50% of patients were graded 3 on the Cotton-Meyer grading system and most procedures were intended to be curative in both groups. There were no statistically significant differences in grade and location of stenosis between the BD and RD groups. In the BD group, the balloon catheters were inflated once (53%) or twice (47%) in each session.

Table 2. The characteristics, treatment and outcome of the upper airway stenosis

	Balloon dilatation (69 procedures)	Rigid dilatation (48 procedures)
Grade of stenosis**		
Grade 1	16 (23.2%)	5 (10.5%)
Grade 2	15 (21.7%)	16 (33.3%)
Grade 3	38 (55.1%)	27 (56.2%)
Location of stenosis		
Subglottic	12 (17.4%)	6 (12.5%)
Cricotracheal junction	11 (15.9%)	8 (16.6%)
Upper tracheal	37 (53.6%)	27 (56.2%)
Mid-tracheal	5 (7.3%)	7 (14.6%)
Lower tracheal	2 (2.9%)	0
Upper + mid-tracheal	2 (2.9%)	0
Surgical indication		
Curative	54 (78.2%)	29 (60.4%)
Bridging before CTR	3 (4.4%)	10 (20.8%)
Revision post CTR	12 (17.4%)	9 (18.8%)
Overall complication rate	2.9%	4.2%
Mean time to recurrence (weeks)	27.9 (range 1–200)	19.6 (range 1–192)
Remission after > 8 weeks	49 (71.0%)*	15 (31.2%)*

**Cotton-Meyer grading system
*$P < 0.05$
CTR= Cricotracheal segmental resection with end-to-end anastomosis

There were 15 patients with a tracheostomy. Decanulation was essentially achieved in 2 of 7 patients treated by BD and 4 of 8 patients undergoing RD.

The mean time interval to recurrence following BD and RD was 27.9 and 19.6 weeks, respectively ($P = 0.3$). Remission intervals were 31.7, 40.2, and 19.1 weeks in the BD group, and 18, 23.7, and 21.6 weeks in the RD group for grades 1, 2, and 3 stenosis, respectively. Remission intervals for subglottic, cricotracheal, upper-tracheal, and mid-tracheal in the BD and RD groups were 24.2, 30.2, 28.3,15.8, and 14.5, 17.5, 21.7, and 18.3 weeks, respectively. The differences between the mean remission time length for grades 1, 2, and 3 stenosis and for the different locations of stenosis were not statistically significant in either group. In the BD group the mean remission time length for idiopathic/inflammatory etiology and other etiologies (thermal, caustic, or radiation-induced injury) were 27.5 and 22.5 weeks, respectively.

Remission lasting more than 8 weeks (prolonged remission) was achieved in 71% (n=49) of BD procedures compared to 31.2% (n=15) of RD ($P < 0.05$) with a mean follow-up period of 22 weeks in both groups (range 6–192 weeks).

BD achieved similar prolonged remission rates for all indications. However, in the RD group, revision dilatations post-CTR showed higher prolonged remission rates compared to primary intervention (67% vs. 31%, $P = 0.05$). The association between prolonged remission and the etiology, characteristics, site and severity of the stenosis is described in Table 3. Patients undergoing BD for subglottic stenosis showed significant higher rates of prolonged remission (91.6%, $P < 0.05$) compared to BD and RD of other locations. However, when analyzing the results of all BD procedures, the prolonged remission rates in idiopathic/inflammatory etiology versus previous endotracheal intubation did not differ significantly (81% vs. 64%, $P = 0.2$).

On univariate and multivariate analysis age and gender did not correlate with remission length in the study population ($P = 0.4$ and 0.2, respectively). In the BD group inflammatory/idiopathic etiology did not correlate with remission length ($P = 0.37$).

Table 3. Association between prolonged remission and the etiology, site and severity of the stenosis

Number of procedures that achieved prolonged remission (> 8 weeks)		
	Balloon dilatation (69 procedures)	**Rigid dilatation (48 procedures)**
Grade of stenosis**		
Grade 1	13/16 (81.2%)	2/5 (40%)
Grade 2	12/15 (80%)	5/16 (31%)
Grade 3	24/38 (63.1%)	8/27 (30%)
Location of stenosis		
Subglottic	11/12 (91.6%)*	1/6 (17%)
Crico-tracheal junction	9/11 (81.2%)	4/8 (50%)
Upper tracheal	25/37 (67.6%)	9/27 (33.3%)
Mid-tracheal	1/5 (20%)	1/7 (14%)
Lower tracheal, upper+mid-tracheal	3/4 (75%)	
Etiology of stenosis (balloon dilatation group)		
Idiopathic/ inflamatory	13/16 (81.25%)	
Endotracheal intubation	36/53 (67.9%)	15/48 (31.2%)

**Cotton-Meyer grading system
*$P < 0.05$

Thirteen procedures (3 BD and 10 RD) were intended as bridging interventions before open surgery (CTR) was performed. The mean duration between BD and RD to CTR was 18 and 4.8 weeks, respectively (range 1–26 weeks) and none underwent tracheostomy.

Complications were encountered in two patients of both groups (2.9% for BD and 4.2% for RD). Partial thickness tear of the posterior (membranous) tracheal wall occurred, once, in both groups, and was treated conservatively. Mucosal bleeding obscuring the airways necessitated emergent tracheostomy occurred during BD for a grade 3 subglottic stenosis in a 21-year-old woman with aggressive granulomatosis with polyangiitis. Decanulation was achieved after 14 days of high dose steroid therapy.

In the RD group, immediate postoperative respiratory failure and desaturation that necessitated re-intubation occurred in one patient who was successfully extubated after 48 hours.

DISCUSSION

Reconstructive techniques of LTS can be divided into two modalities: endoscopic and open-field surgery. The preferred technique is determined by the general condition of the patient, the etiology of the stenosis and its features (site and length), and the experience of the surgeon [10].The main cause for LTS in this study, like in previous reports [1,5-7], was endotracheal intubation and tracheostomy. The estimated incidence of symptomatic post-intubation and post-tracheotomy tracheal stenosis in the general population is 4.9 per million per year [12,13].

Of the BD cohort 62% were female, of whom 22% were considered to have idiopathic LTS. Essentially, all idiopathic LTS patients were women in their second to fifth decade of life, which correlates with previous literature [14,15].

We found that a dilatation procedure performed either with rigid instrumentation or with a balloon catheter will achieve a mean remission of over 20 weeks with a rather wide range of duration of approximately 1–190 weeks in both groups. A mean remission length of approximately 20 weeks was noted also for advanced (grade 3) stenosis in both groups. Also, the rates of prolonged remission were not affected by the site of stenosis, except for treatment of subglottic lesions treated by BD that achieved higher rates of long-term remissions. Treatment of mid-tracheal stenosis achieved lower rates of prolonged remission (20% for BD and 14% for RD) but this did not reach statistical significant, perhaps due to a relatively small number of cases with mid-tracheal stenosis. Therefore, factors other than location and severity of the stenosis may affect the success rate of endoscopic dilatation. These factors may be related to the scar form (i.e., circumferential versus band like), scar consistency, cartilage support, and patient co-morbidities [16]. The latter states that the parameters for selection of the proper modality have not been clarified yet.

BD achieved higher rates of prolonged remission compared to RD (71% vs. 31.2%, $P < 0.05$). It may be assumed that while dilatation by rigid instrumentation mainly causes tearing of scar tissue, dilatation with a balloon causes both tearing and pressure ischemia of the peripheral tissue and lower the rates of re-stenosis. Another possible explanation is that during balloon dilatation a more uniform pressure is applied on the tissue, which causes less deep tissue damage and tearing. This difference in method of operation may explain the higher success rates of BD in treatment of LTS found in our study.

The fact that the two study groups were disparate in their distribution of gender and etiology of stenosis (more females and inflammatory/idiopathic etiology in the BD group) may challenge the results of this study. There is also a case selection bias in our choice of treatment method. To address these limitations, the possible confounders were analyzed independently and collectively. Age, gender, and inflammatory/idiopathic etiology did not correlate with remission length ($P = 0.4$, 0.2, and 0.37, respectively). Also, the prolonged remission rates in idiopathic/inflammatory etiology versus previous endotracheal intubation did not differ significantly (81% vs. 64%, $P = 0.2$). This finding emphasizes that although BD and RD groups vary in gender and etiology of stenosis, the improved results achieved by BD were not influenced by theses possible confounding factors.

Our cohort consisted of patients who underwent dilatation of benign LTS for three intentions: curative, bridging as an alternative for tracheostomy, and touching up post-CTR. The remission intervals were similar for all indications of BD. However, in the RD group, dilatation as a revision post-CTR showed higher rates of prolonged remission. This result could be related to a very short, band-like fibrotic scar that involved the anastomosis line. When patients show re-stenosis at the anastomosis site following CTR, endoscopic dilatation could be a useful adjunct treatment that will optimize the final result.

The idea of bridging dilatation as an alternative for a tracheostomy in patients intended for open neck surgery was found highly effective. Major interventions may not be conducted temporarily due to patient medical status. When open surgery (i.e., CTR) is intended as the definite procedure, avoidance of tracheostomy is preferable as it was shown to increase the success rate [4]. In our cohort, bridging procedures (3 BD and 10 RD) enabled us to postpone the definite intervention for 1–26 weeks (mean 14.9) and none ended up with a stoma.

Previous reports described tracheal wall laceration as the most common complication of BD, with rates of up to 50% of procedures [17]. It is reasonable to assume some degree of tissue laceration in all mechanical dilatations and one must question whether to consider uneventful scar laceration as a complication at all. We also described BD that ended up with a short-term tracheostomy. However, this result was an unusual severe subglottic stenosis in a young woman with aggressive granulomatosis with polyangiitis (Wegener's granulomatosis) who was rushed to the operating room with severe dyspnea. Profuse mucosal bleeding obstructing the narrowed subglottic

space started on touching the mucosa with the balloon catheter leading to loss of airways and effective ventilation. The involvement of the subglottic mucosa in Wegener's granulomatosis has already been described [18]; however, emergent tracheostomy is rarely encountered.

Only few reports described the use of balloon dilatation for benign laryngotracheal lesions in adults, and currently no guidelines or universally accepted methods of comparing pre- and postoperative parameters exist. In our study we defined improvement based on patient symptoms and subjective evaluation of endoscopic findings. Objective measures are still the main limitation of the evaluating the success of airway dilatation.

CONCLUSIONS

Balloon dilatation and rigid dilatation were found to be effective and safe modalities for the treatment of benign laryngotracheal stenosis. Both procedures can be performed as primary treatment, as revision post-open surgery, and as an alternative for a tracheostomy (bridging procedure) until the intended open surgery can be conducted. Overall, BD achieved slightly better long-term results compared to RD.

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Capsule

A large-scale screen to target SARS-CoV-2

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome is initially expressed as two large polyproteins. Its main protease, Mpro, is essential to yield functional viral proteins, making it a key drug target. **Günther** and colleagues used X-ray crystallography to screen more than 5000 compounds that are either approved drugs or drugs in clinical trials. The screen identified 37 compounds that bind to Mpro. High-resolution structures showed that most compounds bind at the active site but also revealed two allosteric sites where binding of a drug causes conformational changes that affect the active site. In cell-based assays, seven compounds had antiviral activity without toxicity. The most potent, calpeptin, binds covalently in the active site, whereas the second most potent, pelitinib, binds at an allosteric site.

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