

BMJ Open Dilation versus laser resection in subglottic stenosis: protocol for a prospective international multicentre randomised controlled trial (AERATE trial)

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ABSTRACT

Introduction Subglottic stenosis (SGS) is a rare condition that results from progressive narrowing of the upper airways. Outcomes and treatment options depend on the benign or complex nature of the stenosis. Treatment options for SGS include surgery and endoscopic techniques. The main endoscopic techniques used are dilation and laser resection. Observational and retrospective studies suggest that endoscopic laser resection may be more effective than dilation. We, therefore, aimed to compare the effectiveness of dilation and laser resection in preventing recurrence of SGS. **Methods and analysis** AERATE (dilation vs laser Endoscopic Resection in subglottic tracheal stenosis) is a multicentre, investigator-initiated, randomised controlled trial, comparing endoscopic dilation to endoscopic laser resection for simple benign SGS (less than 1 cm long without underlying cartilaginous damage) referred for endoscopic treatment (first treatment or recurrence). The study will be conducted in three centres in France and one in Canada with other centres from France and Canada expected to join. The primary outcome is the recurrence rate of stenosis at 2 years. Recurrence is defined as having a new onset of symptoms along with a stenosis of more than 40% (confirmed by bronchoscopy) requiring a new procedure. A sample size of 100 patients is calculated for the primary endpoint assuming a 10% recurrence rate in the laser resection group and 33% in the dilation group with a statistical significance level of 5%, a power of 80%. **Ethics and dissemination** This study is approved by local and national ethics committees as required. Results will be published, and trial data will be made available. **Trial registration number** NCT04719845.

INTRODUCTION

Background and rationale

Simple benign subglottic stenosis (SGS) is a rare condition that results from progressive inflammatory narrowing of the upper airways. Its pathophysiology remains unclear.¹ Gradually worsening dyspnoea is the hallmark symptom along with stridor in severe SGS.

Strengths and limitations of this study

- This is the first randomised controlled trial comparing endoscopic procedures in subglottic stenosis (SGS) and is in fact the first randomised controlled trial in the field of SGS to our knowledge.
- The primary endpoint is symptomatic endoscopically confirmed recurrence rate at 2 years which is an objective clinical endpoint. This outcome will allow us to provide a definitive answer to an important clinical question: 'What is the most effective endoscopic technique to treat SGS?'
- Adequate statistical power, however, relies on sufficient recruitment which can be a challenge in rare disease.

Treatment options include endoscopic procedures and open surgery with resection of the affected tracheal segment and end-to-end anastomosis.^{2–4} Although open surgery is an effective therapeutic option with a recurrence rate of less than 10%,^{3–5} it is associated with a 10%–30% morbidity, mainly including dysphagia, dysphonia and anastomosis dehiscence.^{6,7} In addition, it is important to consider that results of open surgery come from few centres of great expertise.^{4,8}

Results of endoscopic procedures are variable with reported success rates ranging from 40% to 90%.^{2,4,9,10} Despite their lower success rates than open surgery, endoscopic techniques are generally preferred as first-line therapy, as patients with a recurrence can still be referred for surgery and patients without recurrence will avoid the morbidity associated with surgery.^{2,4,9,10} The main therapeutic endoscopic procedures include dilation and laser resection.¹ Although dilation is the most commonly used technique, observational studies have suggested that endoscopic laser

Table 1 Outcomes**Primary outcome**

Recurrence rate of subglottic stenosis at 2 years. Recurrence is defined as having a new onset of symptoms along with SGS of more than 40% (confirmed by bronchoscopy) requiring a new procedure.

Secondary outcomes

Time to first recurrence of SGS.

Recurrence rate of SGS at 1 year.

Impact on dyspnoea (mMRC, Visual Analogue Scale, Clinical COPD Questionnaire), dysphonia (VHI-10) and quality of life (SF-12).

Measurement of stenosis by cephalo-caudal length at endoscopic follow-up at 1 and 2 year.

Rate of surgical resection following symptomatic recurrence.

Total no of recurrences over 2 years.

Rate and type of complications and adverse effects.

Depth, length and density of fibrotic reaction in the surgical resection specimen in patients undergoing surgical resection.

COPD, chronic obstructive pulmonary disease; mMRC, modified medical research council; SF-12, Short Form Survey-12; SGS, subglottic stenosis; VHI, Voice Handicap Index.

resection may be more effective in preventing recurrence of SGS.⁴ However, current knowledge on endoscopic procedures is mainly based on observational and retrospective studies in which techniques used vary considerably.^{2 9 11}

Due to the heterogeneity of endoscopic approaches, we propose to conduct the AERATE trial (dilAtion vs laser Endoscopic Resection in subglottic trAcheal sTENosis) comparing dilation and endoscopic laser resection for simple benign SGS.

We hypothesise that the success rate of endoscopic laser resection differs from dilation in preventing recurrence of SGS.

Objective

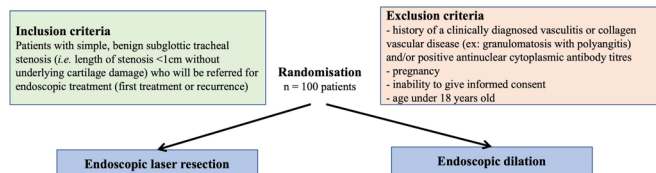
The overall objective of this study is to compare the efficacy of endoscopic laser resection and dilation in the treatment of SGS. The primary endpoint is the recurrence rate of symptomatic SGS at 2 years. Several secondary endpoints (see below) will also be evaluated (table 1).

Trial design

AERATE is a prospective, multicentre, investigator-initiated study. It is a randomised, controlled, single-blinded, 1:1 parallel-group trial.

METHODS AND ANALYSIS**Study setting**

The study will be conducted in three university-affiliated hospitals in France (Toulouse, Grenoble and Marseille) and one in Canada (Québec) with other centres from France and Canada expected to join. All are academic centres that are tertiary referral centres for SGS and thus

**Figure 1** Summary inclusion/exclusion criteria and study design.

have significant experience treating this rare condition. Nearly all patients with SGS are ultimately referred for care and cluster at such high-volume centres allowing us to anticipate enrolling a representative patient cohort. Each research site has appropriate infrastructure for study setting.

Eligibility criteria

We will include patients with simple (ie, length of stenosis <1 cm without underlying cartilage damage)¹² benign SGS referred for endoscopic treatment (first treatment or recurrence) after evaluation by an interventional bronchoscopist (figure 1). Exclusion criteria include history of a clinically diagnosed vasculitis (eg, granulomatosis with polyangiitis), pregnancy, inability to give informed consent and age under 18 years old (figure 1).

Assignment of interventions

Once consented and enrolled, participants will be randomised (1:1) to receive dilation or laser resection utilising a clinical electronic data capture (EDC) software (REDCap). The randomisation will be stratified on the type of stenosis (first treatment vs recurrence, idiopathic vs other type) and the centre. Stratification, which normalises the impact of type of SGS on patient outcomes, has no impact on the statistical power of the trial. The patient will be blinded to the type of endoscopic treatment received.

Interventions

Each patient will perform spirometry and complete questionnaires before performing the endoscopic procedure. Details of these examinations and questionnaires are available in the data collection section. The inclusion visit and the endoscopic procedure can be carried out on the same day.

The endoscopic procedure will be performed under general anaesthesia by an interventional bronchoscopist. Performance of procedures will be limited to two bronchoscopists per centre with experience in both procedures. Additional anaesthesia of the respiratory tract may be performed by local instillation of lidocaine. Ventilation during the procedure will be carried out by a laryngeal mask or a rigid bronchoscope.

In the endoscopic laser resection arm, a CO₂ or diode (IntermedicTM, Surgical 120, Barcelona, Spain) or similar wavelength laser will be used. The diode laser has an operational wavelength of 808 nm. This laser resection technique is already used and described in SGS.^{4 13–16} Its

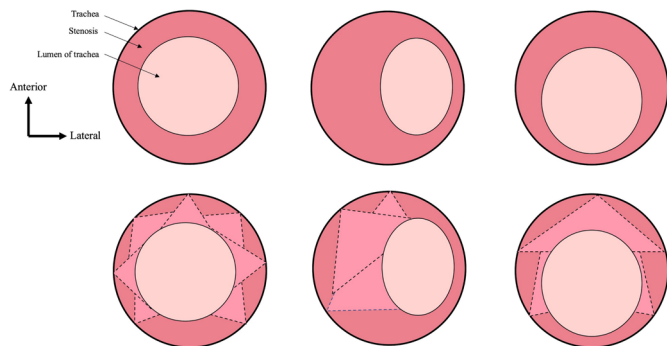


Figure 2 Proposed technique for laser resection. Triangular portions of the stenosis will be delimited by laser vaporisation and subsequently resected mechanically or vaporised. Multiple triangles with their tip at the depth of the underlying normal tracheal mucosa will allow us to obtain a residual stenosis of less than 20% while minimising thermal trauma to underlying tissues. No triangle will have its tip on the posterior membrane of the trachea and laser will not be applied circumferentially.

tissue absorption is higher than the Nd: YAG laser, the coagulation effect is similar to that of the argon laser, and the tissue vaporisation is similar to that of the CO₂ laser.^{13 16} Power outputs starting from five watts and up to 40 watts with pulses of 200 to 400 milliseconds and pauses of 200 milliseconds will be used to obtain the desired effect on the stenosis. Triangular portions of the stenosis will be delimited by laser vaporisation and subsequently resected mechanically or vaporised. Multiple triangles with their tip at the depth of the underlying normal tracheal mucosa will allow us to obtain a residual stenosis of less than 20% while minimising thermal trauma to underlying tissues (figure 2). No triangle will have its tip on the posterior membrane of the trachea and laser will not be applied circumferentially. If a residual stenosis of less than 20% cannot be obtained, rescue dilatation is allowed but will be reported.

In the dilation arm, a pulmonary dilation balloon (Merit MedicalTM, Elation, Jordan, United States or Boston ScientificTM, CRE, Natick, USA or other similar product) will be inserted in a flexible or rigid bronchoscope and gradually inflated to a diameter corresponding to the diameter of the patient's non-stenotic trachea.^{4 17} The balloon will be held at the target diameter for at least 10 s. The dilation can be repeated up to three times to obtain the desired result. The operator may also alternatively proceed with sequential dilation using a rigid tracheoscope or bronchoscope up to the diameter of the patient's non-stenotic trachea. One radial mechanical incision can be made before dilating the stenosis with an endoscopic scissor or similar mechanical device. The choice of technique will be left to the discretion of the operator and will be reported.

Patients in both groups will receive 4 mg of intravenous dexamethasone during the procedure and 2 mg twice daily for 48 hours after the procedure. No patient will have endoscopic drug therapy during the procedure

(ie, intralesional corticosteroids, mitomycin or others) or have an endobronchial stent placed.

Proton pump inhibitor (PPI) has shown a potentially protective effect against the recurrence of SGS and is generally very well tolerated.^{4 10} The main rationale for PPI treatment is based on data supporting a high prevalence of gastro-oesophageal reflux disease (GERD) in patients with SGS and the possible impact of GERD on recurrence.^{18 19} PPI has however, be mainly reported in combination to laser resection. In studies comparing laser resection in combination to PPI to dilation alone, PPI might be a confusing factor in the evaluation of endoscopic treatment effect (ie, laser resection vs dilation).⁴ In order to evaluate the effect of the endoscopic technique, we therefore decide to standardise the postoperative intervention in the current study. All patients included in the study will be prescribed PPI at the time of the screening visit and those already taking this medication will continue it. All patients will continue PPI at least until the first recurrence of the SGS or until 2 years if there is no recurrence. Continuation beyond this period will be at the discretion of the treating team. In the presence of side effects attributed by the attending physician to this medication, it may be stopped and its discontinuation must be reported.

No other medication (long-term trimethoprim-sulfamethoxazole, oral corticosteroids) aimed at preventing restenosis will allowed in the current study. If such medication is started for another condition, this would be reported.

Outcomes

The primary outcome is the recurrence rate of SGS at 2 years. We defined recurrence as having a new onset of symptoms along with SGS of more than 40% (confirmed by bronchoscopy) requiring a new procedure. Endoscopies will be recorded and sent for central blinded review to confirm the degree of stenosis.

Subgroup analyses will be performed for the primary outcome by stenosis aetiology (idiopathic vs other), number of previous endoscopic procedures (first procedure vs second or more) and type of endoscopic procedure (balloon vs rigid dilatation).

Secondary outcomes include time to first recurrence of SGS, recurrence rate of SGS at 1 year, impact on dyspnoea (mMRC, Visual Analogue Scale, clinical chronic obstructive pulmonary disease (COPD) questionnaire),²⁰ dysphonia (Voice Handicap Index 10, VHI-10)²¹ and quality of life (Short Form Survey, SF-12)²² of both procedures, measurement of stenosis by cephalocaudal length at endoscopic follow-up at 1 and 2 years, rate of surgical resection following symptomatic recurrence; depth, length and density of fibrotic reaction in the surgical resection specimen in patients undergoing surgical resection, total number of recurrences over 2 years, rate and type of complications and adverse effects depending on the procedure.

	Endoscopic procedure	M1	M6	M12	M18	M24
Physical examination	x	x	x	x	x	x
PROs (mMRC, CCQ, VAS dyspnoea, VHI-10, SF-12)	x	x	x	x	x	x
Spirometry	x	x	x	x	x	x
Bronchoscopy*				(x)		(x)

Figure 3 AERATE's enrolment, intervention and follow-up schedule. *Endoscopic evaluation is optional. AERATE; dilAtion vs laser Endoscopic Resection in subglottic trAcheal sTEnosis; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; mMRC, modified medical research council; PROs, patient-reported outcomes; SF, Short Form Survey; VAS, Visual Analogue Scale; VHI, Voice Handicap Index.

Participant timeline

Patients will attend a follow-up visit at 1, 6, 12, 18 and 24 months after the endoscopic procedure. At each visit, a clinical examination, questionnaires and spirometry will be performed. There will be an optional endoscopic follow-up at 12 and 24 months at the discretion of the treating physician and the patient. In addition to scheduled visits, patients will be seen by their treating physician if they present symptoms suggestive of SGS recurrence. Planned follow-up with questionnaires and testing of patients in the study will be stopped when the primary endpoint is met but all patients will attempt a final visit at 24 months to assess total number of recurrences, occurrence of surgical resection of stenosis and undergo bronchoscopy if they consent.

AERATE's enrolment, intervention and follow-up schedule is shown in [figure 3](#).

Sample size

For the primary endpoint, we calculated a sample size of 48 patients per arm assuming a 10% recurrence rate in the laser resection arm, 33% in the dilation arm and a two-sided hypothesis with a statistical significance level of 5% and 80% power using R V.4.0.3 and RStudio V.1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria). The assumed recurrence rate of dilation and laser resection at 2 years were based on rates reported in the North American Airway Collaborative PR02 study.⁴ A total sample size of 100 patients (50 per arm) is therefore planned.

Recruitment

The participation of 4–10 centres is planned with an annual recruitment of 5–10 patients per centre over a recruitment period of ~5 years.

Data collection and management

Data collection for the proposed clinical trial will include the following case report forms, implemented in an EDC system (REDCap):

- ▶ **Baseline:** At initial patient presentation, baseline data collected will include demographics, relevant medical and surgical history and specific history regarding SGS.

- ▶ **Patient-reported outcomes (PROs):** Five validated PRO instruments will be used to assess patient's symptoms. These relate to voice (VHI-10),²¹ breathing (clinical COPD questionnaire, mMRC scale and EVA scale)²⁰ and general QOL (SF-12).²² Patients will be asked to complete PROs at baseline. In addition, PROs will be repeated at routine intervals post-procedure during the follow-up visits (at 6, 12, 18, 24 months). For patients unable to attempt visit, completion of PROs will be via mailed paper forms or over the phone with an investigator.

- ▶ **Spirometry:** a spirometry will be performed at baseline and during the follow-visits in accordance with recommended techniques.²³

- ▶ **Procedure:** Details of the endoscopic procedure will be captured in details; data elements will include date of procedure, operator who performed the procedure, operative findings (eg, type, length and degree of narrowing within the trachea), detailed endoscopic procedure and complications.

Recurrence: At patient recurrence, a subset of features captured at baseline will be captured again; in addition, the characteristics of SGS by endoscopic evaluation and the details of the repeat procedure will be reported.

The trial will be monitored centrally by the coordinating centre, the Institut Universitaire de Cardiologie et Pneumologie de Quebec. Data entry will be monitored continuously on REDCap, checking for timely data entry, missing data or suspected faulty data.

Statistical analysis

Primary and secondary endpoint analyses will be performed by intention to treat for all randomised patients. In addition, subgroup analyses will be performed for the primary and secondary outcomes by type of stenosis (idiopathic vs other, first procedure vs second or more).

The statistical test for the primary endpoint will be based on a χ^2 test comparing the recurrence rate between the dilation group and the laser resection group.

For the secondary endpoints, comparisons between groups will be performed with χ^2 test for categorical data and with a Student test for quantitative data. In addition, analysis of time to recurrence will be based on a log-rank test, comparing the survival distribution of the time-to-first event for the recurrence.

Multivariate logistic regression analysis will be performed to evaluate factor influencing recurrence.

All reported P values will be two sided, with a significance level set at $p < 0.05$.

Statistical analysis will be performed with R version 4.0.3 and RStudio V.1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria).

Data monitoring

Monthly follow ups will be made with all participating sites to ensure all patients are followed as specified in the protocol and that data is entered appropriately.

Harms

Dilation and endoscopic laser resection are two safe and commonly used techniques in interventional bronchoscopy.^{13 15} Complications are rare and mostly include transient hypoxia during the procedure. Furthermore, tracheal perforation is a theoretical complication of endoscopic laser resection, but has never been reported to date.

Vital signs will be monitored throughout the procedure according to the local protocol in the interventional bronchoscopy room and an interventional bronchoscopist will be present.

The adverse events expected in this study are those known and related to all endoscopic procedure²⁴ (rare, or even exceptional when the contraindications set out in the protocol are respected), that are:

- ▶ Desaturation >90% of >10 s.
- ▶ Intraoral, nasal or endobronchial bleeding.
- ▶ Labial or dental injury.
- ▶ Bronchial laceration.
- ▶ Pneumothorax/pneumomediastinum.
- ▶ Laryngeal oedema.
- ▶ Tissue desquamation causing bronchial plug.
- ▶ Pneumonia.

All adverse events will be documented and reported according to Canadian and European Union legislation.

Ethics and dissemination

The protocol has site ethics committee and Institutional Review Board (IRB) approval (IUCPQ 22016). All patients will provide written informed consent using a form reviewed and approved by the IRB (online supplemental). In addition, the study will be conducted in accordance with Good Clinical Practice guidelines and all applicable country, state, and local regulations.

Results of the study, whether completed or not, will be analysed and made available through publication. Deidentified individual patient data collected during the trial will be made available for an unlimited time period following publication of trial results.

Patient and public involvement

SGS is a rare condition without evidence of a therapeutic option with a high standard of proof. Endoscopic techniques are the most used treatment options including dilation and laser resection. Current knowledge on these two procedures is mainly based on observational studies. These techniques have not been compared yet in a randomised trial. The AERATE trial will therefore help to determine to best endoscopic option in patients with SGS.

Patients and public were not involved in the study design or conduct, or reporting, or dissemination plans of this research. Participants will have access to the findings of the study on request.

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Contributors TS, NG, IA, YL, HD and MF conceived the study. TS and MF initially designed the study. NG, IA, HD and MF elaborated the laser intervention. TS, YL and MF elaborated the statistical design of the study. TS and MF wrote the first manuscript draft. All authors made critical revisions and approved the final manuscript.

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