The Journal of Laryngology & Otology

cambridge.org/jlo

Systematic review and meta-analysis of laryngeal reinnervation techniques in adults with unilateral and bilateral vocal fold palsies

Anjola Onifade[1], Elizabeth Vincent[2] and Neil Tolley[3]

[1]Imperial College London, London, UK, [2]University Hospitals Sussex, Brighton, UK and [3]Imperial Healthcare NHS Trust, London, UK

Main Article

Anjola Onifade takes responsibility for the integrity of the content of the paper

Presented at the World Congress on Thyroid Cancer 2023, 15–17 June 2023, London, UK.

Cite this article: Onifade A, Vincent E, Tolley N. Systematic review and meta-analysis of laryngeal reinnervation techniques in adults with unilateral and bilateral vocal fold palsies. *J Laryngol Otol* 2024;**138**:732–746. https://doi.org/10.1017/S0022215123001950

Received: 15 May 2023
Revised: 22 July 2023
Accepted: 11 August 2023
First published online: 20 November 2023

Keywords:
Humans; adult; electromyography; deglutition; vocal cord paralysis; thyroid neoplasms; phonation; acoustics

Corresponding author:
Anjola Onifade;
Email: anjola.onifade@nhs.net

Abstract

Objective. To evaluate the outcomes of reinnervation techniques for the treatment of adult unilateral vocal fold paralysis and bilateral vocal fold paralysis.
Methods. A literature review was conducted in the Embase and Medline databases in English, with no limitations on the publication date. The outcome parameters of interest included visual, subjective perceptual, acoustic, aerodynamic analysis and electromyography. A meta-analysis with a random-effects model and inverse variance was calculated.
Results. The systematic Preferred Reporting Items for Systematic Reviews and Meta-Analyses approach resulted in 27 studies, totalling 803 patients (747 unilateral cases and 56 bilateral cases). Thyroid cancer and/or surgery had caused unilateral vocal fold paralysis in 74.8 per cent of cases and bilateral vocal fold paralysis in 69.6 per cent of cases. Statistically significant improvements in patients were observed for voice, deglutition and decannulation (bilateral vocal fold paralysis). Meta-analysis of 10 reinnervation techniques was calculated for the maximum phonation time of 184 patients.
Conclusion. Reinnervation was shown to improve voice, swallowing and decannulation, but studies lacked control groups, limiting generalisability. Larger studies with controls are needed.

Introduction

Laryngeal paralysis poses a distinct and diverse challenge that necessitates an individualised approach focused on the patient and a variety of treatment options tailored to both the type of laryngeal paralysis and the patient's individual factors. Laryngeal reinnervation is increasingly used as a surgical option for adults with unilateral vocal fold palsies and bilateral vocal fold palsies.[1,2] In unilateral vocal fold paralysis, non-selective reinnervation medially positions the affected vocal fold by restoring muscle tone and bulk, which improves phonation. This approach commonly involves direct anastomosis of the ansa cervicalis to the distal stump of the recurrent laryngeal nerve (ansa-RLN). In patients with bilateral vocal fold paralysis, airway compromise is common because of the loss of vocal fold abduction and often necessitates a tracheostomy. Selective reinnervation aims to re-establish physiologic inspiratory abduction while maintaining phonation in patients with bilateral vocal fold paralysis. Laryngeal reinnervation has several advantages over other treatment options. Reinnervation can be performed immediately in patients with pre-existing palsy or intra-operative nerve transection. In addition, patient safety can be ensured with injection augmentations prior to the procedure, which preserves glottic competence until the effects of reinnervation become evident. Despite modifications to reinnervation techniques, studies have produced varying reports on the efficacy of different approaches. The aim of our study was to review systematically existing published studies to determine the effectiveness and suitable applications of different techniques.

Material and methods

The systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines. The main research question was developed as follows: What are the outcomes of existing laryngeal reinnervation techniques for managing adults with unilateral vocal fold paralysis and bilateral vocal fold paralysis?

The search

A literature search was conducted on 10 October 2022 in the Embase and Medline databases. The search terms used were 'laryngeal', 'vocal cord', 'vocal fold', 'vocal ligament' and 'reinnervate'. No date restrictions were applied. The search was limited to human studies only. The reference lists of the identified articles were screened for additional relevant studies (Appendices 1 and 2).

Eligibility criteria

The eligibility criteria were: primary research studies, studies that included data on the adult population, studies that investigated unilateral vocal fold paralysis or bilateral vocal fold paralysis and reinnervation techniques, studies that documented the outcomes of the reinnervation techniques for unilateral vocal fold paralysis or bilateral vocal fold paralysis, and studies that did not have duplicate patients or were not based on similar datasets.

The exclusion criteria were: absence of outcome parameters, description of only alternative techniques or novel techniques, review articles, studies not in English and animal or post-mortem studies.

Study selection and data extraction

All three authors were involved in the study selection and data extraction. Two authors (AO and EV) read the articles identified in full and independently assessed each study based on the exclusion criteria. No disagreement occurred between the authors regarding which studies met the inclusion criteria ($K = 1.0$). Data extraction was performed independently by two authors (AO and EV) on piloted forms. The qualitative synthesis and descriptive statistics extracted from the results were reported.

The data extracted were: patient age range, gender, type of palsy, aetiology of vocal fold palsy, design, level of evidence, intervention, supplemental interventions, outcome measure and parameters, duration of paralysis before reinnervation, length of follow up and time until first signs of reinnervation.

Outcomes

The outcome measures recorded from each study included subjective and objective parameters: visual, subjective perceptual, acoustic, aerodynamic or laryngeal electromyography. For bilateral vocal fold paralysis, spirometry and decannulation rates were assessed for improvement in voice and airway. Data included mean values, standard deviations, confidence intervals and/or p values when available. Generalised scales were utilised across studies and are reported in the results section.

Meta-analysis

Average values of the pre- and post-operative maximum phonation time were obtained through meta-analysis, with a 95 per cent confidence interval (CI). Calculations were made for articles with raw data. Meta-analysis was performed with a random-effects model and inverse variance weighting because of the high data heterogeneity. I^2 determined the proportion of variance. Statistical heterogeneity was assessed by prediction interval. The prediction interval was analysed to determine how much the effects varied.[3] Statistical significance was held at $p \leq 0.05$. RevMan v5.4 software (Cochrane) was used to calculate the maximum phonation time effect size between reinnervation techniques. Jasp v16.4 software (University of Amsterdam, the Netherlands) was used to calculate Egger's regression test.

Assessment of the level of evidence and quality

The studies were classified according to the type and level of evidence specified in the 2011 Oxford classification.[4] The quality of each study was assessed by determining a score from 0 (low quality) to 8 (high quality) using the following system: data collection purpose (1 indicates patient care or not stated, 2 indicates research purposes); sample selection (consecutive or not: 1 indicates none or not stated, 2 indicates consecutive); follow-up period of one year or more (1 indicates less than one year or not stated, 2 indicates one year or more), post-operative or follow-up data status (1 indicates lack of data not accounted for or not stated, 2 indicates accounted for).

Results

Study selection

The initial search revealed 801 articles. After removing duplicate articles, title/abstract and full-text screening, and adopting the selection criteria, 27 articles were eligible for inclusion in the systematic review. Of these, 10 were included in the meta-analysis for maximum phonation time (Figure 1).[5–14]

Methodological quality

All but two studies, one case-control[15] and one prospective cohort,[16] were case series. Only four studies used consecutive samples.[8,12,17,18] All but five studies had a median follow-up period of at least 12 months after reinnervation.[6,7,19–21] One study did not describe the surgical technique.[22]

Population characteristics

Study sample sizes ranged from 2 to 237 patients, totalling 803 patients (66.5 per cent female) with a mean age of 49.2 years (range, 12–82 years) who underwent reinnervation (Table 1). The median duration of paralysis before reinnervation was 2.7 months (range, 1–366 months). The median follow-up period was 14 months (standard deviation (SD) = 1.53) and 534 out of 803 patients had pre- and post-operative data reported. However, the patient characteristics describe all 803 patients because it was not possible to differentiate the data within the studies. Thyroid cancer and/or surgery accounted for most unilateral and bilateral vocal fold palsies, 74.8 per cent (559 of 747 cases) and 69.6 per cent (39 of 56 cases), respectively (Tables 2 and 3). This was followed by idiopathic (6.2 per cent, 46 of 747 cases) for unilateral vocal fold paralysis and laryngeal trauma (21.4 per cent, 12 of 56 cases) for bilateral vocal fold paralysis. Three studies described selective reinnervation in bilateral vocal fold paralysis using different nerve combinations,[11,13,23] one study reported both selective and non-selective reinnervation,[16] and the remaining studies explored non-selective reinnervation. Ansa-RLN anastomosis was performed in 511 patients, supplemented with cricothyroid reinnervation in 74 high vagal injuries.[5,17,21] Seven studies reported two techniques with shared demographics.[5,10,12,16,22,24,25] Eleven studies involved supplementation with injection, using Permacol, AlloDerm or Gelfoam.[8,16–22,24–26]

Visual analysis

Glottic closure and vocal fold movement

Glottic closure was the most frequently described parameter. Data were collected using a scale from 0 to 3, where 0 indicated complete closure and 3 indicated severely incomplete closure. One study reported this using a different scale, with 0 indicating severely incomplete closure and 3 representing complete

https://doi.org/10.1017/S0022215123001950

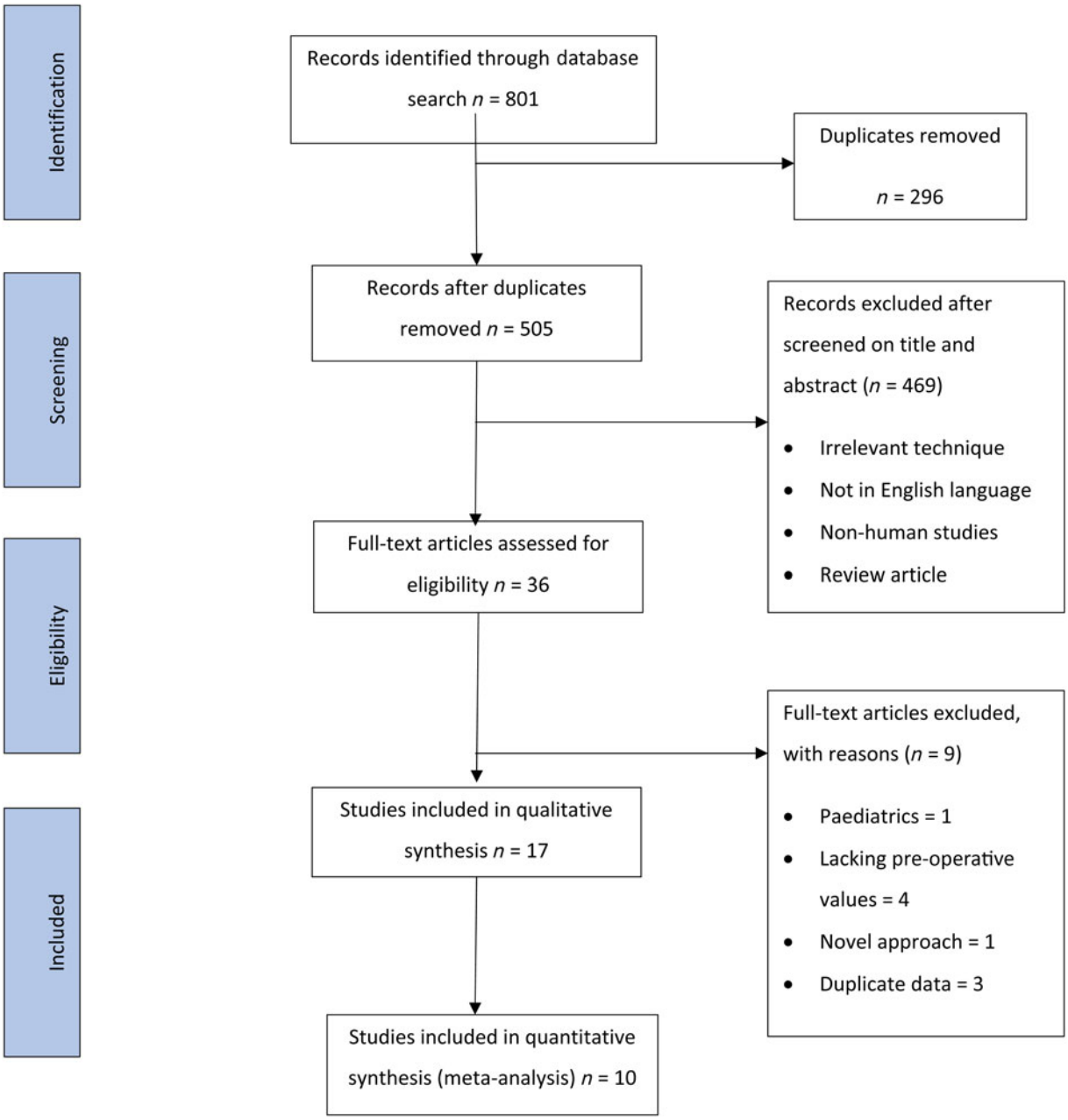


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses ('PRISMA') diagram. SD = standard deviation; IV = intravenous; CI = confidence interval

closure.[12] It was not possible to adjust this because of the lack of raw data. Nine of the 10 studies showed improvement in glottic closure/gap,[7,9,10,12,15,17,18,24,27] with *p* values in 5,[7,10,12,15,17] 4 of which demonstrated significant improvement (Table 4).[12,15,17,28] Three studies explored visual findings for two techniques collectively.[10,12,24] However, using the Mann–Whitney test, one study showed no significant differences in voice parameters between direct RLN and ansa-RLN reinnervation at baseline and 12 months, respectively.[12] One study showed no difference in glottal gap.[11] Only one study measured vocal fold movement and reported significant improvement in the functional abduction of both vocal folds.[11]

Mucosal wave, true vocal fold edge and true vocal fold position

Data were collected using a scale from 0 to 3 (0, absent mucosal wave; 3, intact mucosal wave), except for one study in which the scale was used in reverse.[19] Three studies showed an improvement in the mucosal wave,[10,12,19] with two demonstrating significance[10,12] (Table 5). One study showed no difference.[23] True vocal fold edge was measured using a scale from 0 to 3 (0, straight; 1, mildly bowing; 2, moderately bowing; 3, severely bowing). Three studies recorded improved vocal fold edge,[15,17,18] with two showing significance.[15,17] No difference in vocal fold edge was found for bilateral vocal fold paralysis.[11] The true vocal fold position scale was 0 (midline) and 3 (lateral), with heterogeneous findings. One study showed significant improvement in vocal fold position[15] and another reported an insignificant improvement.[9] Vocal fold position was worse in two studies,[17,18] while another showed no difference.[24]

Supraglottic effort and vertical height difference

Two studies recorded supraglottic effort and vertical height (Table 5).[17,18] Both showed improvement in effort and an insignificant difference in height. The supraglottic effort scale ranged from 0 (normal) to 3 (severe effort). For vertical height, a scale from 0 (no change) to 1 (height difference) was used.

https://doi.org/10.1017/S0022215123001950

Table 1. Study characteristics

Study	Score	Intervention(s)	Supplemental procedure	Surgical subjects (*n*)
Mansor (2021)[25]	7	Primary RLN; Ansa-RLN	Injection	3
Candelo (2021)[16]	7	SLR phrenic; Ansa-RLN	Injection; medialisation	8
Buyukatalay (2021)[22]	6	Ansa-RLN; NMP	Injection	10
Yuan (2020)[27]	7	Primary RLN; Ansa-RLN; Vagus-RLN; FNG	None	37
Wang (2020)[28]	7	Ansa-RLN	None	53
Ab Rani (2019)[14]	7	Ansa-RLN	None	9
Li (2019)[13]	7	SLR phrenic and hypoglossal	None	7
Mat Baki (2018)[23]	7	SLR phrenic and ansa	None	2
Kodama (2015)[29]	7	NMP + AA	None	33
Lee (2014)[12]	8	Primary RLN; Ansa-RLN	None	19
Li (2013)[11]	7	SLR left phrenic	None	44
Wang (2011)[15]	7	Ansa-RLN	None	237
Sanuki (2010)[10]	6	Primary RLN; Ansa-RLN; FNG	None	12
Miyauchi (2009)[5]	7	Primary RLN; Ansa-RLN	None	88
Smith (2008)[8]	7	Ansa-RLN	Injection; medialisation	6
Lorenz (2008)[17]	7	Ansa-RLN ± CT MNM	Injection	46
Su (2007)[9]	7	Implantation	None	10
Lee (2007)[18]	7	Ansa-RLN ± CT MNM	Injection	25
Chou (2003)[7]	6	Primary RLN	None	8
Maronian (2003)[24]	7	Ansa-RLN; NMP	Injection	9
El-Kashlan (2001)[21]	5	Ansa-RLN + CT MNM	Injection; medialisation	3
Paniello (2000)[6]	6	Hypoglossal-RLN	None	9
Olson (1998)[26]	6	Ansa-RLN	Injection	12
Zheng (1996)[30]	7	Ansa-RLN	None	8
Crumley (1991)[19]	4	Ansa-RLN	Injection	12
Tucker (1989)[31]	6	NMP	None	73
May (1986)[20]	5	NMP	Injection	20
Total				803

Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; Injection = injection laryngoplasty with Permacol, Alloderm or Gelfoam; SLR phrenic = SLR of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR left phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with left phrenic nerve; Medialisation = arytenoid medialisation; NMP = ansa cervicalis to thyroarytenoid neuromuscular pedicle; Vagus-RLN = vagus to recurrent laryngeal nerve anastomosis; FNG = free nerve grafting of supraclavicular, transverse cervical or ansa cervicalis to recurrent laryngeal nerve; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve; SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis; NMP + AA = ansa cervicalis to thyroarytenoid neuromuscular pedicle and arytenoid adduction; CT MNM = cricothyroid muscle-nerve-muscle neuromuscular pedicle; Implantation = ansa cervicalis to thyroarytenoid neural implantation; Hypoglossal-RLN = hypoglossal to recurrent laryngeal nerve anastomosis

Perceptual analysis

The Overall Grade, Roughness, Breathiness, Asthenia and Strain rating scale and the Consensus Auditory-Perceptual Evaluation of Voice scale were used to measure severity, roughness, breathiness and strain. Apart from one study that used a scale ranging from 0 to 120 and was adjusted to a scale of 0 to 3,[26] the Overall Grade, Roughness, Breathiness, Asthenia and Strain scores ranged from 0 (normal) to 3 (severe dysphonia). Three studies[7,10,13] showed significant improvement in the Overall Grade, Roughness, Breathiness, Asthenia and Strain score. Six studies[7,10,13,23,24,26] showed improvements in overall grade, five studies[7,10,23,24,26] in roughness and breathiness, and in three studies,[7,24,26] asthenia and strain demonstrated improvements (Table 6). Two earlier studies[17,18] used the Consensus Auditory-Perceptual Evaluation of Voice scale and demonstrated an improvement in all the categories (Table 7) on a scale from 0 (normal) to 100 (severe dysphonia).

The Eating Assessment Tool – 10 was used to assess dysphagia. Two studies showed improvements following reinnervation (Table 8).[22,23]

Subjective assessment

Three studies[12,14,23] reported improvements in the Voice Handicap Index (Table 9). One study[12] reported findings for two different techniques – Primary RLN and Ansa-RLN anastomosis. One study[14] was statistically significant.

Acoustic analysis

The mean noise-to-harmonics ratio and measures of phonation stability, namely jitter and shimmer, were reported as percentages. Statistical analysis using the Mann–Whitney test showed no significant differences in voice parameters between

https://doi.org/10.1017/S0022215123001950

Table 2. Aetiologies of unilateral vocal fold paralysis patients who underwent non-selective laryngeal reinnervation

Procedure	Cases (*n*)	Ansa-RLN (*n*)	Ansa-RLN ± CT MNM (*n*)	NMP (*n*)	Primary RLN (*n*)	Vagus-RLN (*n*)	Implantation (*n*)	Hypo-glossal -RLN (*n*)	FNG (*n*)
Thyroid cancer ± surgery	559	406	14	48	61	17	4		9
Idiopathic	46	15	19	9			1	2	
Mediastinal mass surgery	24	1	14	5			1	3	
Neck/laryngeal trauma	8	2	1	5					
Aortic surgery	18	4	7	7					
Spine surgery	18	4	9	1			3	1	
Vagal paraganglioma	16	3	12	1					
Skull base tumour	8	2	1	5					
Parathyroidectomy	7		2		3		1	1	
Cerebrovascular accident	6			4				1	
Oesophageal cancer ± surgery	4		2	2					
Jugular paraganglioma	3	1	2						
Neck mass excision	3		2					1	
Lung cancer	3		1	2					
Endarterectomy	2			2					
Mediastinoscopy	3	1	2						
Multinodular goitre	2	1			1				
Patent ductus arteriosus ligation	2	2							
Pulmonary tuberculosis	3	2		1					
Scar tissue lysis	3		3						
Thymus tumour	2			2					
Vagal schwannoma	3	2		1					
Vagal neurofibroma	2		2						
Graves disease	1			1					
Intubation	1	1							

Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; CT MNM = cricothyroid muscle-nerve-muscle neuromuscular pedicle; NMP = ansa cervicalis to thyroarytenoid neuromuscular pedicle; Primary RLN = primary recurrent laryngeal nerve anastomosis; Vagus-RLN = vagus to recurrent laryngeal nerve anastomosis; Implantation = ansa cervicalis to thyroarytenoid neural implantation; Hypoglossal-RLN = hypoglossal to recurrent laryngeal nerve anastomosis; FNG = free nerve grafting of supraclavicular, transverse cervical or ansa cervicalis to recurrent laryngeal nerve

Table 3. Aetiologies of bilateral vocal fold paralysis patients who underwent selective laryngeal reinnervation

Etiology	Patients (*n*)	SLR phrenic (*n*)	SLR phrenic and ansa (*n*)	SLR phrenic and hypoglossal (*n*)
Thyroid cancer ± surgery	39	32		7
Neck/laryngeal trauma	12	12		
Vagal paraganglioma	5	3	2	

SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of the hypoglossal nerve

primary RLN and ansa-RLN at baseline and 12 months after reinnervation.[12] Four studies demonstrated improvement of noise-to-harmonics ratio *p* values (Table 10),[11–14] and two studies were statistically significant.[12,13] For jitter and shimmer, nine studies demonstrated an improvement (Table 11).[6,9,11–14,21,23,27] Four studies were statistically significant.[9,12,13,27]

Aerodynamic analysis

All 10 studies measuring maximum phonation time values showed improvements (Table 12).[5–14] Four studies demonstrated statistical significance.[7,9,10,13] The mean airflow rate from one study showed a significant improvement (Table 13).[10]

Electromyography

A scale ranging from 0 (full interference) and 3 (no motor unit potential) was used to measure electromyography. Two studies showed a significant improvement in thyroarytenoid muscles,[15,29] while another showed a significant improvement in bilateral posterior cricoarytenoids and no difference in thyroarytenoids (Table 14).[11] In one study, full interference of bilateral posterior cricoarytenoid during inspiration and bilateral thyroarytenoid during phonation were recorded, but moderate electric potentials were observed in the left interarytenoid muscle.[13]

Pulmonary function tests and decannulation rate

Two studies measuring pulmonary function parameters showed recovery to normal reference values within 12 months after reinnervation, except for PI_{max} (Table 15).[11,13] High decannulation rates were observed in both studies (Table 16). No significant pulmonary function morbidity with SLR was observed in one study.[23]

Meta-analysis

Ten studies describing 12 techniques were subjected to meta-analysis to assess pre- and post-operative maximum phonation time,[5–14] with 184 patients (Figure 2). Two studies were incalculable as a result of a lack of SD data.[6,8] Two studies described selective laryngeal reinnervation while all the others described non-selective laryngeal reinnervation.[11,13] There was a statistically significant increase of 1.32 seconds (95 per cent CI 0.79–1.85). Two studies[11,14] were outside the 95 per cent CI (Appendix 2), suggesting the presence of publication bias. I^2 is equal to 73 per cent with a prediction interval between –0.35 and 2.99 (Figure 2).

Discussion

The existing literature on adult reinnervation techniques mainly consists of case series, and only a few case-control studies have explored reinnervation for unilateral vocal fold paralysis, with a recent randomised, controlled trial (RCT) comparing reinnervation with medialisation for unilateral

Table 4. Glottic closure

Study	Intervention(s)	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Chou (2003)*[7]	Primary RLN	8	2.25 (1.16)	0.5 (0.53)
Zheng (1996)[30]	Ansa-RLN	8	2.26	0.75
Lorenz (2008)*,†,‡,§[17]	Ansa-RLN; Ansa-RLN + CT MNM	21	0.68	0.19
Lee (2007)‡[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	1	0.1
Maronian (2003)‡[24]	Ansa-RLN; NMP	7	1.85	0.28
Su (2007)**[9]	Implantation	9	2	0
Sanuki (2010)*[10]	Primary RLN; Ansa-RLN	6	1.5 (0.84)	0.34 (0.52)
Wang (2011)*[15]	Ansa-RLN	237	2.86 (0.35)	0.1 (0.42)
Li (2013)[11]	SLR left phrenic	44	1.3 (1.05)	1.36 (1.04)
Lee (2014)*[12]	Primary RLN, Ansa-RLN	19	0.59 (0.79)	2.60 (0.57)

*Statistical significance noted; †Confidence interval of 0.04 to 0.9 recorded; ‡Supplementation with injection laryngoplasty: Permacol, micronised AlloDerm or Gelfoam; **Supplementation with medialisation thyroplasty; §Pre-operative value is baseline probability, post-operative value is odds ratio. SD = standard deviation; Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; CT MNM = cricothyroid muscle-nerve-muscle neuromuscular pedicle; NMP = ansa cervicalis to thyroarytenoid neuromuscular pedicle; Implantation = ansa cervicalis to thyroarytenoid neural implantation; SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR left phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with left phrenic nerve

https://doi.org/10.1017/S0022215123001950

Table 5. Vocal fold movement

Parameter	Study	Intervention(s)	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Mucosal wave	Crumley (1991)†**[19]	Ansa-RLN	5	1	0.2
	Sanuki (2010)*[10]	Primary RLN; Ansa-RLN	6	1.2 (1.0)	2.5 (0.5)
	Lee (2014)*[12]	Primary RLN, Ansa-RLN	19	0.47 (0.71)	2.33 (0.48)
True vocal fold edge	Lorenz (2008)*,†,‡[17]	Ansa-RLN; Ansa-RLN + CT MNM	21	0.69	0.25
	Lee (2007)†[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	1	0.66
	Wang (2011)*[15]	Ansa-RLN	237	2.06 (1.0)	0.08 (0.36)
	Li (2013) Left[11]	SLR left phrenic	44	0.73 (0.85)	0.93 (0.9)
	Li (2013) Right[11]		44	0.61 (0.72)	0.77 (0.77)
True vocal fold position	Maronian (2003)[24]	Ansa-RLN; NMP	7	2.38	2.38
	Lorenz (2008)†,‡[17]	Ansa-RLN; Ansa-RLN + CT MNM	21	0.38	0.33
	Lee (2007)†[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	1.23	1.13
	Su (2007)[9]	Implantation	9	2.25	2.81
	Wang (2011)*[15]	Ansa-RLN	237	1.37 (0.67)	0.34 (0.56)
Supraglottic effort	Lorenz (2008)†,‡[17]	Ansa-RLN; Ansa-RLN + CT MNM	21	0.78	1.34
	Lee (2007)†[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	1.3	0.95
Vertical height difference	Lorenz (2008)†,‡[17]	Ansa-RLN; Ansa-RLN + CT MNM	21	0.14	0.2
	Lee (2007)†[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	0	0

*Statistical significance noted; †Supplementation with injection laryngoplasty: Permacol, micronised AlloDerm or Gelfoam; ‡Pre-operative value is baseline probability, post-operative value is the odds ratio; **Confidence interval of 0.24 to 1.36 recorded. SD = standard deviation; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; Primary RLN = primary recurrent laryngeal nerve anastomosis; CT MNM = cricothyroid muscle-nerve-muscle neuromuscular pedicle; SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; NMP = ansa cervicalis to thyroarytenoid neuromuscular pedicle; Implantation = ansa cervicalis to thyroarytenoid neural implantation

vocal fold paralysis.[12] The studies investigating bilateral palsies are limited to case series, indicating that reinnervation techniques are mostly supported by level 4 evidence. Our objective was to systematically review the literature on adult reinnervation techniques to assess their effectiveness.

- Significant improvements in multidimensional voice outcomes were observed in adults after reinnervation for both unilateral and bilateral palsies, as well as decannulation rates for bilateral vocal fold paralysis
- Reinnervation of bilateral palsies is more complex and supported by limited evidence compared to unilateral palsies
- A meta-analysis of 10 reinnervation techniques involving 184 patients demonstrated favourable outcomes in terms of maximum phonation time
- The studies included in the review were highly heterogeneous, mostly consisting of small case series without control groups
- Future studies should include larger sample sizes, differentiate between reinnervation techniques, separate unilateral and bilateral palsies, and incorporate control groups to provide more robust evidence

The distribution of true effects (Figure 3) shows that reinnervation primarily improves the maximum phonation time for unilateral and bilateral palsies. However, two studies were not statistically significant,[11,23] and another showed no significant difference.[14] For example, in one study a patient had a lack of vocal fold abduction, which may have been partly attributed to old age, leading to less vigorous axonal regrowth and an increased risk of general anaesthesia associated with elderly patients.[11] The inconsistency in results highlights the requirement for careful patient selection for reinnervation.

Only two outliers are identified in the funnel plot (Appendix 3). When assessed visually, there is an asymmetrical pattern, with most studies scattered on the right side. This may be indicative of publication bias. In addition, this suggests the presence of a small-study effect. It is possible that the small subject case series included were only those with significant reinnervation effects, while unpublished studies with similar standard errors, but smaller and less significant reinnervation effects, were excluded.[30,31]

Other factors should be considered, such as selective reporting of outcomes and chance. For example, the operating surgeons may only report findings based on their experiences while the less favourable outcome parameters go unreported. This may have been the case in studies where raw data were unavailable. This can lead to an overestimation of the true reinnervation effects observed. Importantly, the funnel plot does not assess the existence of publication bias but instead provides a visual aid. Hence, statistical analysis with Egger's test was performed to further evaluate publication bias.[32]

Egger's regression test detects publication bias in a meta-analysis by assessing the funnel plot for asymmetry. Because a p value of <0.05 was calculated (Figure 4), we can report the presence of publication bias. Importantly, the test only measures small study bias, which can include publication bias. The test also considers other features of small study bias, such as the differences in study designs.[30] By calculating Egger's test, we assume that the analysis consists of a sufficient number of studies and severe bias is absent, which is necessary for the test to have sufficient power. However, it is only applicable if a range of study sizes with a minimum of a medium-sized study are included.[33] One could therefore argue against its use because our studies are mostly limited to a small number of subjects. Another attempt was made to adjust for publication bias with the precision-effect test and precision-effect estimate with standard errors method. This is an approach aimed at small-study effects that adjusts for the correlation between effect sizes and standard errors.[34] We were unsuccessful in using this technique because of the inability to calculate the correlation for the effect size. Possible explanations include abnormal distribution of data, inadequate data and the presence of outliers.

https://doi.org/10.1017/S0022215123001950

Table 6. Grade, Roughness, Breathiness, Asthenia, Strain scale analysis

Study	Intervention	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Grade				
– Chou (2003)*[7]	Primary RLN	8	1.75 (0.71)	0.38 (0.52)
– Olson (1998)†[26]	Ansa-RLN	11	1.75	1.02
– Maronian (2003)†[24]	Ansa-RLN	5	2	1.4
– Maronian (2003)†[24]	NMP	3	1.8	0.53
– Sanuki (2010)*[10]	Primary RLN; Ansa-RLN	6	1.2 (0.8)	0.3 (0.8)
– MatBaki (2018)[23]	SLR phrenic and ansa	2	1 (1.41)	0.5 (0.71)
– Li (2019)*[11,13]	SLR phrenic and hypoglossal	7	0.8	0.4
Roughness				
– Chou (2003)*[7]	Primary RLN	8	1.5 (0.53)	0.5 (0.53)
– Olson (1998)†[26]	Ansa-RLN	11	3	0.78
– Maronian (2003)†[24]	Ansa-RLN	5	1.94	1.14
– Maronian (2003)†[24]	NMP	3	1.6	0.67
– Sanuki (2010)*[10]	Primary RLN; Ansa-RLN	6	1.0 (0.6)	0.2 (0.4)
– MatBaki (2018)[23]	SLR phrenic and ansa	2	1 (1.41)	0 (0)
Breathiness				
– Chou (2003)*[7]	Primary RLN	8	1.38 (0.74)	0.5 (0.93)
– Olson (1998)†[26]	Ansa-RLN	11	1.21	0.56
– Maronian (2003†[24]	Ansa-RLN	5	1.66	0.66
– Maronian (2003)†[24]	NMP	3	0.9	0.2
– Sanuki (2010)*[10]	Primary RLN; Ansa-RLN	6	0.7 (0.8)	0.2 (0.4)
– MatBaki (2018)[23]	SLR phrenic and ansa	2	0.5 (0.7)	0.5 (0.71)
Asthenia				
– Chou (2003)*[7]	Primary RLN	8	1.25 (0.71)	0.125 (0.35)
– Olson (1998)†[26]	Ansa-RLN	11	1.03	0.64
– Maronian (2003)†[24]	Ansa-RLN	5	1.48	0.54
– Maronian (2003)†[24]	NMP	3	0.76	0.3
Strain				
– Chou (2003)*[7]	Primary RLN	8	1 (0.76)	0.25 (0.46)
– Olson (1998)†[26]	Ansa-RLN	11	0.98	0.91
– Maronian (2003)†[24]	Ansa-RLN	5	0.06	0
– Maronian (2003)†[24]	NMP	3	0.43	0

*Statistical significance noted; †Supplementation with injection laryngoplasty: Permacol, micronised AlloDerm or Gelfoam. SD = standard deviation; Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; NMP = ansa cervicalis to thyroarytenoid neuromuscular pedicle; SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve

The review showed improvements in voice and deglutition for unilateral vocal fold paralysis following reinnervation. Ansa-RLN anastomosis, the most studied approach, demonstrated significant improvement in glottic closure, mucosal wave, Eating Assessment Tool–10, Voice Handicap Index and the Consensus Auditory-Perceptual Evaluation of Voice scoring, jitter and shimmer, maximum phonation time, and laryngeal electromyography. Ansa-RLN was mostly associated with thyroid disease and/or surgery followed by idiopathic aetiology. To our knowledge, the largest study, published by Wang *et al.*,[15] with improvements in voice quality, analysed 237 ansa-RLN anastomosis patients for unilateral vocal fold paralysis along with age- and gender-matched normal subjects. Ansa cervicalis to thyroarytenoid neuromuscular pedicle was the second most studied reinnervation technique. Vocal fold vibration, aerodynamic analysis and perceptual evaluation showed significant improvements. Laryngeal electromyography data for the neuromuscular pedicle technique was limited. One study showed positive outcomes when neuromuscular pedicle technique was combined with arytenoid adduction.[28] The neuromuscular pedicle approach was more prevalent following aortic and mediastinal mass surgery, cerebrovascular accident, skull base tumours and neck trauma.

Primary RLN was the third most studied technique, and was almost exclusively reserved for thyroid cancer and/or surgical aetiology. The vagus-RLN anastomosis technique demonstrated an improvement in maximum phonation time and Overall Grade, Roughness, Breathiness, Asthenia and Strain score.[35] Post-operative voice outcomes also

https://doi.org/10.1017/S0022215123001950

Table 7. Consensus Auditory-Perceptual Evaluation of Voice scale analysis

Study	Intervention(s)	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Severity				
– Lee (2007)[†18]	Ansa-RLN; Ansa-RLN + CT MNM	13	100	35
– Lorenz (2008)*,[†17]	Ansa-RLN; Ansa-RLN + CT MNM	21	61.3 (5.6)	37.9 (7.3)
Roughness				
– Lee (2007)[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	100	30
– Lorenz (2008)*,[†17]	Ansa-RLN; Ansa-RLN + CT MNM	21	41.4 (5.3)	23.1 (7.1)
Breathiness				
– Lee (2007)[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	100	0
– Lorenz (2008)*,[†17]	Ansa-RLN; Ansa-RLN + CT MNM	21	53.3 (6)	43.8 (8)
Strain				
– Lee (2007)[18]	Ansa-RLN; Ansa-RLN + CT MNM	13	100	66
– Lorenz (2008)*,[†17]	Ansa-RLN; Ansa-RLN + CT MNM	21	24.7 (5.6)	15.6 (7.4)

*Statistical significance noted; [†]Supplementation with injection laryngoplasty: Permacol, micronised AlloDerm or Gelfoam. SD = standard deviation; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; CT MNM = cricothyroid muscle-nerve-muscle neuromuscular pedicle

Table 8. EAT-10 score

Study	Intervention(s)	Subjects (*n*)	Pre-operative	Post-operative
MatBaki (2018)[23]	SLR phrenic and ansa	2	6	2
Buyukatalay (2021)*[22]	Ansa-RLN; NMP	6	13	7

Voice-related quality of life was assessed using the Voice Handicap Index questionnaire in three studies,[12,14,23] all of which showed improvements. *Supplementation with injection laryngoplasty: Permacol, micronised AlloDerm or Gelfoam. SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; NMP = ansa cervicalis to thyroarytenoid neuromuscular pedicle

Table 9. Voice Handicap Index

Study	Intervention(s)	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Lee (2014)[12]	Primary RLN	12	85.2 (17.4)	40.7 (22.9)
Lee (2014)[12]	Ansa-RLN	7	84.4 (17.7)	49.1 (26.6)
MatBaki (2018)[23]	SLR phrenic and ansa	2	8 (11.31)	3 (2.83)
Ab Rani (2019)*[14]	Ansa-RLN	10	18.57 (18.08)	1.57 (2.57)

*Statistical significance noted. SD = standard deviation; Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis

Table 10. Noise-to-Harmonics ratio

Study	Intervention(s)	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Lee (2014)*[12]	Primary RLN; Ansa-RLN	19	16.8 (5.3)	34.9 (1.2)
Li (2013)[11]	SLR left phrenic N	44	0.08 (0.04)	0.09 (0.14)
Li (2019)*[13]	SLR phrenic and hypoglossal	7	0.09 (0.03)	0.06 (0.02)
Ab Rani (2019)[14]	Ansa-RLN	10	0.32 (0.53)	0.06 (0.11)

*Statistical significance noted. SD = standard deviation; Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; SLR left phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with left phrenic nerve; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve

improved when free nerve grafting was carried out.[10,35] A free nerve grafting study attributed voice improvements to the return of thyroarytenoid tone and bulk without providing any data on atrophy.[10] However, only two studies recorded an improvement in the atrophy of the thyroarytenoid muscle so it was not possible to make a comparison.[9,24] One study performed hypoglossal-RLN anastomosis.[6] This could be possibly due to its association with high donor site morbidity.[6,36] Implantation of the ansa cervicalis into the thyroarytenoid was performed when the RLN could not be located, with improvements in 6 out of 10 patients.[9]

https://doi.org/10.1017/S0022215123001950

Table 11. Jitter and shimmer

Study	Intervention(s)	Subjects (*n*)	Pre-operative jitter (% (SD))	Post-operative jitter (% (SD))	Pre-operative shimmer (% (SD))	Post-operative shimmer (% (SD))
Zheng (1996)*[30]	Ansa-RLN	8	2.03 (1.25)	0.43 (0.23)	8.83 (2.24)	3.22 (2.11)
El-Kashlan (2001)†[21]	Ansa-RLN + CT MNM	3	10.6	0.64	1.02	0.15
Su (2007)*[9]	Implantation	9	2.19 (0.71)	0.54 (0.31)	7.18 (0.97)	2.47 (1.22)
Paniello (2000)[19]	Hypoglossal-RLN	5	7.75	0.87	10.5	3.5
Li (2013)[11]	SLR left phrenic	44	1.19 (0.54)	1.07 (0.36)	7.92 (2.33)	7.19 (1.71)
Lee (2014)*[12]	Primary RLN, Ansa-RLN	19	4.86 (5.82)	1.73 (1.07)	8.05 (5.33)	5.11 (4.03)
MatBaki (2018)[23]	SLR phrenic and ansa	2	1.0 (0.66)	0.97 (0.61)	2.24 (0.67)	2.02 (0.49)
Li (2019)*[13]	SLR phrenic and hypoglossal	7	0.96 (0.47)	0.59 (0.16)	6.13 (1.33)	4.26 (0.96)
Ab Rani (2019)[14]	Ansa-RLN	10	2.24 (2.06)	1.20 (0.76)	8.11 (5.01)	0.06 (0.11)

*Statistical significance noted; †Injection medialisation supplementation with Permacol, AlloDerm or Gelfoam. SD = standard deviation; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; CT MNM = cricothyroid muscle-nerve-muscle neuromuscular pedicle; Implantation = ansa cervicalis to thyroarytenoid neural implantation; Hypoglossal-RLN = hypoglossal to recurrent laryngeal nerve anastomosis; SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR left phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with left phrenic nerve; Primary RLN = primary recurrent laryngeal nerve anastomosis; SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve

Table 12. Maximum phonation time

Study	Intervention(s)	Subjects (*n*)	Pre-operative MPT (SD)	Post-operative MPT (SD)
Chou (2003)*[7]	Primary RLN	8	4.9 (1.3)	10.1 (1.8)
Miyauchi (2009)[5]	Primary RLN	7	3.95 (2.21)	7.26 (2.68)
Smith (2008)†[8]	Ansa-RLN	6	6.5	13.2
Miyauchi (2009)[5]	Ansa-RLN	63	3.95 (2.21)	7.05 (2.93)
Su (2007)*[9]	Implantation	9	7 (1.22)	16 (5.52)
Paniello (2000)[19]	Hypoglossal-RLN	5	2	15.6
Sanuki (2010)*[10]	Primary RLN; Ansa-RLN	6	7.1 (2.6)	16.2 (6.2)
Li (2013)[11]	SLR left phrenic	44	8.9 (3.2)	9.2 (1.6)
Lee (2014)[12]	Primary RLN	12	7.77 (3.170	10.57 (2.33)
Lee (2014)[12]	Ansa-RLN	7	6.01 (1.86)	10.23 (2.51)
MatBaki (2018)[23]	SLR phrenic and ansa	2	15 (0)	9.5 (0.71)
Li (2019)*[13]	SLR phrenic and hypoglossal	7	8.28 (2.08)	12.16 (1.59)
Ab Rani (2019)[14]	Ansa-RLN	10	11.58 (4.88)	15.29 (5.82)

*Statistical significance noted; †Injection medialisation supplementation with Permacol, AlloDerm or Gelfoam. MPT = maximum phonation time; SD = standard deviation; Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; Implantation = ansa cervicalis to thyroarytenoid neural implantation; Hypoglossal-RLN = hypoglossal to recurrent laryngeal nerve anastomosis; SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR left phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with left phrenic nerve; SLR phrenic and ansa = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and ansa cervicalis; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve

Table 13. Mean airflow rate

Study	Intervention	Subjects (*n*)	Pre-operative (SD)	Post-operative (SD)
Sanuki 2010* [10]	Primary RLN; Ansa-RLN	6	271 (325.1)	110.3 (38.4)

*Statistical significance noted. SD = standard deviation; Primary RLN = primary recurrent laryngeal nerve anastomosis; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis

Four articles reported outcomes following selective reinnervation with improvements in vocal fold abduction while maintaining phonation.[11,13,16,23] The phrenic nerve was used either solely or in combination with another (ansa cervicalis or hypoglossal nerve), with favourable results in vocal fold abduction, Overall Grade, Roughness, Breathiness, Asthenia and

https://doi.org/10.1017/S0022215123001950

Table 14. Electromyographic data

Study	Intervention	Subjects (*n*)	Pre-operative TA (SD)	Post-operative TA (SD)	Pre-operative PCA (SD)	Post-operative PCA (SD)
Wang (2011)[15]	Ansa-RLN	209	1.81 (0.51)	0.26 (0.46)	–	–
Li (2013)[11]	SLR left phrenic	31 left	1.81 (0.83)	2.0 (0.45)	2.0 (0.77)	0.16 (0.37)
		31 right	1.9 (0.7)	2.06 (0.44)	2.0 (0.73)	0.42 (0.50)

SD = standard deviation; Ansa-RLN = ansa cervicalis to recurrent laryngeal nerve anastomosis; TA = thyroarytenoid; PCA = posterior cricoarytenoid; SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve

Table 15. Pulmonary function parameters

Study	Intervention(s)	Subjects (*n*)	Parameter	Pre-operative (SD)	Post-operative (SD)
Li (2013)[11]	SLR left phrenic	38	VC	2.64 (0.71)	3.30 (0.84)
			FVC	2.68 (0.74)	3.25 (0.80)
			FEV1	2.29 (0.66)	2.78 (0.69)
			PI_{max}	62.39 (14.89)	66.13 (11.29)
Li (2019)[13]	SLR phrenic and hypoglossal	7	VC	2.19 (0.22)	2.71 (0.34)
			FVC	2.14 (0.27)	2.74 (0.39)
			FEV_1	1.77 (0.33)	2.25 (0.23)
			PI_{max}	55.29 (13.56)	75.57 (7.09)

SD = standard deviation; SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve; VC = vital capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; PI_{max} = maximal inspiratory pressure

Strain rating score, laryngeal electromyography, pulmonary function tests and decannulation rates. For thyroid surgery or neck trauma, the left phrenic nerve was shown to improve several vocal function parameters and decannulation rates in 39 out of 44 patients without any posterior cricoarytenoid synkinesis. However, abnormal spontaneous activity was noted in the thyroarytenoid of the four failed patients.[11]

Voice and swallowing improvements were demonstrated without any significant vocal fold abduction in vagal paragangliomas using the phrenic nerve and ansa cervicalis.[23] The phrenic and a branch of hypoglossal nerve showed significant improvement in all parameters measured for six out of seven patients, with moderate electric potentials of the left interarytenoid in the failed patient.[13] The failure of vocal fold movement was likely due to moderate aberrant reinnervation. Importantly, this study showed mild aberrant reinnervation did not affect recovery of vocal fold movement. Another study using the phrenic nerve for selective reinnervation failed to produce any vocal fold abduction in three patients.[16]

Reinnervation of bilateral palsies is far more complex than that of unilateral ones, with limited evidence. The existing literature involves a small group of surgeons who have made further improvements to their techniques. For example, in 2013, Li *et al.*[11] explored the reinnervation of bilateral posterior cricoarytenoid using the left phrenic nerve and in 2019[13] anastomosed the phrenic-hypoglossal nerves. As a result, improvements in voice and swallowing function were observed less often for bilateral palsies. In addition, the complexity of selective reinnervation makes it more difficult for otolaryngologists to learn and undertake the techniques which pioneering surgeons such as Roger Crumley and Professor Marie have shown to be beneficial. Some experts have suggested that the developments made in selective reinnervation have potential for global dissemination.[2] Our review found many studies describing multidimensional voice outcome parameters, which will help support this suggestion. However, larger studies are required to improve the safety and feasibility of reinnervation. Unfortunately, it remains difficult to recruit subjects for a sufficiently powered RCT. A potential solution was identified from a feasibility RCT to include controls with multidimensional voice and swallowing outcomes.[37]

Significantly, non-selective reinnervation seeks to maintain effective glottic closure, thereby preserving voice quality, while selective reinnervation aims to restore normal inspiratory abduction. Consequently, the outcomes of these two techniques differ, suggesting the need to analyse them as distinct entities. Nonetheless, if studied separately, the lack of reliable primary data makes obtaining substantial findings unlikely. The present study serves the purpose of providing a valuable resource for otolaryngologists interested in this field and emphasises the need for well-designed prospective studies with proper controls.

Table 16. Decannulation rate

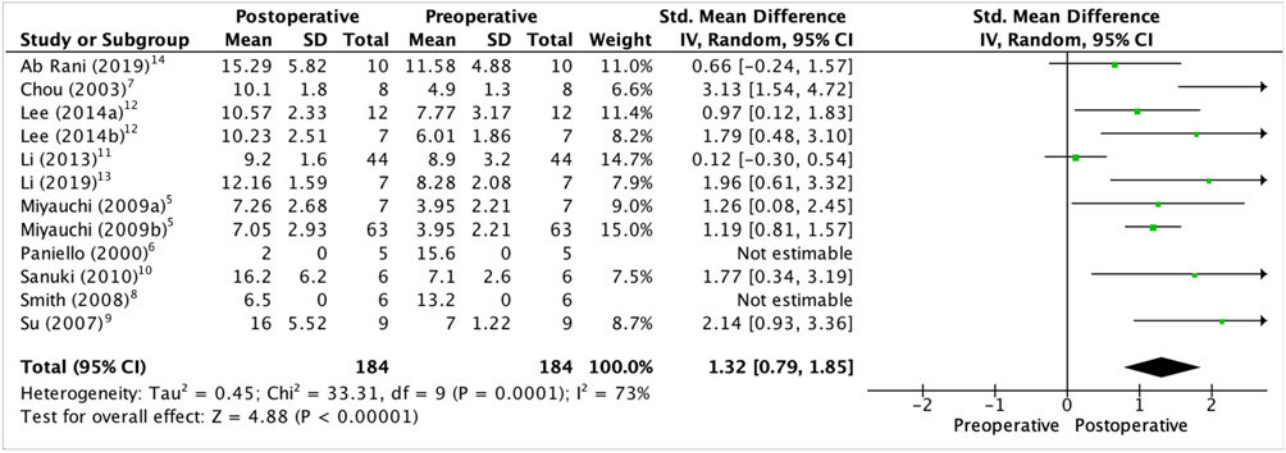
Study	Intervention	Subjects (*n*)	Decannulation rate (*n* (%))
Li (2013)[11]	SLR left phrenic	44	38 (87)
Li (2019)[13]	SLR phrenic and hypoglossal	7	6 (86)

SLR phrenic = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic nerve; SLR phrenic and hypoglossal = selective laryngeal reinnervation of bilateral posterior cricoarytenoid muscles with phrenic and branch of hypoglossal nerve

Limitations

Several limitations were identified in the study. Firstly, significant heterogeneity existed between the studies, including patient age, type and duration of paralysis, follow-up time,

https://doi.org/10.1017/S0022215123001950



Study or Subgroup	Postoperative Mean	Postoperative SD	Postoperative Total	Preoperative Mean	Preoperative SD	Preoperative Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ab Rani (2019)[14]	15.29	5.82	10	11.58	4.88	10	11.0%	0.66 [−0.24, 1.57]
Chou (2003)[7]	10.1	1.8	8	4.9	1.3	8	6.6%	3.13 [1.54, 4.72]
Lee (2014a)[12]	10.57	2.33	12	7.77	3.17	12	11.4%	0.97 [0.12, 1.83]
Lee (2014b)[12]	10.23	2.51	7	6.01	1.86	7	8.2%	1.79 [0.48, 3.10]
Li (2013)[11]	9.2	1.6	44	8.9	3.2	44	14.7%	0.12 [−0.30, 0.54]
Li (2019)[13]	12.16	1.59	7	8.28	2.08	7	7.9%	1.96 [0.61, 3.32]
Miyauchi (2009a)[5]	7.26	2.68	7	3.95	2.21	7	9.0%	1.26 [0.08, 2.45]
Miyauchi (2009b)[5]	7.05	2.93	63	3.95	2.21	63	15.0%	1.19 [0.81, 1.57]
Paniello (2000)[6]	2	0	5	15.6	0	5		Not estimable
Sanuki (2010)[10]	16.2	6.2	6	7.1	2.6	6	7.5%	1.77 [0.34, 3.19]
Smith (2008)[8]	6.5	0	6	13.2	0	6		Not estimable
Su (2007)[9]	16	5.52	9	7	1.22	9	8.7%	2.14 [0.93, 3.36]
Total (95% CI)			**184**			**184**	**100.0%**	**1.32 [0.79, 1.85]**

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 33.31$, df = 9 (P = 0.0001); $I^2 = 73\%$
Test for overall effect: Z = 4.88 (P < 0.00001)

Figure 2. Forest plot: a comparison of reinnervation studies that assessed the maximum phonation time values

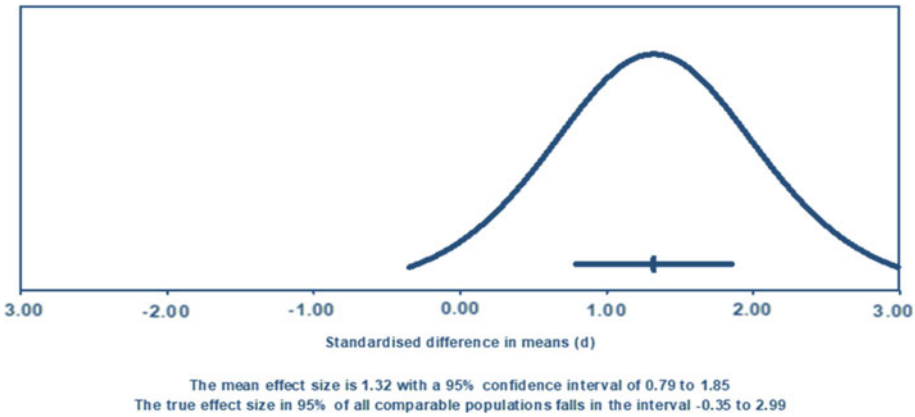


Figure 3. Distribution of true effects.
d = standardised difference in means

supplemental medialisation, surgeon's experience, outcomes measured and type of reinnervation. For example, we cannot clearly determine the effect of reinnervation when it is supplemented with augmentation. However, many agree that the effects of vocal fold augmentation are temporary and largely determined by the material used, with Restylane lasting for 6 months, fat for 12 months and calcium hydroxyapatite for 18 months.[38–41] As a result, the lack of consistency between studies makes it challenging to generalise findings. Secondly, some studies that investigated multiple reinnervation techniques did not differentiate outcomes for each. Three studies pooled pre- and post-operative data for ansa-RLN and primary RLN.[5,10,12] Two studies combined ansa-RLN and NMP data.[22,24] Furthermore, two studies pooled data for ansa-RLN and ansa-RLN + cricothyroid muscle-nerve-muscle neuromuscular pedicle.[12,17] This makes it impossible to attribute findings to one technique. Thirdly, as is generally the case, the review is limited by the quality of studies. Only one study[12] fulfilled all criteria for quality checks. Other studies had weaknesses in follow-up periods, data collection purposes and incomplete data. In addition, certain studies did not provide raw data and were excluded from quantitative synthesis. The authors were contacted to provide this information, but no response was received at the time of writing this paper.

Regression test for funnel plot asymmetry (Egger's test)

	z	p
sei	2.835	0.005

Figure 4. Egger's test. sei = standard error of the intercept

Conclusion

Based on the review of 803 adults, surgical reinnervation demonstrated improvements in both voice and swallowing for unilateral and bilateral palsies, with improvements in decannulation rates also observed for bilateral palsies. Our meta-analysis provides clinical evidence supporting the effectiveness of reinnervation. However, the lack of control groups in most studies prevented a clear determination of the true effect of reinnervation.

Despite significant advances in standardisation for measuring outcome parameters and reinnervation, our study identified several limitations, such as small sample sizes and highly heterogeneous studies, which limit the generalisability of our findings to the broader adult population. Although reinnervation techniques are considered safe and viable alternatives, particularly when other treatments have failed to address vocal fold palsies, larger studies with control groups and more precise recordings of each technique are necessary to accurately determine their true effects. This information will be critical in identifying the patients who would most benefit from these techniques and enabling global dissemination of improved reinnervation techniques.

Moreover, non-selective reinnervation aims to preserve glottic closure and voice quality, while selective reinnervation focuses on restoring inspiratory abduction. Analysing these techniques separately is necessary because of their differing

https://doi.org/10.1017/S0022215123001950

outcomes, but the lack of reliable data makes it challenging to obtain meaningful results. Our paper provides a valuable resource for otolaryngologists and highlights the importance of well-designed prospective studies.

Acknowledgements. The authors thank the librarians at Imperial College London, UK for their contribution to the systematic review search, notably Rebecca Jones.

Competing interests. None declared

References

1 Misono S, Merati AL. Evidence-based practice: evaluation and management of unilateral vocal fold paralysis. *Otolaryngol Clin North Am* 2012;**45**:1083–108
2 Fancello V, Nouraei SR, Heathcote KJ. Role of reinnervation in the management of recurrent laryngeal nerve injury: current state and advances. *Curr Opin Otolaryngol Head Neck Surg* 2017;**25**:480–5
3 IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;**6**:e010247
4 Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A *et al*. *OCEBM Levels of Evidence*. Oxford: Centre for Evidence-Based Medicine, University of Oxford, 2021
5 Miyauchi A, Inoue H, Tomoda C, Fukushima M, Kihara M, Higashiyama T *et al*. Improvement in phonation after reconstruction of the recurrent laryngeal nerve in patients with thyroid cancer invading the nerve. *Surgery* 2009;**146**:1056–62
6 Paniello RC. Laryngeal reinnervation with the hypoglossal nerve II. Clinical evaluation and early patient experience. *Laryngoscope* 2000;**110**:739–48
7 Chou F-F, Su C-Y, Jeng S-F, Hsu K-L, Lu K-Y. Neurorrhaphy of the recurrent laryngeal nerve. *J Am Coll Surg* 2003;**197**:52–7
8 Smith ME, Roy N, Stoddard K. Ansa-RLN reinnervation for unilateral vocal fold paralysis in adolescents and young adults. *Int J Pediatr Otorhinolaryngol* 2008;**72**:1311–16
9 Su W-F, Hsu Y-D, Chen H-C, Sheng H. Laryngeal reinnervation by ansa cervicalis nerve implantation for unilateral vocal cord paralysis in humans. *J Am Coll Surg* 2007;**204**:64–72
10 Sanuki T, Yumoto E, Minoda R, Kodama N. The role of immediate recurrent laryngeal nerve reconstruction for thyroid cancer surgery. *J Oncol* 2010;**2010**:846235
11 Li M, Chen S, Zheng H, Chen D, Zhu M, Wang W *et al*. Reinnervation of bilateral posterior cricoarytenoid muscles using the left phrenic nerve in patients with bilateral vocal fold paralysis. *PLoS One* 2013;**8**:e77233
12 Lee SW, Park KN, Oh SK, Jung C-H, Mok J-O, Kim C-H. Long-term efficacy of primary intraoperative recurrent laryngeal nerve reinnervation in the management of thyroidectomy-related unilateral vocal fold paralysis. *Acta Otolaryngol* 2014;**134**:1179–84
13 Li M, Zheng H, Chen S, Chen D, Zhu M. Selective reinnervation using phrenic nerve and hypoglossal nerve for bilateral vocal fold paralysis. *Laryngoscope* 2019;**129**:2669–73
14 Ab Rani A, Azman M, Ubaidah MA, Yunus MRM, Sani A, Baki MM. Nonselective laryngeal reinnervation versus type 1 thyroplasty in patients with unilateral vocal fold paralysis: a single tertiary centre experience. *J Voice* 2021;**35**:487–92
15 Wang W, Chen D, Chen S, Li D, Li M, Xia S *et al*. Laryngeal reinnervation using ansa cervicalis for thyroid surgery-related unilateral vocal fold paralysis: a long-term outcome analysis of 237 cases. *PLoS One* 2011;**6**:e19128
16 Candelo E, Borsetto D, Obholzer R, Clarke P, MatBaki M, Birchall M. Functional outcomes following delayed laryngeal reinnervation of patients with vagal paralysis after paraganglioma and schwannoma surgery. *J Voice* 2023;**37**:610–15
17 Lorenz RR, Esclamado RM, Teker AM, Strome M, Scharpf J, Hicks D *et al*. Ansa cervicalis-to-recurrent laryngeal nerve anastomosis for unilateral vocal fold paralysis: experience of a single institution. *Ann Otol Rhinol Laryngol* 2008;**117**:40–5
18 Lee WT, Milstein C, Hicks D, Akst LM, Esclamado RM. Results of ansa to recurrent laryngeal nerve reinnervation. *Otolaryngol Head Neck Surg* 2007;**136**:450–4
19 Crumley RL. Update: ansa cervicalis to recurrent laryngeal nerve anastomosis for unilateral laryngeal paralysis. *Laryngoscope* 1991;**101**:384–8
20 May M, Beery Q. Muscle-nerve pedicle laryngeal reinnervation. *Laryngoscope* 1986;**96**:1196–200
21 El-Kashlan HK, Carroll WR, Hogikyan ND, Chepeha DB, Kileny PR, Esclamado RM. Selective cricothyroid muscle reinnervation by muscle-nerve-muscle neurotization. *Arch Otolaryngol Head Neck Surg* 2001;**127**:1211–15
22 Buyukatalay ZC, Brisebois S, Sirin S, Merati AL. Does dysphagia improve following laryngeal reinnervation for treatment of hoarseness in unilateral vocal fold paralysis? *J Voice* 2021;**35**:307–11
23 Baki MM, Clarke P, Birchall M. Immediate selective laryngeal reinnervation in vagal paraganglioma patients. *J Laryngol Otol* 2018;**132**:846–51
24 Maronian N, Robinson L, Waugh P, Hillel A. Electromyographic findings in recurrent laryngeal nerve reinnervation. *Ann Otol Rhinol Laryngol* 2003;**112**:314–23
25 Mansor WNW, Azman M, Remli R, Yunus MRM, Baki MM. Primary nonselective laryngeal reinnervation in iatrogenic acute recurrent laryngeal nerve injury: case series and literature review. *Ear Nose Throat J* 2023;**102**:164–9
26 Olson DE, Goding GS, Michael DD. Acoustic and perceptual evaluation of laryngeal reinnervation by ansa cervicalis transfer. *Laryngoscope* 1998;**108**:1767–72
27 Zheng H, Li Z, Zhou S, Cuan Y, Wen W. Update: laryngeal reinnervation for unilateral vocal cord paralysis with the ansa cervicalis. *Laryngoscope* 1996;**106**:1522–7
28 Kodama N, Sanuki T, Kumai Y, Yumoto E. Long-term vocal outcomes of refined nerve-muscle pedicle flap implantation combined with arytenoid adduction. *Eur Arch Otorhinolaryngol* 2015;**272**:681–8
29 Wang W, Liu F, Zhang C, Li M, Chen S, Gao Y *et al*. Immediate ansa cervicalis-to-recurrent laryngeal nerve anastomosis for the management of recurrent laryngeal nerve infiltration by a differentiated thyroid carcinoma. *ORL J Otorhinolaryngol Relat Spec* 2020;**82**:93–105
30 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997;**315**:629–34
31 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;**54**:1046–55
32 Harrer M, Cuijpers P, Furukawa T, Ebert D. *Doing Meta-analysis with R: A Hands-on Guide*. Boca Raton, FL: Chapman and Hall/CRC, 2021
33 Rothstein HR, Sutton AJ, Borenstein M. *Publication bias in meta-analysis: Prevention, assessment and adjustments*. Chichester: Wiley, 2005;1–7
34 Bartoš F, Maier M, Quintana DS, Wagenmakers E-J. Adjusting for publication bias in JASP and R: selection models, PET-PEESE, and robust Bayesian meta-analysis. *Adv Methods Pract Psychol Sci* 2022;**5**
35 Yuan Q, Hou J, Liao Y, Zheng L, Wang K, Wu G. Selective vagus-recurrent laryngeal nerve anastomosis in thyroidectomy with cancer invasion or iatrogenic transection. *Langenbecks Arch Surg* 2020;**405**:461–8
36 Manni J. Laryngeal reinnervation with the hypoglossal nerve. *Laryngoscope* 2001;**111**:1113–14
37 Blackshaw H, Carding P, Jepson M, Baki MM, Ambler G, Schilder A *et al*. Does laryngeal reinnervation or type I thyroplasty give better voice results for patients with unilateral vocal fold paralysis (VOCALIST): study protocol for a feasibility randomised controlled trial. *BMJ Open* 2017;**7**:e016871
38 Lagier A, Polle-Pelletier V, Giovanni A, Marie J. Vocal fold medialization: which are the available fillers in France in 2010. *Eur Ann Otorhinolaryngol Head Neck Dis* 2011;**128**:99–101
39 Laccourreye O, Papon JF, Kania R, Crevier-Buchman L, Brasnu D, Hans S. Intracordal injection of autologous fat in patients with unilateral laryngeal nerve paralysis: long-term results from the patient's perspective. *Laryngoscope* 2003;**113**:541–5
40 Mallur PS, Rosen CA. Vocal fold injection: review of indications, techniques, and materials for augmentation. *Clin Exp Otorhinolaryngol* 2010;**3**:177–82
41 Zeleník K, Walderová R, Kučová H, Jančatová D, Komínek P. Comparison of long-term voice outcomes after vocal fold augmentation using autologous fat injection by direct microlaryngoscopy versus office-based calcium hydroxylapatite injection. *Eur Arch Otorhinolaryngol* 2017;**274**:3147–51

https://doi.org/10.1017/S0022215123001950

Appendix 1. Ovid search terms

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to October 07, 2022>

1 exp Laryngeal Nerves/ or laryngeal.mp. 75529
2 Vocal Cords/ or vocal cord*.mp. 20734
3 vocal fold*.mp. 8057
4 vocal ligament*.mp. 136
5 1 or 2 or 3 or 4 86115
6 reinnervat*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 7094
7 re innervat*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 658
8 6 or 7 7694
9 5 and 8565
10 exp animals/ not humans.sh. 5052892
11 9 not 10 337

10/10/22

Appendix 2. Embase search terms

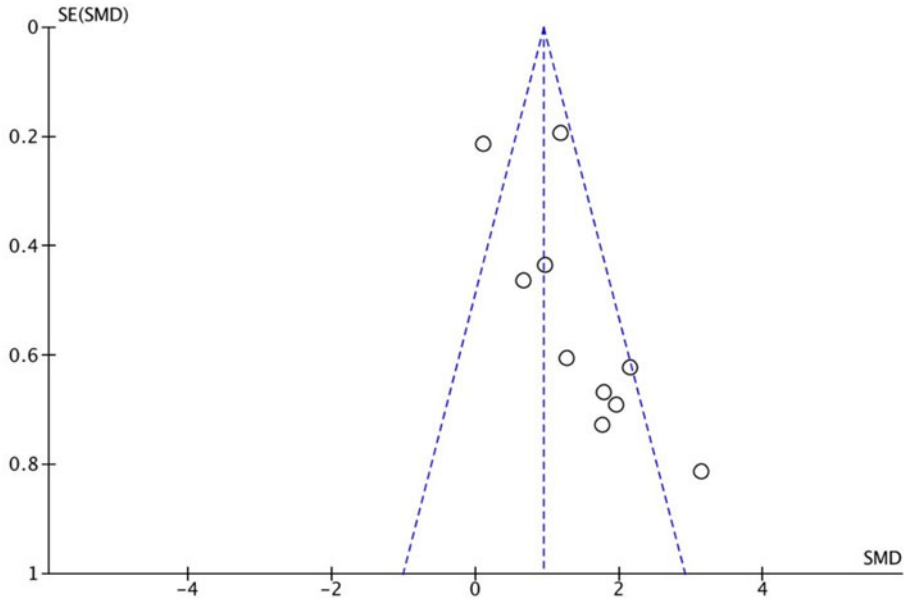
Embase Classic+Embase <1947 to 2022 Week 40>

1 laryngeal.mp. or recurrent laryngeal nerve injury/ 90320
2 vocal cord*.mp. or vocal cord/ 31703
3 vocal fold*.mp. 9576
4 vocal ligament*.mp. 180
5 1 or 2 or 3 or 4 110715
6 exp reinnervation/ 5869
7 reinnervat*.mp. 10187
8 re innervat*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 995
9 6 or 7 or 8 10789
10 5 and 9742
11 (exp animal/ or nonhuman/) not exp human/ 7694473
12 10 not 11 464

date 10/10/22

https://doi.org/10.1017/S0022215123001950

Appendix 3. Funnel plot for meta-analysis of maximum phonation time



SE = standard error; SMD = standardised mean difference

https://doi.org/10.1017/S0022215123001950