European Archives of Oto-Rhino-Laryngology (2019) 276:2649–2659
https://doi.org/10.1007/s00405-019-05587-2

REVIEW ARTICLE

# The surgical treatment of unilateral vocal cord paralysis (UVCP): qualitative review analysis and meta-analysis study

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Received: 9 April 2019 / Accepted: 27 July 2019 / Published online: 2 August 2019


## Abstract

**Purpose** The objectives of this meta-analysis were to summarize the key surgical procedures for UVCP and to evaluate which of these is associated with better results in terms of vocal improvement.

**Methods** A systematic review of the literature was conducted in search of articles focused on the comparison of voice outcome between different techniques for the UVCP treatment. Then, a quantitative analysis was carried out for papers published from 2013 onwards, reporting only adult patients with unilateral paralysis for each study, and each surgical technique was evaluated for its capability of achieving good functional outcomes in terms of GRBAS-I scale and maximum phonation time in seconds (MPT).

**Results** The search identified 1853 publications. A total of 159 articles were stratified and included according to our selection criteria. 21 out of 159 articles were selected for quantitative synthesis. For trans-oral techniques: the mean GRBAS-I scale were 2.33 before injection and 0.41 after injection. The mean MPT before injection were 4.78 and 12.50 after injection. For open techniques the mean GRBAS-I scale were 2.43 before surgery and 0.68 after surgery. For open technique, the mean MPT were 3.50 before surgery and 12.40 after surgery.

**Conclusions** The two types of techniques lead to an improvement in terms of vocal outcomes emphasizing that from the examined literature an indication emerges to perform an early injection because this could reduce the possible need for a more invasive intervention of permanent medialization in the future.

**Keywords** Laryngeal paralysis · Injection laryngoplasty · Thyroplasty · Meta-analysis · Systematic review

## Introduction

Unilateral vocal cord paralysis is defined as the complete immobility of one vocal fold occurring as a consequence of recurrent laryngeal nerve (RLN) injury. This condition potentially leads to severe morbidities including dysphonia, dysphagia and aspiration, and several causes have been attributed to its appearance so far, whereas its etiology has shown changing trends from place-to-place and over time [1]. The most common causes of damage to the RLN include iatrogenic injuries (e.g., thyroid, thoracic and cardiac surgery), malignant neoplastic nerve invasion and idiopathic nerve impairment. Since the 1970s, papers have been reporting that the main causes of UVCP were malignancies (prevalence 25.2–38.1%, including lung neoplasms in 8.7–22.4% of the cases), followed by surgery (10.4–24.4%, with thyroid surgery accounting for 3.7–19.8% of the cases), and idiopathic causes (up to 26.8%) [2]. This trend has been

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00405-019-05587-2) contains supplementary material, which is available to authorized users.

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described up to the first half of the 1990s [3], whilst since the 1995–2005 decade, an increased prevalence of post-surgical cases of UVCP (47.8–51.2%, including 14.1–21.1% after thyroid surgery) has been observed, followed by malignancies (9.9–21.6%, including lung neoplasms in about 6.3% of cases), and idiopathic causes (16.8–17.6%) have been reported in the literature [4, 5]. On the basis of these findings, it seems that over time, there have been a decrease in prevalence of malignant neoplasms causing UVCP (mainly due to a progressive reduction in the occurrence of lung cancer) and a progressive increase in cases attributable to thyroid surgery [6, 7].

In addition, the literature has showed the preponderance of the left side vocal fold paralysis, made more vulnerable to injuries by its anatomy and length. Data relating to these findings date back to the 40s [5, 8].

Patients suffering from UVCP typically complain symptoms as voice changes, hoarseness and swallowing disorder. In this setting, the primary symptom is usually represented by dysphonia. The prevalence of voice disorders in the general population is 6.6% [9] and the incidence of UVCP among patients with voice disorders has been calculated to be at 1.2% [10]. Thus, dysphonia is a constant symptom during UVCP, and its intensity can range from mild dysphonia to whispered voice with breathlessness. Dysphagia incidence is estimated to be about 30% in patients diagnosed with UVCP, and it varies according to the etiology and the topography of the paralysis, it can manifest itself with simple episode of coughing during swallowing of liquids, or in the most serious cases, become the main cause for pneumonia. The third main symptom that might occur in case of UVCP is dyspnoea. This is a rare condition, and less than 3% of patients complain about it. It becomes a big concern in case of bilateral vocal cord paralysis.

Effective management of UVCP requires accurate diagnostic and prognostic information to develop a clear therapeutic approach, always taking into account the needs and lifestyle of patients and the real stated goals of intervention. In fact, after the onset of the UVCP, a variable degree of RLN restoration can occur during the next 6–12 months, depending on the severity of nerve damage which can range from temporary neuropraxia to complete neural disruption. For these reasons, many authors do not recommend early surgical options, to allow for spontaneous recovery, and they endorse observation, speech therapy or temporary injection laryngoplasty during this waiting period [11]. A number of factors are likely to influence treatment selection, including onset of injury, cause, degree of glottal insufficiency, severity of dysphonia and prognosis. There are also other factors that can influence the choice of treatment, such as: patient's age, co-morbidity, patient's expectation, treatment facility, clinicians' knowledge and skills and equipment availability. Usually, the surgical approach, either with injection augmentation of the vocal fold or laryngeal framework surgery, is indicated after a watchful waiting period of about 9–12 months and/or speech therapy (voice) exercises, to restore voice outcomes and improve glottic competence. In this perspective, a wide variety of surgical approaches are available in clinical practice, including medialization thyroplasty (MT), injection laryngoplasty (IL), arytenoid adduction (AA) and laryngeal reinnervation (LR) [12–14].

The efficacy of different therapeutic procedures is generally assessed by objective endoscopic and stroboscopic evaluation and by comparing significant changes in pre-operative and post-operative voice outcome indicators (VOIs). These parameters include both self-perception questionnaire results, as for voice handicap Index (VHI) [15] and CAPE-V [16], the GRBAS-I scale, and objective measures, such as maximum phonation time (MPT), jitter, shimmer, mean air flow (MeAF) fundamental frequency (F0), noise-to-harmonic ratio (NHR/HNR) [17].

The surgical treatment of vocal cord paralysis should be appropriate and tailored to the clinical conditions and needs of each patient. Unfortunately, it is not uncommon for different surgeons to use different nomenclature or different techniques for the same clinical condition. This obviously makes evaluation and comparison among specialists' indications difficult, and it does affect the treatment, in its timing and outcomes. To make this inter-observer variability as much lower as possible, attempts should be made to improve patients' selections and to address surgical indications based on prognostic and predictive factors for post-operative results. Accordingly, the objectives of this systematic review and meta-analysis were to synthesize the key surgical management for unilateral vocal cord paralysis through a review of the latest advances in surgical indications and techniques published over the past 5 years. We attempted to provide a review of the surgical treatment options to manage UVCP, available in clinic practice and the literature, to provide a comprehensive overview of the most recent advances in the treatment of this pathological condition.

## Materials and methods

The systematic review was performed using independently developed search strategies in the literature review methodology, and it was written in accordance with PRISMA Statement (https://www.prisma-statement.org), to guarantee a scientific strategy of research to limit bias by a systematic assembly, critical appraisal and synthesis of all the most relevant studies published on this topic.

The databases interrogated included PubMed Clinical Queries https://www.ncbi.nlm.nih.gov. Reference lists from the identified articles were searched and

cross-referenced to identify additional relevant articles, and national experts in the field were contacted to identify unpublished data.

The search terms included the following various combinations to maximize the yield: unilateral vocal fold paralysis AND treatment; AND laryngeal injection; AND medialization thyroplasty; AND laryngeal implant; AND arytenoid adduction; AND re-innervation; AND voice outcome indicators.

The search was performed for the first time on January 2018 and was set to be automatically updated on a periodical basis until May 2018.

First, duplicates were removed electronically. Then, abstracts were reviewed to exclude obviously irrelevant articles. Non-English language papers and duplicates were excluded. Experimental studies and papers dealing with pathologies other than unilateral vocal fold paralysis were excluded.

The inclusion criteria were set a priori and deliberately kept wide to encompass as many articles as possible without compromising the validity of the results, and they included the following: (1) articles published from 2013 onwards, (2) subjects of 18 years of age or older, (3) the major topic must be a comparison of outcome between different techniques for UVCP treatment, (4) these surgical treatments: laryngeal injection, thyroplasty type I, arytenoid adduction, laryngeal reinnervation, vox implant, thyroplasty I + IV, cricothyroid subluxation, laryngeal reinnervation, (5) a clear description of selection criteria, (6) reporting published series of at least 5 patients.

The search excluded articles concerning UVCP due to vagal nerve injury. This work focused on the analysis of data from the most recent studies (2013 onwards) which were based, on robust and validated data, on the above-mentioned strength-consolidated techniques.

All data were independently extracted by the two authors and quality assessed. Eligibility for inclusion was separately evaluated and—in case of doubts—discussed and decided by consensus.

Abstracts were analyzed to identify papers that fulfilled inclusion criteria and a first qualitative and descriptive review analysis of selected articles was carried out.

A first qualitative and descriptive review analysis of selected articles was carried out, and exclusively publications comparing surgical treatments in terms of post-surgical vocal outcomes improvement were included in our meta-analysis.

For articles not reporting raw data, letters were sent to the corresponding authors requesting them, otherwise they were excluded from the quantitative analysis. Raw data from the meta-analysis were entered into the appropriate contingency tables to allow calculation of GRBAS-I scale and MPT, Younden's index, for each surgical technique.

## Study characteristics and quality assessment

All papers included were graded using the NICE scoring scale for retrospective case series (available at: https://www.nice.org.uk/nicemedia/pdf/Appendix_04_qualityofcase_series_form_preop.pdf). This is a scoring scale with eight items, with each item scoring zero or one based on the study methods (Yes = 1; No = 0). Scores ≥ 6 are considered to indicate a good-quality study, scores between four and five indicate fair and those studies with a score of three are treated as poor quality (Table 1).

## Statistical analysis

Categorical variables were calculated in terms of frequencies and percentages, median, mean and standard deviation (SD) values, and confidence interval (CI) 95%. Fisher's exact test was used for statistical analysis of categorical data for the descriptive review, and a value of $p < 0.05$ was considered significant.

Data were entered into Microsoft Excel (Microsoft Corporation, One Microsoft Way Redmond, WA, 98052-6399) and all statistical analyses were performed using statistical package R version 2.9 (The R Foundation for Statistical Computing, Vienna, Austria).

**Table 1** Quality assessment

| | Quality assessment |
|---|---|
| 1. | Case series collected in more than 1 center |
| 2. | Is the hypothesis/aim/objective of the study clearly described? |
| 3. | Are the inclusion and exclusion criteria (case definition) clearly reported? |
| 4. | Is there a clear definition of the outcome reported? |
| 5. | Were data collected prospectively? |
| 6. | Is there an explicit statement that patients were recruited consecutively? |
| 7. | Are the main findings of the study clearly described? |
| 8. | Are outcomes stratified (i.e., by disease stage, abnormal test result, patient characteristics)? |

Average values of pre-operative and post-operative GRBAS-I scale and MPT were obtained through random effects meta-analyses.

Heterogeneity (or absence of homogeneity) of the results between the studies was assessed graphically by forest plots and statistically using the quantity $I^2$ that describes the percentage of total variation across studies that is attributable to heterogeneity rather than chance.

## Results

### Population characteristics

The search strategy identified 1853 articles in Medline from 1950s to the search date. 408 articles published after the 2013 were selected, imported into Endnote, and the duplicates were removed. The removal of duplicates, non-English language works and articles about other items rather than unilateral vocal fold paralysis yielded a total of 159 publications. These publications were considered for the qualitative systematic review of the literature and only 20 out of 159 were included in the meta-analysis.

The various stages of systematically assessing the abstracts and reasons for exclusion from the review are described in Fig. 1.

Eight out of 20 studies (38%) were prospective [18–25], the remaining 12 studies were retrospective (62%), and only 3 articles reported multicentric studies [26–37]. The vast majority of the articles described one surgical technique outcomes, whilst some of them evaluated more than one type of procedure to correct UVCP. Sample sizes ranged from 5 to 85 patients. According to surgical procedures, five studies evaluated open surgical techniques, whereas injection techniques were described in all the included articles.

The 20 studies selected described a total of 723 patients, of whom 675 underwent trans-oral vocal cord injection (Group I) and the remaining 48 patients had definitive laryngeal framework open surgery (Group II). Group I patients had trans-oral injection by different materials: hyaluronic acid (43%), autologous fat (16%), Radiesse or calcium hydroxylapatite (23%), animal collagen such as Gelfoam, Surgifoam, Zyplast and Zyderm (20%) (Supplementary Table 1).

Etiological categories of UVCP included: idiopathic cause (22%), post-thyroid surgery (19%), other type of surgery (21%), malignant nerve infiltration (16%), other causes (e.g., trauma, prolonged intubation, radiation therapy, etc.) (22%).

Symptoms associated with UVCP were dysphonia (76%), followed by aspiration (14%), while dysphagia was reported in one article only. The main VOIs analyzed were represented by MPT (48%), GRBAS-I scale (38%), VHI (38%), and Shimmer/Jitter (38%). Laryngeal electromyography (LEMG) and the related measurements were used only in 3 studies out of the 21 studies analyzed in the aggregate (14%) [18, 20, 31].

The UVCP surgical procedures described included: vocal cord medialization or type 1 thyroplasty (ML) (23.8%), arytenoid adduction (AA) (4.7%), usually combined with ML, injective laryngoplasty (IL) (76%), generally combined with ML.

The study duration and follow-up varied significantly. The average follow-up time ranged from 1 to 24 months (mean $9.729 \pm 7.056$ SD).

### VOI comparison

Reported voice outcome indicators of each selected study are shown in Table 2.

*Group I* These results referred to a pool of 675 patients with a mean GRBAS-I scale value of $2.33 \pm 1.134$ SD (95% CI 2.09–2.57, median 2.25) pre-operatively, and of $0.41 \pm 0.3847$ (95% CI 0.32–0.51, median 0.3) post-operatively. Regarding MPT, the mean value was $4.78 \pm 2.5523$ SD (95% CI 4.15–5.40, median 4.20) pre-operatively, and $12.50 \pm 6.8060$ SD (95% CI 10.56–14.44, median 10.6) post-operatively (Table 3) (Fig. 2).

Variations of GRBAS-I scale and MPT obtained with different types of material are shown in Fig. 3. *Group II* These results referred to a pool of 48 patients. The mean value of pre-operative GRBAS-I scale was $2.43 \pm 0.288$ SD (95% CI 2.203–2.83, median 2.7) and $0.68 \pm 0.046$ (95% CI 0.34–1.01, median 11) post-operatively. Pre-operative MPT mean value was $3.50 \pm 1.565$ (95% CI 1.95–5.05 median 2.07) and $12.40 \pm 0.378$ (95% CI 10.42–14.38, median 11.3) post-operatively (Table 4) (Fig. 4).

Table 5 shows the comparison in terms of GRBAS-I scale and MPT between open and trans-oral procedures.

## Discussion

The purpose of this systematic review and meta-analysis was to compare the interventional treatment approaches for the treatment of UVCPs in terms of vocal outcomes.

The principle behind the surgery of unilateral laryngeal paralysis is the medialization of the paralytic vocal cord to restore the correct coping of the vocal cords during phonation and rehabilitating the swallowing sphincter.

UVCP is a common condition the head and neck surgeon must cope with. The first key point emerging from our literature review was a changing etiology trend, according to the results reported in the literature. Cantarella et al. [6] compared two cohorts of patients suffering from UVCP treated between 1990–1992 and 2013–2015

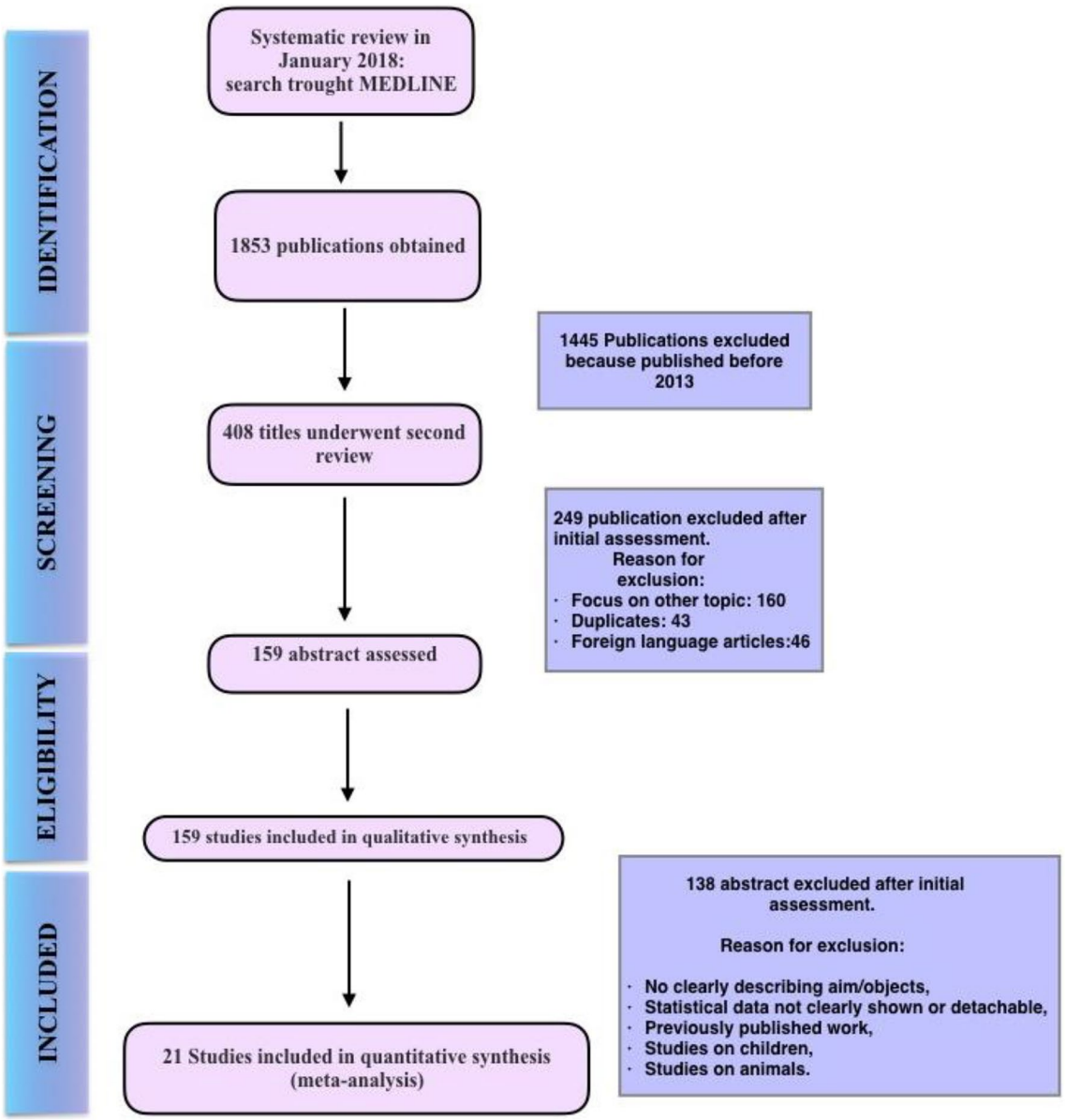


**Fig. 1** Flowchart of article selection

providing evidence of decrease in the post-thyroidectomy incidence and a predominance of idiopathic and post-thoracic surgery UVCP, despite an increase in the number of thyroidectomies throughout the years. In our opinion, the emerging lower rate of post-thyroidectomy paralysis might be related to the progressively routine use of intraoperative nerve monitoring (IONM) by most of the surgeons. In fact, in accordance with the literature, even though RLN visualization is still broadly considered the standard of care, nerve monitoring it may help guide the surgeon in high-risk cases, particularly in the re-operative setting, or provide benefit depending on individual surgeon's comfort level with technology [38].

In clinical setting, the primary symptom of UVCP is dysphonia, showing various degrees ranging from mild dysphonia or whispered voice with breathlessness to classical diplophony. The prevalence of voice disorders in the general population is 6.6% [9] and UVCP accounts for 1.2% [10]. Swallowing disorders associated therewith are estimated at 30%, while symptomatic dyspnea is rare (< 5%).

Examination with flexible laryngoscopy remains the gold standard for the diagnosis of vocal cord impaired motility, even though the use of quantitative characterization of the vibratory pattern by videostroboscopy represents a useful complement in the diagnostic work-up. According to Woo and colleagues, objective measurements of vocal fold

**Table 2** GRBAS-I scale and MPT: pre-operative and post-operative

| References | Quality score | N. of pz | G of GRBAS-I scale pre-op | MPT pre-op | G of GRBAS-I scale post-op | MPT post-op |
|---|---|---|---|---|---|---|
| Verma [26] | 2 | 57 | 2.7 ± 0.67 | – | 0.2 ± 0.21 | – |
| Jamal [27] | 4 | 76 | 2.7 ± 0.78 | – | 0.3 ± 0.11 | – |
| Pei [19] | 6 | 85 | 2.7 ± 0.45 | – | 0.4 ± 0.12 | – |
| Wen [26] | 6 | 60 | – | 5.2 ± 1.7 | – | 10.09 |
| Wang [16] | 5 | 44 | 2.0 ± 0.33 | 5.01 ± 0.98 | 0.4 ± 0.01 | 13.8 (7.7) |
| Mohammed [17] | 6 | 43 | 2.1 ± 0.45 | – | 0.3 ± 0.09 | – |
| Fang [18] | 6 | 34 | – | 4.69 ± 1.2 | – | 8.31 ± 3.50 |
| Lodder [27] | 5 | 31 | 2.2 ± 0.22 | – | 0.3 ± 0.04 | – |
| Gotxi-Erezuma [29] | 6 | 28 | 2.15 ± 0.36 | 6.07 ± 1.09 | 0.21 ± 0.1 | 12.75 ± 4.12 |
| Zelenik [28] | 6 | 20 | – | 3.06 ± 1.34 | – | 11.8 ± 3.11 |
| McLaughlin [35] | 6 | 47 | 2.8 ± 0.87 | – | 0.5 ± 0.1 | – |
| Pagano [30] | 4 | 18 | 2.3 ± 0.9 | 4 .93 ± 6.6 | 0.2 ± 0.09 | 10.05 ± 4.97 |
| Elbadan [31] | 5 | 16 | – | 4.5 ± 1.9 | – | 18.12 ± 2.35 |
| Sielska-Badurek [21] | 4 | 14 | 2.5 ± 0.4 | 6.03 ± 1.52 | 0.9 ± 0.2 | 14.05 ± 3.88 |
| Pei [20] | 6 | 14 | – | 3.03 ± 1.4 | – | 10.3 ± 4.1 |
| Lin [32] | 5 | 23 | 2.3 ± 0.21 | – | 0.5 ± 0.3 | – |
| Cantillo-Banos [33] | 4 | 21 | 2.8 ± 0.67 | – | 1 ± 0.2 | – |
| Tsou [23] | 3 | 9 | 2.02 ± 0.39 | 5.04 ± 1.91 | 1.02 ± 0.28 | 15.72 ± 8.14 |
| Hamdan [36] | 4 | 6 | 2.8 ± 0,64 | – | 1.16 ± 0.18 | – |
| Caffier [24] | 6 | 5 | 2.8 ± 0.8 | – | 0.2 ± 0.12 | - |

**Table 3** Trans-oral technique: GRBAS-I scale and MPT (s) mean value

| | Pre-operative | Confidence interval | $I^2$ (%) | Post-operative | Confidence interval | $I^2$ (%) |
|---|---|---|---|---|---|---|
| GRBAS-I scale | 2.33 | [2.09; 2.57] | 0.1 | 0.41 | [0.32; 0.51] | 0.1 |
| MPT | 4.78 | [4.15; 5.40] | 38.1 | 12.50 | [10.56; 14.44] | 77.8 |

vibration led to a change in the diagnosis and treatment in 10–30% of cases, by revealing residual mobility or fixation of the cord not otherwise visible [39].

Furthermore, several authors [18, 40] acknowledged the use of laryngeal electromyography (LEMG) that shows PPV ranging from 88.2 to 97.9% in predicting permanent RLN damage when the examination of both thyro-arytenoid muscle and posterior crico-arytenoid muscle was performed [41].

Our meta-analysis underlines as main point the lack of consensus statement about the treatment at the time of diagnosis. Many otolaryngologists defer early interventional approaches to allow for spontaneous recovery within the first year to avoid invasive procedures on patients who otherwise would have improved without any surgical treatment [42]. However, further surgery may be necessary in case they do not recover spontaneously, known iatrogenic nerve transection and when symptoms like aspiration or debilitating dysphonia are present [43].

On the other hand, several studies suggest that IL improves symptoms compared with speech therapy and observation during this waiting period. Furthermore, it was documented that, in case of earlier medialization occurring by injection, it was less likely for patients to undergo definitive surgery compared to patients who had been treated with conservative treatment alone or who had delayed treatment after 6 months [44–46]. Vila et al. confirmed this finding in a recent meta-analysis showing that patients who did not receive early injection laryngoplasty (< 6 months) were four times more likely to subsequently undergo thyroplasty [46]. The mechanism whereby early-IL improves symptomatic recovery is still a matter of debate. One hypothesis [47] is that temporary medialization during synkinetic reinnervation may promote a more favorable vocal cord position.

Regarding vocal outcomes, Siu et al. systematically reviewed the current literature showing no definitive evidence suggesting the superiority of any technique on acoustic parameters according to our results [43].

It must be underlined that the interpretation of the pooled dataset may lead to bias due to various factors. First, there was a heterogeneity in pre-operative patient populations,

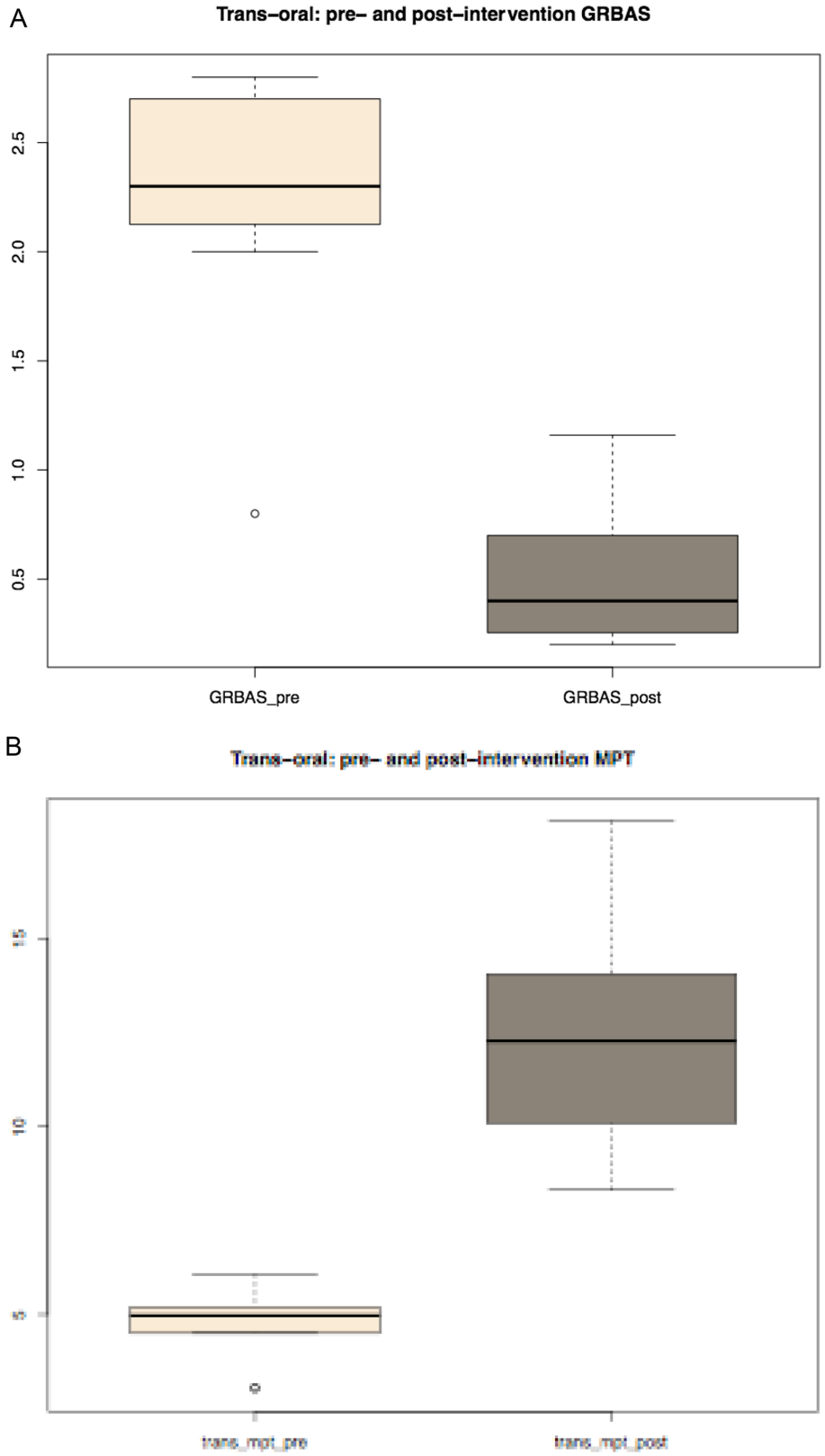


**Fig. 2** Trans-oral procedures: **a** pre- and post-operative GRBAS-I scale; and **b** pre- and post-operative MPT (s)

choice of combined surgical procedure and overall length of mean follow-up. In our review, the waiting period until the last post-operative voice outcome analysis ranges from 6 to 24 months among the selected studies. For this reason, no differences about short- and long-term results on voice outcome can be observed in the existing literature between

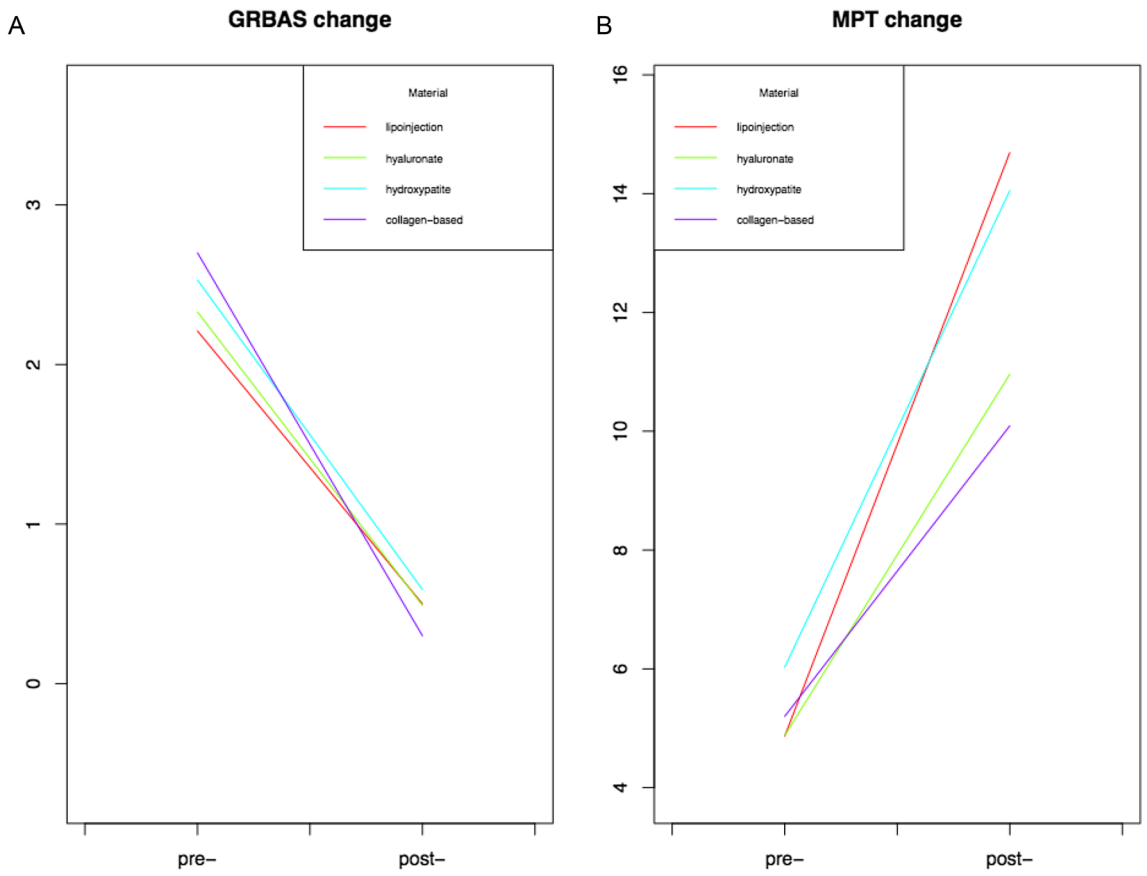


**Fig. 3** Comparison between pre- and post-operative **a** GRBAS-I scale and **b** MPT (s) changes obtained with different injection materials

**Table 4** Open procedures: GRBAS-I scale and MPT (s) mean value

| | Pre-operative | Confidence Interval | $I^2$ (%) | Post-operative | Confidence interval | $I^2$ (%) |
|---|---|---|---|---|---|---|
| GRBAS-I scale | 2.43 | [2.03; 2.83] | 0.1 | 0.68 | [0.34;1.01] | 40.2 |
| MPT[a] | 3.50 | [1.95; 5.05] | – | 12.40 | [10.42;14.38] | – |

[a]The pre- and post-operative MPT mean values actually coincide with the results of Hassan (2014), this being the only article to report them

IL and ML, representing the two main surgical options for UVCP.

In addition, comparison of VOIs between different studies is challenging due to the lack of standardization in outcome measures. In our opinion, this represents the main limit of our meta-analysis.

To establish a consensus on the choice of voice outcome indicators, Desuter et al. performed a literature review to identify the most relevant ones in terms of significant changes in pre- and post-operative measurements to assess UVCP surgical treatments. Among the nine VOIs analyzed, the results indicate that MPT, MeAF and GRBAS-I scale showed the highest percentage of significance (> 80%) [17].

For the same reason, Mattei et al. elaborated a protocol during 2017 IFOS Ent World Congress that represents an implementation of De Jonckere protocol defrayed by the European Laryngological Society (ELS). This international consensus statement on basic voice assessment for UVCP recommended the systematic use of VHI, Hiram's GRB scale and MPT [48, 49].

## Conclusions

This review was performed to compare the main surgical approaches available for UVCP in terms of VOIs. As in the current literature, the results of our meta-analysis did

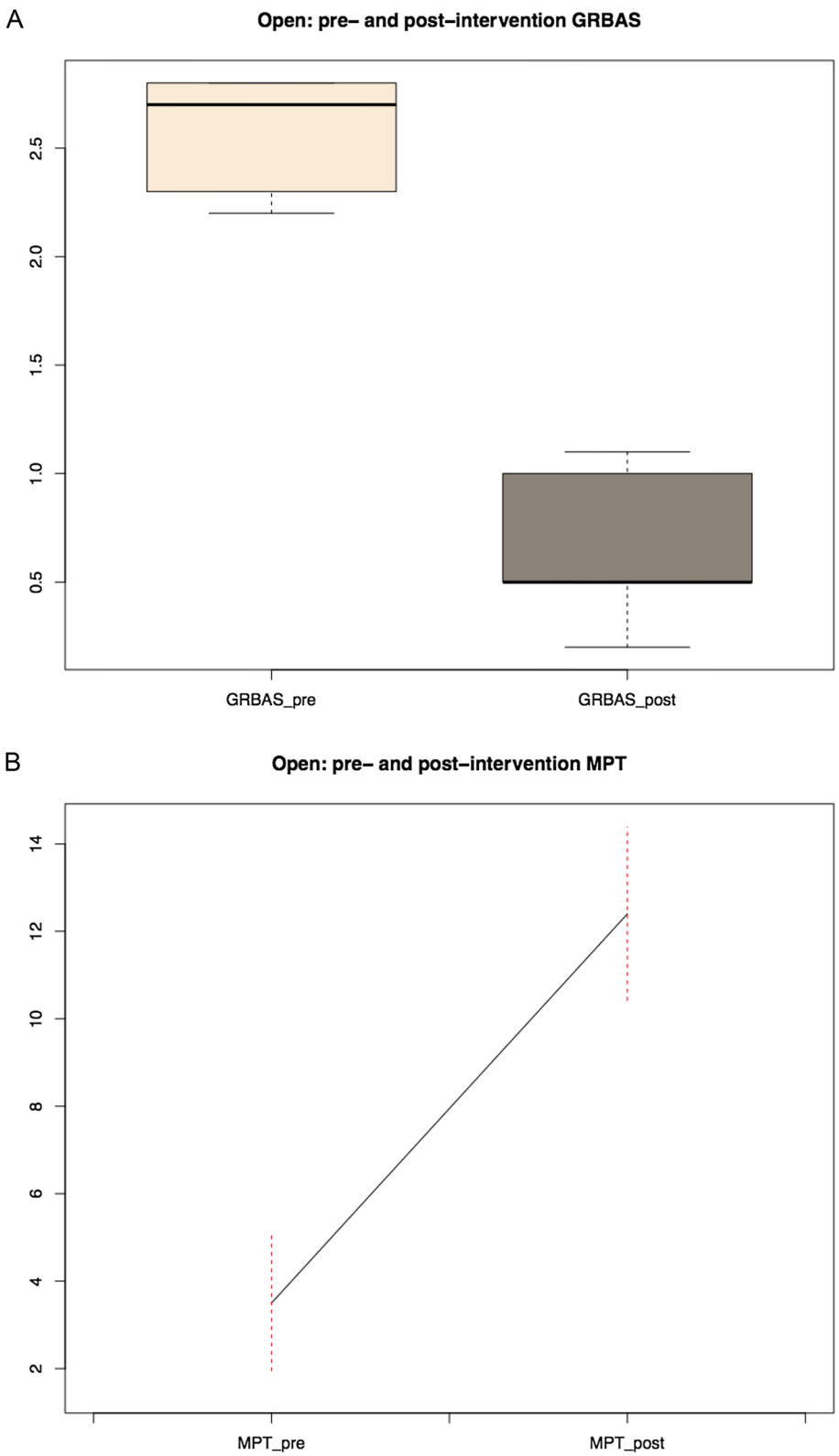


**Fig. 4** Open procedures: pre- and post-operative GRBAS-I scale and MPT (s)

not support the superiority of one technique over the other, showing comparable data between framework surgery and less invasive techniques. In addition, the lack of agreement about the correct timing for intervention remains a critical issue. In our opinion, a wait-and-see approach should be considered only for patients not suitable for any kind of procedure because of comorbidities. In any other case, early medialization with temporary materials should be

**Table 5** Comparison between trans-oral and open procedures: GRBAS-I scale and MPT (seconds) mean value

| | GRBAS | Nr. art | MPT | Nr. art |
|---|---|---|---|---|
| Open | − 1.75 | 5 | 8.90 | 1 |
| Trans-oral | − 1.92 | 15 | 7.72 | 10 |

considered as the first option to restore vocal cord copy and voice and mainly to avoid late invasive procedure.

We underline that the main limit of our study consists of the absence of consensus about voice outcome index and duration of follow-up.

In conclusion, further discussion is needed to establish a consensus statement about time of intervention, VOIs and follow-up.

**Author contributions** All persons designated as the authors have participated sufficiently in the work to take public responsibility for the content of the manuscript. All the authors ensure that they all gave substantial contributions: (1) to conception and design or analysis and interpretation of data (2) drafting of the manuscript or revising it for important intellectual content and (3) for final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Funding** None.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest. This work is a meta-analysis review and no new original data have been analyzed.

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