

A Systematic Review and Meta-analysis of Endoscopic Balloon Dilatation of Pediatric Subglottic Stenosis

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Abstract

Objective. Endoscopic balloon dilatation (EBD) is an inviting, noninvasive option to manage pediatric subglottic stenosis that could preclude the need for tracheostomy and/or laryngeal-tracheal reconstruction (LTR). However, treatment outcomes and patient selection criteria are not well described.

Data Sources. MEDLINE, EMBASE, and the Cochrane databases were systematically searched using multiple search terms.

Review Methods. A systematic review of pediatric EBD was performed and then reported in compliance with PRISMA principles. Inclusion criteria consisted of a sample size of 5 or greater, pediatric patients, and primary EBD without adjuvant procedures. Meta-analysis was performed with random effects modeling and pooled data regression.

Results. After systematic database search and detailed review, 7 studies were included in the final data set with 150 total subjects. All studies were case series (level 4 evidence). The mean sample size was 20 subjects (range, 5–44), and the grand mean age was 2.2 years (range, 2.2–60 months). The random effects model estimate of the overall treatment success (avoidance of tracheostomy or LTR) was 65.3% ($k = 6$ studies, 95% confidence interval [CI] = 60.1%–70.6%, $P < .001$, Q test for heterogeneity = 3.98, $P = .552$, $I^2 = 0\%$). Follow-up was inconsistently reported but averaged 4.6 months (range, 0.25–12.5 months). Only 1 study reported significant complications (1 death, 2 tracheal lacerations). Pooled data multivariate regression indicated that increasing Cotton-Meyers grade was associated with decreased odds of success (odds ratio = 0.198, 95% CI = 0.0451–0.870, $P = .032$). Funnel plot analysis suggested the possibility of publication bias.

Conclusions. EBD is successful in most patients over short-term follow-up. The reported complication rates are low. Increasing severity of subglottic stenosis increases the odds of treatment failure.

Keywords

subglottic stenosis, balloon dilatation, systematic review meta-analysis

Pediatric subglottic stenosis (SGS) often presents unexpectedly and requires urgent treatment. In many cases, invasive surgical procedures such as tracheostomy and/or laryngotracheal reconstruction (LTR) must be undertaken to stabilize the problem and ultimately correct it. A simple, effective, and noninvasive therapy for pediatric SGS would be of great benefit to many infants and children. Endoscopic balloon dilatation (EBD) of pediatric SGS has the potential to provide just such a simple and noninvasive treatment that could effectively manage many cases of pediatric SGS. However, despite an increasing number of reports of its use, the outcomes of pediatric EBD, determination of which patients are best suited for the procedure, and its limitations and complications are not well known. The primary aim of this study was to systematically identify all relevant published data regarding the use of primary EBD alone for the management of pediatric SGS, critically evaluate the success of the technique, clarify which patients are the best candidates for the procedure, and estimate the complication rate for the procedure (to include the need for a repeat dilatation procedure). The secondary aim was to attempt to specifically identify factors, including age and severity of SGS, that influenced treatment success.

Methods

Systematic reviews of published data are exempt from Institutional Research Committee review at our institution. The MEDLINE, EMBASE, and Cochrane databases were systematically searched in January 2013 using multiple search terms with the aid of a biomedical librarian. The PUBMED search strategy included “(laryngostenos* OR subglottic stenosis* OR laryngeal stenosis* OR tracheal

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Table 1. Evidence table.

Authors and Year	N	Mean Age, mo	Treatment Success	Mean No. of Dilations	Dilation Technique
Hebra et al, ² 1991	37	60	20 of 37 (54%)	4.27	Pressure not reported, duration until desaturation; unknown number of patients had electrocautery of granulation tissue or stent placement for 72 h
Durden and Sobol, ³ 2007	10	4.8	7 of 10 (70%)	1.3	Two atmospheres, duration until desaturation, topical steroids, intubation for 24-48 h
Bent et al, ⁴ 2010	10	24.5	7 of 10 (70%)		10-12 cm H ₂ O for average of 40 s, injected and topical steroids used after dilation
Primary EBD	4	17.8	4 of 4 (100%)	1.75	"
Secondary EBD	6	34.5	3 of 6 (50%)	2.17	"
Schweiger et al, ⁵ 2011	8	5.2	6 of 8 (75%)	1	Two atmospheres for 2 min or until desaturation; no topical steroids or mitomycin C
Whigham et al, ⁶ 2012	28	42	16 of 28 (57%)		Two dilations per procedure, 8-16 atmospheres for 2 min or until desaturation; no topical steroids or mitomycin C
Primary EBD	15	30	9 of 15 (60%)	1.5	"
Secondary EBD	13	60	7 of 13 (54%)	2.15	"
Hautefort et al, ⁷ 2012	44	26	31 of 44 (70%)		Pressure not reported, duration for 30 s or until desaturation, 1-3 dilations per procedure, mitomycin C (1 mg/mL) applied for 2 min
Primary EBD	31	26	20 of 31 (64%)	2	"
Secondary EBD	21	27	17 of 21 (81%)	1.8	"
Collins et al, ⁸ 2012	5	2.2	4 of 5 (80%)	2.2	Four atmospheres, duration until desaturation, no topical steroids or mitomycin C use reported

Abbreviation: EBD, endoscopic balloon dilation.

stenos*) AND (laryngoplast* OR (glottis/surgery AND larynx/surgery) OR (laryngeal AND reconstruct*) OR laryngo-tracheoplast* OR laryngo-tracheoplast* OR tracheoplast* OR dilation* OR dilatation*) AND balloon” with limits set for pediatric patients 0 to 18 years of age. Inclusion criteria consisted of (1) sample size of 5 or greater, (2) use of EBD for pediatric patients (0-18 years), and (3) use of EBD as the primary treatment of pediatric SGS to avoid more definitive airway management to include tracheostomy and/or LTR.

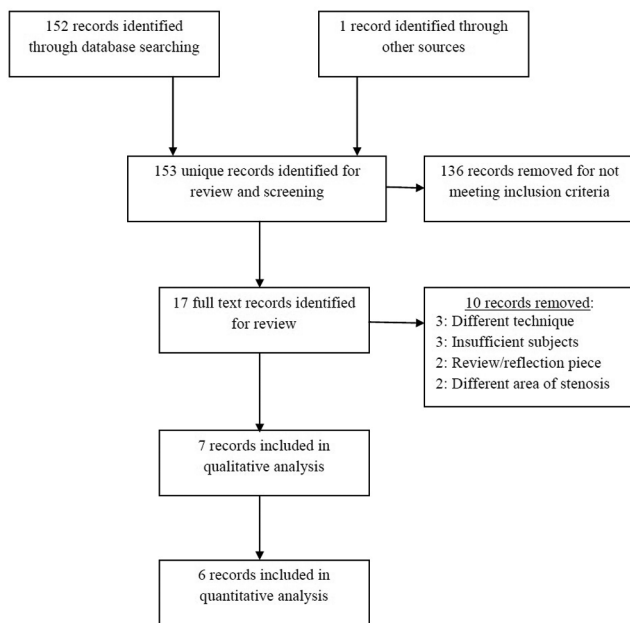
The results of the selected studies that met the inclusion criteria were summated in an evidence table. The Preferred Reporting of Meta-Analysis and Systematic Reviews (PRISMA) (www.prisma-statement.org) principles for study reporting and presentation were followed as much as applicable. The results were analyzed with a primary outcome measure of EBD treatment success (%) in avoidance of more invasive procedures. Some of the studies reported outcomes for both the use of EBD as the primary (only) treatment of SGS and the use of EBD as a salvage treatment after LTR or tracheotomy. These data were separated and analyzed independently. Secondary outcome measures of need for revision EBD and complications were also recorded. Effect modification by age and the severity of

SGS as measured by the Cotton-Myers grade (I-IV)¹ was also assessed. The data were extracted by 2 reviewers independently, with a third reviewer used to settle any discrepancies if needed. Extracted data included sample size, mean age of subjects, severity of SGS (Cotton-Meyers stage), treatment success, number of dilations performed, follow-up time, details of the dilation procedure used, and complications (see **Table 1**). Treatment success was defined as the use of EBD in the avoidance of a more invasive procedure to include tracheostomy and/or LTR. Meta-analysis was performed if the studies were judged to be sufficiently similar to produce meaningful results. Quality assessment and analysis of the individual studies were performed and are shown in **Table 2**.

Statistical analysis was performed with statistical software (STATA 8.2, College Station, TX). Random effects modeling (standard error estimate = inverse of the sample size) was used to calculate summary effect measures with corresponding 95% confidence intervals, and Forest plots were generated. The I² statistic was used to assess between-study heterogeneity. In some cases, the between-study heterogeneity was not significant, and therefore the random effect modeling estimate equaled the fixed effects estimate. Data were pooled to perform logistic regression to assess

Table 2. Study quality assessment.

Study	Method of Data Collection	Sampling Method	Length of Follow-up	Data Reporting	Overall
Hebra et al, ² 1991	Retrospective (–)	Complete (+)	<6 mo (–)	Incomplete (–)	+
Durden and Sobol, ³ 2007	Retrospective (–)	Complete (+)	<6 mo (–)	Complete (+)	++
Bent et al, ⁴ 2010	Retrospective (–)	Complete (+)	>6 mo (+)	Complete (+)	+++
Schweiger et al, ⁵ 2011	Prospective (+)	Complete (+)	<6 mo (–)	Complete (+)	+++
Whigham et al, ⁶ 2012	Retrospective (–)	Complete (+)	<6 mo (–)	Complete (+)	++
Hautefort et al, ⁷ 2012	Retrospective (–)	Complete (+)	<6 mo (–)	Incomplete (–)	+
Collins et al, ⁸ 2012	Retrospective (–)	Incomplete (–)	<6 mo (–)	Complete (+)	+

**Figure 1.** Literature search flowchart (PRISMA format).

the effects of age, number of dilations, and Cotton-Meyers grade on the primary outcome measure of treatment success. Possible publication bias was assessed using graphical funnel plot analysis. Duval and Tweedie “trim and fill” methods were then used to estimate the effects of possible publication bias.⁹ A *P* value of less than .05 was considered significant. A *P* value between .05 and .10 was considered borderline and was considered for hypothesis generation only.

Results

The results of the literature search are shown in **Figure 1**. One hundred fifty-two studies were identified in the initial search. After review and application of the inclusion and exclusion criteria, the final study group included 7 studies²⁻⁸ (see **Table 1**). All 7 studies were of case series design (level 4 evidence). Study quality was formally assessed in terms of the method of data collection (prospective versus retrospective), sampling method (complete sample versus convenience sample), length of follow-up (more or less than

6 months), and data reporting (complete reporting for each patient versus compiled reporting only; see **Table 2**). All but one² of the studies were published within the past 5 years. This older study was included even though it did not completely meet the inclusion criteria as it included the use of concurrent procedures (electrocautery of granulation tissue [*n* = 2] and/or short-term-stenting [*n* = 3] in a small number of subjects [5 of 37 = 13.5% of patients]). It was ultimately decided to include this study as it was the only study that reported complications with EBD, which was a key objective of this systematic review. Treatment success data were not included from this study to prevent bias of the results. One hundred fifty total subjects were included. The mean sample size of the included studies was 20 subjects (range, 5-44). The grand mean age was 23.5 months (range, 2.2-60 months). Six of 7 studies reported a duration of follow-up after EBD. The mean reported follow-up time was 7.0 months (range, 2-14.4 months). The grand mean number of reported dilation procedures per patient was 1.9 (range, 1-4.3). Only 1 study² reported complications, which included atelectasis (3 patients), tracheitis (2 patients), pneumomediastinum (asymptomatic, 1 patient), tracheal laceration (2 patients), and death (1 patient, from tracheal laceration). No other study reported significant complications. Three of the studies^{4,6,7} provided data on patients who underwent EBD both as the primary (initial and only) therapy and as a secondary (following tracheotomy or LTR) therapy. These data were analyzed separately.

The studies included were diverse but also had many similarities. Differences among the studies included the use of topical steroids or mitomycin C immediately after dilation, the use of transient postoperative intubation after EBD, and the specifics of the balloon pressure used. Similarities included the general technique of the procedure, which was performed endoscopically under general anesthesia while spontaneously breathing; the duration of dilation; the use of perioperative intravenous steroids; the use postoperative proton pump inhibitor therapy; and the definition of treatment success. Considering these factors, it was judged that there were sufficient similarities such that a quantitative meta-analysis would produce meaningful results. Random effects modeling was used to produce a summary estimate of the treatment success of using primary EBD. Success

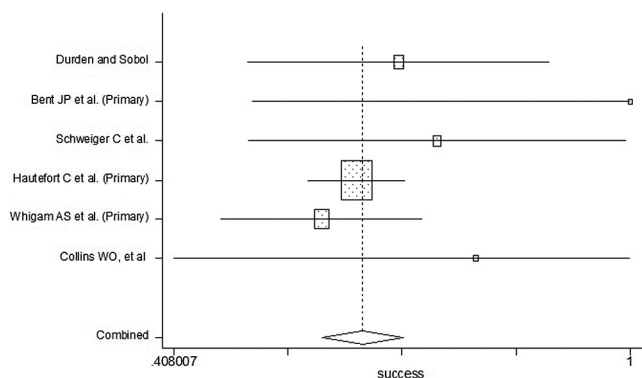


Figure 2. Forest plot of the treatment success of using endoscopic balloon dilation as the primary therapy for pediatric subglottic stenosis. The summary estimate is 65.3% (k = 6 studies, 95% CI = 60.1%-70.6%, $P < .001$, Q test for heterogeneity = 3.98, $P = .552$, $I^2 = 0\%$).

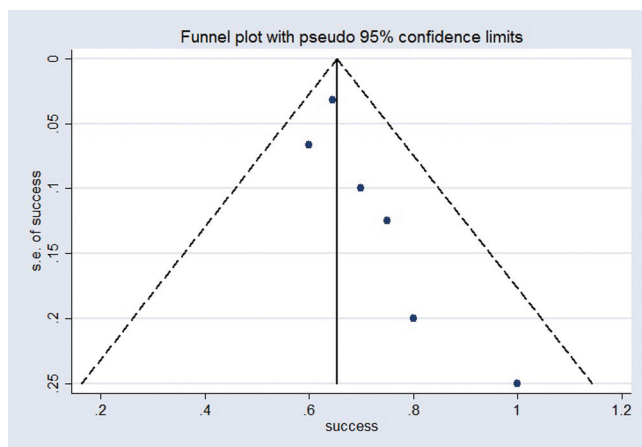


Figure 3. Funnel plot of endoscopic balloon dilation (EBD) treatment success. The sparsely filled left side of the funnel suggests a possibility of publication bias, with a lack of published studies reporting lower success rates for EBD.

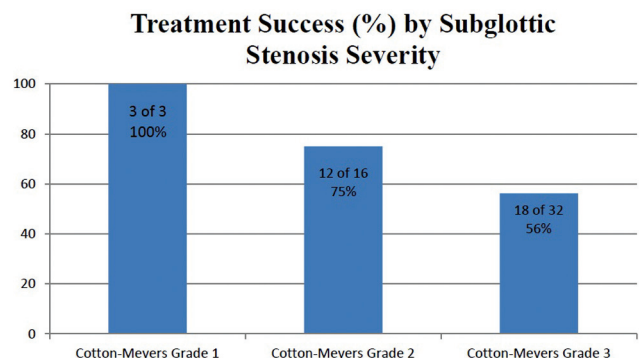


Figure 4. Success rate of primary endoscopic balloon dilation based on the initial Cotton Myers stage. Multivariate logistic regression resulted in a significant odds ratio (OR) for treatment failure with increasing Cotton-Meyers stage (OR = 5.048, 95% confidence interval = 1.149-22.18, $P = .032$).

was defined as avoidance of tracheostomy and/or LTR. The summary estimate of primary treatment success with EBD of pediatric SGS was 65.3% (k = 6 studies, 95% confidence interval [CI] = 60.1%-70.6%, $P < .001$, Q test for heterogeneity = 3.98, $P = .552$, $I^2 = 0\%$). The Forest plot is shown in **Figure 2**. For studies that included use of EBD as a secondary therapy following either tracheotomy or LTR, the summary estimate of the treatment success (decannulation) rate was very similar at 61.2% (k = 3 studies, 95% CI = 44.5%-78.0%, $P < .001$, Q test for heterogeneity = 25.2, $P < .001$, $I^2 = 88\%$). However, there was significantly more heterogeneity ($I^2 = 88\%$) in these secondary EBD data, and they should therefore be interpreted with full recognition of this limitation. The mean number of dilation procedures for secondary therapy (2.1 dilation procedures per patient) was higher than for primary patients (1.6), but this difference was of only borderline significance ($P = .08$, 2-tailed t test).

Publication bias was assessed with graphical funnel plot analysis (**Figure 3**). Visual inspection of the funnel plot suggests that there is a possibility of publication bias, with an absence of studies reporting lower success rates of EBD. Using the Duval and Tweedie nonparametric “trim and fill” method of accounting for publication bias, the “filled” summary estimate of primary EBD treatment success was 64.2% (3 studies “filled,” 95% CI = 59.1%-69.2%), suggesting the statistical effects of publication bias on the analysis would be expected to be negligible to the overall conclusion reached from the data analysis.

Pooled analysis with logistic regression was performed as a secondary analysis to assess the effects of clinical predictors on primary EBD treatment success. Three studies^{3,4,9} presented data in sufficient detail to allow a pooled analysis for a total of 51 patients. Pooled univariate logistic regression did not show that increasing age quartile (odds ratio [OR] = 0.957, 95% CI = 0.565-1.62, $P = .870$) or performing more dilation procedures (OR = 1.33, 95% CI = 0.398-4.47, $P = .641$) was associated with increased odds of treatment success. However, on univariate analysis, increasing SGS severity as quantified by the Cotton-Meyers grade was borderline associated with decreased odds of treatment success (OR = 0.295, 95% CI = 0.869-1.003, $P = .051$), or perhaps stating this more intuitively, increasing Cotton-Meyers stage was borderline associated with increased odds of treatment failure (OR = 3.387, 95% CI = 0.997-11.51, $P = .051$). Graphical evaluation of the trends of the pooled raw data did suggest that a lower Cotton-Myers stage had a higher treatment success rate (**Figure 4**). Multivariate logistic regression showed that increasing age quartile (OR = 0.691, 95% CI = 0.358-1.334, $P = .271$) and increasing number of dilations (OR = 1.160, 95% CI = 0.738-1.823, $P = .519$) were again not associated with increased odds of treatment success. However, in this multivariate analysis, increasing Cotton-Meyers grade was associated with decreased odds of treatment success (OR = 0.198, 95% CI = 0.0451-0.870, $P = .032$), or conversely stated, increasing Cotton-Meyers grade was associated with increased odds of

treatment failure (OR = 5.048, 95% CI = 1.149-22.18, $P = .032$).

Discussion

This study critically evaluates the published literature reporting on the success of EBD in the treatment of pediatric SGS. EBD as a primary treatment to prevent the need for tracheostomy and/or LTR was successful in approximately two-thirds of patients over short-term follow-up averaging approximately 7 months and a mean number of dilation procedures of approximately 1.6 per patient. The use of EBD as a secondary treatment after tracheostomy and/or LTR was also reported to be successful in approximately two-thirds of patients with a mean number of dilations of 2.1 per patient. Complications were rarely reported but were potentially severe, including 1 death due to tracheal laceration. Subgroup analysis suggested that increasing severity of SGS was associated with increasing odds of treatment failure. Age and number of dilation treatments were not found to be predictive of treatment outcomes.

EBD is a highly attractive technique because of its simplicity and noninvasiveness. The technique is clearly gaining popularity based on the observation that almost all of the included studies were published recently. This study confirms that EBD is successful in most patients, with a very low reported complication rate. Yet this inviting, relatively new technique should be approached with some judicious caution. Because most studies were published very recently, the available data regarding longer-term treatment outcomes are lacking. Only one study⁸ reported a mean follow-up of more than 1 year. Treatment failure in the form of recurrent acute airway obstruction would be expected to be a short-term complication. The short-term follow-up reported by most of the included studies would be likely to capture this occurrence. Therefore, the otolaryngologist performing EBD can feel confident that acute airway obstruction is unlikely to be a long-term complication of EBD. Still, the long-term effects of EBD to include the effect on tracheal growth in neonates undergoing EBD are largely unknown. Elucidating the histologic effects of EBD and its long-term effects on neonates should be a focused research priority before it is formally accepted as the first-line management approach for younger patients.

The observation that the mean number of dilation procedures per patient was nearly 2 is an important finding that should be considered carefully before undertaking EBD as a primary treatment option. This indicates that many patients underwent the procedure more than once, likely because of recurrent airway obstruction. Consequently, otolaryngologists who intend to include EBD as a therapy for their treatment of pediatric SGS will need to consider how to manage the reality that many patients could fail the initial attempt and will require in some cases urgent repeat EBD. Acknowledgment of this fact at a minimum will require the otolaryngologist to perform careful preoperative counseling with parents, contemplate how one's facility will optimally manage these patients if they present with acute airway

obstruction, and ensure that appropriate size balloons and all necessary equipment are available in the operating room at all times for use. Most authors in the included studies indicated they brought all EBD patients back for routine surveillance laryngoscopy and bronchoscopy and redilation if the stenosis was beginning to return. This approach is certainly ideal for the collection of scientific treatment outcomes data. However, this would also mean that a performance of a second EBD procedure does not necessarily constitute a complication or clear evidence that the initial EBD treatment would have failed. But it does indicate that close follow-up with the ability to perform a repeat minimally invasive EBD is recommended and would be the preferred approach to manage all EBD patients safely. Otolaryngologists who are planning to use EBD as a primary therapy for SGS should consider it a choice for a systematic approach to manage patients with requisite follow-up and monitoring rather than just use of an isolated, noninvasive procedure. Further research into which factors are most predictive of the need for a repeat procedure (eg, stenosis severity, the thickness of the stenosis, etc) and consequently which patients require the closest follow-up is needed.

There are several important limitations to consider in the interpretation of the results of this study. As with any meta-analysis or systematic review, this study is limited by the heterogeneity of the data. Statistically, there was little heterogeneity. However, as the evidence table (**Table 1**) clearly shows, there were several methodological differences between the studies with regard to how EBD was performed. Reported success rates within the studies varied substantially, although they were reported to be greater than 50% in all of the included studies. Thus, it appears that treatment success can be obtained using many techniques, and it remains unclear which method in terms of dilation pressure, duration of dilation, use of topical steroids, and so forth is the superior method. Further research in this area will be required to ascertain the best method of EBD. An additional weakness is that all of the included studies were case series. Case series do not contain a control group and can hence be prone to selection bias and confounding. This certainly is a limitation of the current published evidence supporting EBD. Nonetheless, EBD is unquestionably simpler and less invasive than the alternative treatments of tracheostomy and LTR, to which it might be compared in a controlled study. As a result, any measurable success of EBD can still be considered important and useful. Last, funnel plot analysis indicated the possibility of publication bias. Specifically, there were no published studies that reported a low success rate with EBD. Combining this with the observation in this systematic review that only 1 study reported severe complications with EBD raises reasonable concern that there is a possibility that the negative effects of EBD have not yet been reported. This is a legitimate concern that will need to be addressed in future, larger, longer-term studies of EBD and is a vital concern of which the otolaryngologist using EBD should be aware.

Conclusion

The use of EBD as a primary treatment of pediatric SGS is successful in most patients with short-term follow-up. Reported complications are rare but can be severe and life threatening. Increasing severity of SGS may be associated with increasing odds of treatment failure. Age does not appear to be predictive of treatment outcomes.

Disclaimer

Michael Lang, study conception and design, acquisition of data, analysis and interpretation of data, revising of manuscript, final approval; **Scott E. Brietzke**, study conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, final approval.

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