Randomized controlled trial of awake transnasal laser-assisted surgery (TNLS) and microlaryngeal surgery for vocal cord cyst

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Background

Office-based awake transnasal laser-assisted surgery (TNLS) has been gaining popularity in treating different laryngeal lesions, with the advantages of avoiding general anesthetic risks and minimizing healthcare-related costs. [1-4] In addition, the general waiting time for surgeries under general anesthesia in public hospitals is getting longer due to the increasing population and limited resources. We have recently conducted a novel randomized controlled trial in 2021-2022 comparing the functional and cost-effectiveness of traditional microlaryngeal surgery (MLS) under general anesthesia and TNLS for benign laryngeal lesions (vocal cord polyps, nodules, cysts, granuloma and Reinke's edema), and found that TNLS was superior to MLS in terms of length of stay, intraoperative complications, perioperative throat discomfort and hospital costs; while it was equivalent to MLS in terms of functional outcome, operative time and recurrence rate. [5] However, since our previous study's main goal was to compare TNLS to MLS in a macroscopic perspective in terms of functional outcomes and cost-effectiveness, it had included a wide variety of benign laryngeal lesions, and different vocal cord lesions may respond differently to laser surgery.

Vocal cord cyst is a fluid-filled sac inside the vocal cord, with 2 subtypes: 1) Epidermoid cyst due to epithelial inclusion 2) Mucous retention cyst due to glandular ductal obstruction. Vocal cord cysts typically do not resolve with voice therapy, and are traditionally excised with microlaryngeal surgery with microflap technique or marsupialization. [6,7] In our previous RCT study, subgroup analysis did not show a significant difference of vocal cord cyst recurrence in both TNLS and MLS group. However, our cohort had a higher overall vocal cord cyst recurrence rate (13.8%) compared to historic cohort rate of 2.2-8.7%[5, 8] , which may be accounted by that our vocal cord cysts were ablated and marsupialized instead of removed in the TNLS group. Nevertheless, a recent case series by Gao and colleagues showed a good functional outcome of awake KTP-laser marsupialization in selected cases. [9] A larger cohort is warranted to compare TNLS to MLS for vocal cord cyst. Therefore, our authors would like to conduct a randomized controlled trial to compared tradition MLS surgery to TNLS, with hypothesis that TNLS would be non-inferior to traditional microlaryngeal surgery in benign laryngeal lesions, and with its additional benefits on minimization of anesthetic risks and hospital expenses, hopefully to expand its further application.

Methodology

Study setting

This is a prospective, single-cluster randomized controlled trial conducted at two tertiary referral hospitals (Prince of Wales Hospital and Alice Ho Miu Ling Nethersole Hospital, NTEC) in Hong Kong to compare the clinical and functional outcomes of office-based TNLS to traditional microlaryngeal surgery under general anesthesia for vocal cord cysts.

Eligibility criteria

All consecutive patients with vocal cord cysts interested in operative management will be screened for eligibility.

Inclusion criteria

Patients who are (i) older than 18-year-old; (ii) able to independently provide consent; and (iii) able to tolerate flexible laryngoscopy would be recruited.

Exclusion criteria

Patients who are (i) under 18-year-old; (ii) unable to independently give an informed consent; (iii) unable to tolerate flexible laryngoscopy; (iv) allergic to local anesthesia; (v) had unfavorable anatomy such as prolapsing epiglottis precluding adequate visualization, extensive lesions and an expected difficult operation as judged by the surgeons; and (vi) with pathologies other than vocal cord cyst would be excluded from the study.

Study intervention

The active comparator is traditional microlaryngeal surgery under general anesthesia, which is the standard surgical care for vocal cord cyst at our institution. The experimental intervention would be awake transnasal laser-assisted surgery under local anesthesia, carried out in minor operation theater as a day-case basis in ENT ambulatory center.

Microlaryngeal surgery (MLS)

For traditional MLS under general anesthesia, the patient is admitted on the same day morning of the surgery with prior outpatient anesthetist assessment, or one day earlier to receive inpatient anesthesia assessment in special cases. The patient will be kept fast according to anesthetist assessment before surgery begins. After general anesthesia and intubation with microlaryngeal tube, the patient would be positioned on head-ring support for better alignment and access to glottis. After insertion of teeth guard, a laryngoscope will be inserted transorally under direct vision, and suspended with chest table support. Vocal cord cysts are visualized with microscope, and removed with microsurgery instruments with microflap technique and sent for routine section. Hemostasis is ascertained, then the laryngoscope is removed carefully under direct vision and injuries to pharyngeal walls, tongue base, teeth, lips and temporomandibular joints are checked. After the surgery, the patient is kept nil-by-mouth until fully awake, and is discharged on same day or the next day depending on the post-operative recovery. Patient will be discharged with voice rest for 3 days and prescription of Pantoprazole 40mg daily 4 weeks and Paracetamol as needed.

Awake transnasal laser-assisted surgery (TNLS)

For TNLS, patients are admitted to the day ward center on the same morning or afternoon of the surgery with fasting prior 6 hours. Physical examination would be repeated to ensure that the patient is fit and able to tolerate transnasal laser surgery under local anesthesia. The surgery would be done by or under supervision of ENT specialists with laryngeal laser experience. Following administration 2-4 puffs of 5% lidocaine/0.5% phenylephrine (Co-phenylcaine) nasal spray and 2 puffs of 10% oral Xylocaine spray, a transnasal channel flexible laryngoscope is introduced. The epiglottis, laryngeal inlet and subglottis are further anesthetized with 3ml 2% xylocaine during phonation via working channel. Adequacy of anesthesia is confirmed with absence of gag reflex or discomfort when gently palpating the epiglottis and arytenoids with endoscope tip. Should the patient still have insufficient anesthesia, another 1-2ml 2% xylocaine will be injected with 20G needle for superior laryngeal nerve block. The total dose of local anesthesia shall not exceed maximum dose per kg body weight. A 445nm blue laser is introduced via a working channel of bronchoscope and laser ablation of vocal cord cyst is performed. During the operation, patient will receive continuous SpO2 monitoring with regular blood pressure monitoring. Standardized emergency trolley will be available in case of airway emergency. After the procedure, patients are kept nil-by-mouth for 2 hours until anesthesia wears off, meanwhile with close observation in day ward with continuous SpO2 monitor for 1 hour. Patients will be discharged on the same day of the procedure, with voice rest for 3 days and prescription of Pantoprazole 40mg daily 4 weeks and Paracetamol as needed.

Laser safety

Laser surgery is regarded as a high-risk aerosol generating procedure during the COVID pandemic. Full personal protective equipment with N95 mask, laser eye-shield would be worn by all team members throughout the laser surgery. Doctors and nurses participating in the surgery would receive prior laser surgery safety training. For patients who are on anticoagulant or antithrombotics, the medications will be withheld according to our local hospital guideline balancing on the bleeding and thrombotic risks.

Recruitment and Pre-operative assessment, Consent and Withdrawal of consent

All eligible patients will be assessed in our out-patient clinic in a standardized manner as follow:

1. History taking
2. Complete head and neck physical examination
3. Flexible laryngoscopy for confirmation of diagnosis, with photo documentation of site and size (in relative to length of vocal cord in full abduction)

Diagnosis would be explained to patients, and management options of conservative, microlaryngeal surgery under general anesthesia, and TNLS with their pros and cons would be discussed. Patient information sheet and informed consent are provided to facilitate the

process. Should the patient decide to participate in the study, consent of the study would be signed in the same clinic session. Patient would be informed of his randomized treatment group, and consent of the surgery would be also signed in the same section. Participation is voluntary and any study subject can decide to withdraw at any time of the study period. Upon study withdrawal, the patient will continue to receive standard treatment according to disease status.

In addition to above mentioned assessments, patient would also be assessed in a multidisciplinary voice clinic undergoing a detailed voice assessment co-organized with speech language pathologist, including Voice-Handicap Index (VHI-30), perceptual evaluation of voice, acoustic voice analysis, aerodynamic measures and laryngeal imaging.

Failure of study intervention

When patients cannot tolerate the allocated intervention, for example patients randomized to MLS group but contraindicated to general anesthesia, or patients randomized to TNLS but cannot tolerate transnasal laser surgery due to discomfort or anxiety, can crossover to other study arm. Outcomes would be analyzed by intention-to-treat principle.

Follow-up schedule

All patients would have follow-up in a multi-disciplinary voice clinic on post-op 2 weeks, 6 weeks, 3 months, 6 months and 1 year. During the postoperative follow-ups, patients are required to fill in a questionnaire and undergo voice assessments as mentioned above.

Primary outcome

The primary outcome was to compare the pre- and post-operative Voice-Handicap Index (VHI-30) of TNLS and MLS groups. The VHI-30 is a 30-item self-administered questionnaire, which has been shown to be a reliable measure for voice treatment outcome. [10,11] It consists of three subscales, namely physical, functional and emotional. It provides an overall measurement of a person's vocal function and how it influences a person's everyday functioning and experience.

Secondary outcomes

The secondary outcomes included other voice-related outcomes (i.e. perceptual analysis, acoustic voice analysis, aerodynamic measure, visual analog scale (VAS) on voice quality), procedure-oriented outcomes, patient-oriented outcomes and hospital costs. Perceptual evaluation of voice using the GBRAS scale, in which patients would be required to produce sustained vowel and connected speech voice samples. Two experienced speech-language pathologists blinded to the patient's information would rate the audio recordings. For acoustic voice analysis, it would be conducted using PRATT program with parameters including

jitter, shimmer, noise-to-harmonic ratio measures and cepstral peak performance. For aerodynamic measure, maximal phonation time (MPT) would be measured by instructing patients to phonate /a:/ sound for as long as possible after maximal inspiration, at a spontaneous, comfortable pitch and loudness level, for three consequent trials. In VAS, patients would be asked to self-rate their voice quality on a visual analog scale of 0 (best) to 10 (worst). Videostroboscopy would be conducted on all patients to identify any anatomical and physiological changes, which included presence of laryngeal pathology, vocal fold closure pattern, and mucosal wave pattern.

Procedure-oriented outcomes include operation time, completeness of lesion removal, complications in Clavien-Dindo classification, length of hospital stay, disease recurrence rate, and reoperation.

Patient-oriented outcomes included peri-operative throat, nose, and overall discomfort in visual analogue scale, a 10-point scale with 0 (least uncomfortable) to 10 (most uncomfortable).

Medical costs of both interventions would be also calculated respectively, including costs for inpatient hospital stay, medical staff, operating theater and consumables.

Sample size calculation

Power calculation demonstrated that with a sample size of 21 per group, a two-arm study has a power of 80% to demonstrate a non-inferiority margin 7 absolute score, with one-sided significance of 0.05 regarding the primary outcome parameter, i.e. VHI-30. The calculation was based on published data from Misono et al. [12] in which a VHI-30 score over 16 was determined as a minimal important difference. Assuming a 20% drop-out rate, at least 54 patients were required, with 27 patients in each arm.

Participant timeline

	D1	Allocation	Post-allocation		Close-out
TIMEPOINT	Pre-op assessment		Intra-operative	Immediate post-operative	FU at 2w, 6w, 3mo, 6mo, 1y
Enrolment					
Eligibility screen	X				
Informed consent	X				
Randomization					
MLS		X			
TNLS		X			
Assessment					
Demographics					
	X				
Age at operation	X				
Gender	X				
Smoker	X				
Occupation	X				
Comorbidities	X				
Disease					
	X				
Type of lesion	X				
Site of lesion	X				
Size of lesion	X				
FL / Videostroboscopy	X		X		X
Anaesthetic assessment					
ASA	X				
Functional assessment					
	X				X
VHI30					
Other secondary voice-related outcomes (MPT, Acoustic analysis etc)	X				X
Procedural data					
			X	X	
Operation time			X	X	
Peri-op tolerance scale			X	X	
Peri-op pain score					
Post-operative outcome					
				X	
LOS				X	X
Residual lesion				X	X
Complications					X
Recurrence					
Reoperation					X
Pathology					X

Randomization

Patients are randomized to receive either MLS under general anesthesia or TNLS under local anesthesia. Block randomization is used to ensure equal distribution between two treatment arms. To avoid selection bias, the blocking mechanism is designed by a third party not involved in the study, and is not disclosed to investigators. Randomization is only performed on the day of recruitment, which the recruiter shall contact the third party for the result randomized treatment group. Both the patients and the laryngologists cannot be blinded due to the nature of operation.

Statistical method

All outcome measurements will be analyzed with an intention-to-treat principle. Independent samples t-test will be used for parametric continuous variables; Mann-Whitney U test will be used for non-parametric continuous variables; chi-square test will be used for categorical variables. A p-value less than 0.05 will be considered to be statistically significant. All statistical analysis will be performed using SPSS version 26.0.

Data monitoring and confidentiality

Patient demographics and clinical data are obtained from a territory-wide electronic medical record system named as Clinical Management System (CMS). Individual patient medical information obtained as a result of this study is considered strictly confidential and disclosure to third parties is prohibited. Only the principal investigator, co-investigators, study personnel and research assistants assigned for data collection with the approval of the principal investigator are allowed to have access of the data. Full access to the final data set will be reserved for the principal investigator and the statistician involved in this study. All information will be stored in a password protected hospital authority computer and a locked file cabinet with the key kept by the principal investigator. An Prince of Wales Hospital ENT specialist not involved in the study and with surplus experience on laryngeal surgery will be responsible for safety monitoring. Names of participants will not be used. Information will be retained for a minimum of 10 years after study completion, after which all data will be completely destroyed without any identifiable personal information. All serious adverse events will be reported to the committee within 24 hours.

Research ethics approval and protocol amendments

Approval will be obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, which is the institutional review board of our university. The study will be conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation, Good Clinical Practice Guidelines (ICH-GCP). Prior approval from the committee and the designated trial registry will be obtained prior to implementation of important protocol modifications.

Access to data

The Chinese University of Hong Kong will control the final trial dataset. Any requests for data access can be made to the lead principal investigator. A detailed plan with specific objectives and types of data request has to be formulated and submitted. Upon approval, the requested information will be available, on request to the corresponding author.

Dissemination policy

The results of the study will be presented at relevant international conferences and published in peer-review journals.

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