Cochlear Implantation for Treatment of Tinnitus in Single-sided Deafness: A Systematic Review and Meta-analysis

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Objective: Quantify the benefit of cochlear implantation (CI) for tinnitus relief among individuals with single-sided deafness (SSD).

Data Sources: PubMed, Scopus, and Cochrane databases were searched through July 10, 2019. Search strategies used a combination of subject headings (e.g., MeSH in PubMed) and keywords for the following three concepts: single-sided deafness, cochlear implantation, and tinnitus.

Study Selection: English articles that reported the preintervention (baseline) tinnitus-related patient-reported outcome measures (e.g., Tinnitus Handicap Inventory [THI] and Visual Analog Scale [VAS] for loudness) in patients with SSD that underwent CI were included.

Data Extraction: Number of patients, mean age, etiology of hearing loss, duration of deafness, baseline and follow-up THI and VAS scores.

Data Synthesis: A total of 17 studies met inclusion criteria encompassing 247 patients with SSD receiving a cochlear implant (mean age 50.2 yr, range 23–71). For THI, CI resulted in a mean difference of −35.4 points [95% CI −55.8 to −15.0, $p < 0.001$]. VAS decreased by −4.6 points [CI −6.0 to −3.3, $p < 0.001$]. A weighted proportion of 14.9% [CI 6.4–26.1] of patients experienced complete resolution of tinnitus, while 74.5% [CI 63.1–84.5] experienced partial improvement; 7.6% [CI 4.1–12.6] of patients had no change in severity, and 3.0% [CI 1.0–6.7] experienced worsening of their tinnitus.

Conclusions: On both THI and VAS, patients reported significant reduction in their scores, representing an overall improvement in tinnitus severity while wearing the cochlear implant. Most patients with SSD will experience partial improvement or complete resolution of tinnitus with a cochlear implant. **Key Words:** Asymmetric hearing loss—Cochlear implant—Patient-reported outcome measures—Ringing—Single-sided deafness—Tinnitus—Unilateral deafness.

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Single-sided deafness (SSD) is a debilitating condition resulting in reduced sound localization, poor speech comprehension (in both quiet and noise), and a decreased quality of life (QoL) (1). SSD is also associated with severe tinnitus in many patients which can further diminish QoL (1). Although the exact cause of tinnitus remains elusive, one hypothesis posits that reduced or absent auditory input leads to changes in neural activity (2).

A variety of interventions exist for SSD, which generally send sound from the poor-hearing ear to the better hearing ear. With the exception of a cochlear implant, these interventions do not improve hearing or tinnitus in the poor-hearing ear. Although approaches such as contralateral routing of sound (CROS) and bone conduction devices can recuperate some measures of speech understanding under various listening situations, they fail to effectively ameliorate other critical domains such as sound localization and tinnitus (3,4). Rather than rerouting sound to the normal ear as with CROS and bone conduction devices, cochlear implantation (CI) directly stimulates the acoustic nerve of the poor-hearing ear, thus providing binaural information to the patient's auditory system. The resulting stimulation provides a more robust therapeutic effect compared with other options (5,6). Previous research has shown that in patients with SSD, CI improves not only hearing, speech recognition, and QoL (1,7–9), but substantially reduces the severity of tinnitus (1,5,7,8,10). Unfortunately, most of these investigations are limited to small sample sizes from international locations. This prevents generalizability of published data and restricts any meaningful cross-study comparisons. Up until now, narrow indications for CI in the United States can account for the paucity of studies on this subject. However, the US Food and Drug Administration recently approved the MED-EL CI for patients with SSD age 5 and older (11).

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In an effort to better understand the overall benefit of CI for individuals with SSD, this study aims to systematically analyze existing published data to determine the pooled efficacy of CI on tinnitus reduction.

METHODS

Data Collection and Selection

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (12). Searches were undertaken in PubMed (NLM NIH), Scopus (Elsevier), and Cochrane Library (Wiley). The databases were searched from inception through July 10, 2019, and results were limited to English language. The search strategies used a combination of subject headings (e.g., MeSH in PubMed) and keywords for the following three concepts: unilateral hearing loss, cochlear implantation, and tinnitus. The PubMed search strategy was modified for the other databases, replacing MeSH terms with appropriate subject headings and maintaining similar keywords (see Appendix 1, Supplementary Digital Content 1, http://links.lww.com/MAO/A993, detailed search strategy). To identify additional articles, the reference lists of relevant articles were hand searched, as well as citing articles. References were uploaded to EndNote (Clarivate Analytics, Philadelphia, PA) and screened for relevance by authors D.A.L. and J.A.L.

Selection Criteria

SSD was defined as pure-tone average (PTA) more than or equal to 70 dB in one ear with PTA less than or equal to 25 dB in the better-hearing ear. Asymmetric hearing loss (AHL) was defined as PTA more than or equal to 70 dB in one ear with PTA more than25 dB in contralateral ear. All patients were required to have CI in the deafened ear. Studies were required to report the effect of CI on existing tinnitus preceding implantation; studies that reported tinnitus as a result of implantation were excluded. Additional exclusion criteria were 1) unevaluable data defined as incomplete or missing statistical data; 2) SSD not specified or not reported independently; 3) tinnitus was not evaluated; 4) article inaccessible; 5) effect of CI not directly evaluated; 6) review article, letter to the editor, conference abstract, personal opinion, case report, or book chapter. Case series including three or fewer patients were excluded.

Articles were critically appraised to assess level of evidence using the Oxford Center for Evidence-Based Medicine criteria (13). The risk of bias was assessed by two authors (D.A.L. and J.A.L.) according to the Cochrane Handbook for Systematic Reviews of Interventions (14). Risk of bias items included the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias for each aspect is graded as ''low,'' ''unclear,'' or ''high.''

Data Extraction

When available, the following data were extracted from each publication: author, year, location, population demographics (age and sex), PTA of both ears, age at onset-duration of HL, etiology of HL, as well as implant model, processor and program used for each patient.

All outcome measures relevant to tinnitus were considered for inclusion in the meta-analysis and discussion. These include tinnitus-related patient-reported outcome measures (PROMs) such as the tinnitus handicap inventory (THI), self-reported intensity of tinnitus symptoms, perceived loudness on visual analogue scale (VAS), duration of tinnitus relief, as well as overall perceived improvement in symptoms. Time between implantation and each follow-up measurement were extracted. No specific tinnitus outcome parameters were used as a basis for inclusion or exclusion for this study. Ultimately, only PROMs were reported in more than one study were amenable to meta-analysis and included in quantitative analysis. In instances of incomplete data, two attempts were made to contact the primary author via email for clarification or sharing of primary de-identified data. When part or all of the patient populations were reported in more than one publication, only the most comprehensive and updated study was included in the final analysis.

Subgroup Analysis

An auxiliary objective of the present analysis was to determine any potential difference in outcomes related to hearing status of the contralateral ear (SSD versus AHL). To accomplish this, individual patient data from studies that included patients with AHL were extracted when available. This resulted in the formation of two subgroups: 1) patients with SSD and 2) patients with AHL. A subgroup comparison of outcomes was performed using the methods described in the following section.

Statistical Analysis

Meta-analysis of included studies utilized pre-intervention (baseline) to post-intervention measures (implant turned on), with all subjects serving as their own controls. If more than one post-intervention measure was reported, the latest measure with the most complete dataset was used for comparison. In addition, studies that provided both short-term follow-up (defined as $\leq$6 months) and intermediate-term follow-up (defined as $>$6 months) were used to compare interval mean difference between the early and later follow-ups. Intervention was defined as unilateral CI for any indication in the deafened ear. Analyses of continuous measures (means and standard deviations between pre- and post-intervention) were performed with Cochrane Review Manager ''RevMan'' version 3.5 (Nordic Cochrane Centre, Cochrane Collaboration, 2011, Copenhagen, Denmark). During this analysis, heterogeneity was assessed first using the Q statistic test whereby a subgroup analytical result with a p-value $\leq$0.05 was considered as statistically significant and a result with a p-value $>$0.05 was considered statistically insignificant. In addition, heterogeneity was also assessed by the I^2 test. In this case, the lower the I^2 value, the lower the heterogeneity, and in contrast, heterogeneity increased with an increasing I^2 value. A fixed statistical effect model was used if the I^2 value was less than 50% or else, a random statistical effect model was used (15).

In addition, we aimed to determine if CI had any effect on the percentage of patients who received subjective symptomatic improvement, using explicitly reported outcomes (or VAS scores). Patients were categorized into one of the following groups: reported complete resolution (or post-intervention VAS score of 0), partial resolution (any reduction in VAS score), unchanged and worsened (increase in VAS score). To accomplish this, a meta-analysis of proportions was performed using MedCalc 19.0.7 (MedCalc Software bvba, Belgium). The program MedCalc lists the proportions (expressed as a percentage), with their 95% confidence intervals, found in the individual studies included in the meta-analysis. MedCalc used a Freeman-Tukey transformation (16) to calculate the weighted summary proportion under the fixed and random effects model. Each study was weighted according to the number of patients included. Both the fixed effects model and the random effects

model were used in this study. Exploratory post-hoc analysis was performed when available to compare outcomes between individuals with SSD and individuals with AHL; this was accomplished using individual patient data that were provided in published articles or from de-identified data furnished by authors upon our request.

Finally, the Sterne and Egger tests were performed for further assessment of risk of publication bias (17,18). Potential publication bias was evaluated by visual inspection of the funnel plot and Egger's regression test, which statistically examines the asymmetry of the funnel plot. In a funnel plot, treatment effect is plotted on the horizontal axis and MedCalc plots the standard error on the vertical axis (19). The vertical line represents the summary estimated derived using fixed-effect meta-analysis. Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 SE) around the summary effect for each standard error on the vertical axis. These show the expected distribution of studies in the absence of heterogeneity or of selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines. Publication bias results in asymmetry of the funnel plot.

RESULTS

Search Results and Study Characteristics

The systematic literature search produced 634 unique articles. Screening by title and abstract eliminated 557 articles, leaving 77 for full text review. A total of 17 studies met criteria for final quantitative analysis (Fig. 1).

Articles were published between 2008 and 2019 in 10 different countries. Six studies provided data on THI (20,22,25,26,28,30) while seven studies documented tinnitus loudness on VAS (1,5,7,10,23,25,30). Five studies reported outcomes at various follow-up periods and were included in the interval analysis between follow-up periods. Other tinnitus-related measures, cochlear implant device, and study-specific information can be found on Table 1 (21,27,29,31,32). The risk of bias was assessed for each included study (Fig. 2); see also Figure 1, Supplementary Digital Content 2, http://links.lww.com/MAO/A994, Funnel plot.

Patient Characteristics

A total of 247 patients were included in analysis (mean age 50.2 ± 5.5 yr [range 23–71], 52% men). Etiology of hearing loss was reported in 10 studies (n = 128, 52%), with the most common etiologies being sudden sensorineural hearing loss (n = 38, 29.7%) and infectious/inflammatory causes (n = 20, 15.6%). Other etiologies included trauma (n = 11, 8.6%), iatrogenic (n = 7, 5.5%), otosclerosis (n = 4, 3.1%), and Menière's disease (n = 3, 2.3%). Etiology was unknown in 31 patients (24.2%), while 14 (10.9%) had other causes not mentioned above.

The weighted mean PTA of the deaf ear was reported in seven studies and was 99.3 ± 8.4 dB; in the contralateral ear, the weighted mean PTA was 22.0 ± 8.0 dB for all subjects (14.9 ± 5.4 dB in 44 patients with SSD; 50.7 ± 13.9 dB in 16 patients with AHL). The weighted mean duration of deafness was 61.5 ± 41.1 months as reported in 13 studies. Seven studies selected patients with SSD only, while eight other studies consisted of patients with either SSD or AHL (four of which contained individual patient data used for subgroup analysis). A summary of patient characteristics can be found on Table 1, Supplementary Digital Content 3, http://links.lww.com/MAO/A995, patient characteristics.

Improvement in Tinnitus-related Measures

According to six studies, CI resulted in a mean THI difference of −35.4 [−55.8 to −15.0] with significant overall effect ($p < 0.001$) (Fig. 3). The mean follow-up period was 8.6 (range 3–13) months post-implantation. In three studies containing multiple follow-up intervals for THI, comparison of short-term (≤6 mo) and intermediate-term (>6 mo) measures demonstrated a mean difference of −4.1 [−8.9–0.7] ($p = 0.09$) (Fig. 4).

According to seven studies, VAS loudness measures on a scale of 0 to 10 demonstrated a post-implantation mean difference of −4.6 [−6.0 to −3.3] ($p < 0.001$) (Fig. 5). The mean follow-up duration was 14.8 (range 6–28) months, although four studies did not document follow-up time. From three studies, the mean difference between short-term (≤6 mo) and intermediate-term (>6 mo) VAS scores was 0.2 [−0.6–1.0] and was not significant ($p = 0.56$) (Fig. 4).

Subgroup Analysis

Post-hoc comparisons were performed between the two subgroups: SSD and AHL. Significant reductions in THI were seen following CI for the SSD subgroup (MD −54.1, [−71.5 to −36.7], $p < 0.001$), but not the AHL subgroup (MD −16.2, [−33.9 to 1.5], $p = 0.07$). Post-hoc analysis revealed significant difference between the SSD and AHL subgroups ($p = 0.003$) (Fig. 3). For VAS for loudness, there was a significant reduction following CI for the SSD subgroup (MD −5.3, [−6.4 to −4.3], $p < 0.001$) and the AHL subgroup (MD −4.4, [−7.6 to −1.2], $p < 0.001$) with no difference between subgroups ($p = 0.58$) (Fig. 5).

Subjective Improvement

Thirteen studies documented subjective improvement either explicitly or determined from changes in VAS scores, which were combined in these analyses. An overall weighted proportion of 14.9% [6.4–26.1] of patients experienced complete resolution, while 74.5% [63.1–84.5] of patients experienced partial improvement (Fig. 6). Only 7.6% [4.1–12.6] of patients had no change in tinnitus severity, and 3.0% [1.0–6.7] of patients experienced worsening of their tinnitus. See also Table 2, Supplementary Digital Content 4, http://links.lww.com/MAO/A996, for separately reported proportions of improvement based only on changes in VAS scores.

DISCUSSION

This study presents a systematic review and meta-analysis of the collective effect of CI on tinnitus among patients with SSD. Representing a relatively novel intervention for a unique population, it is difficult to obtain

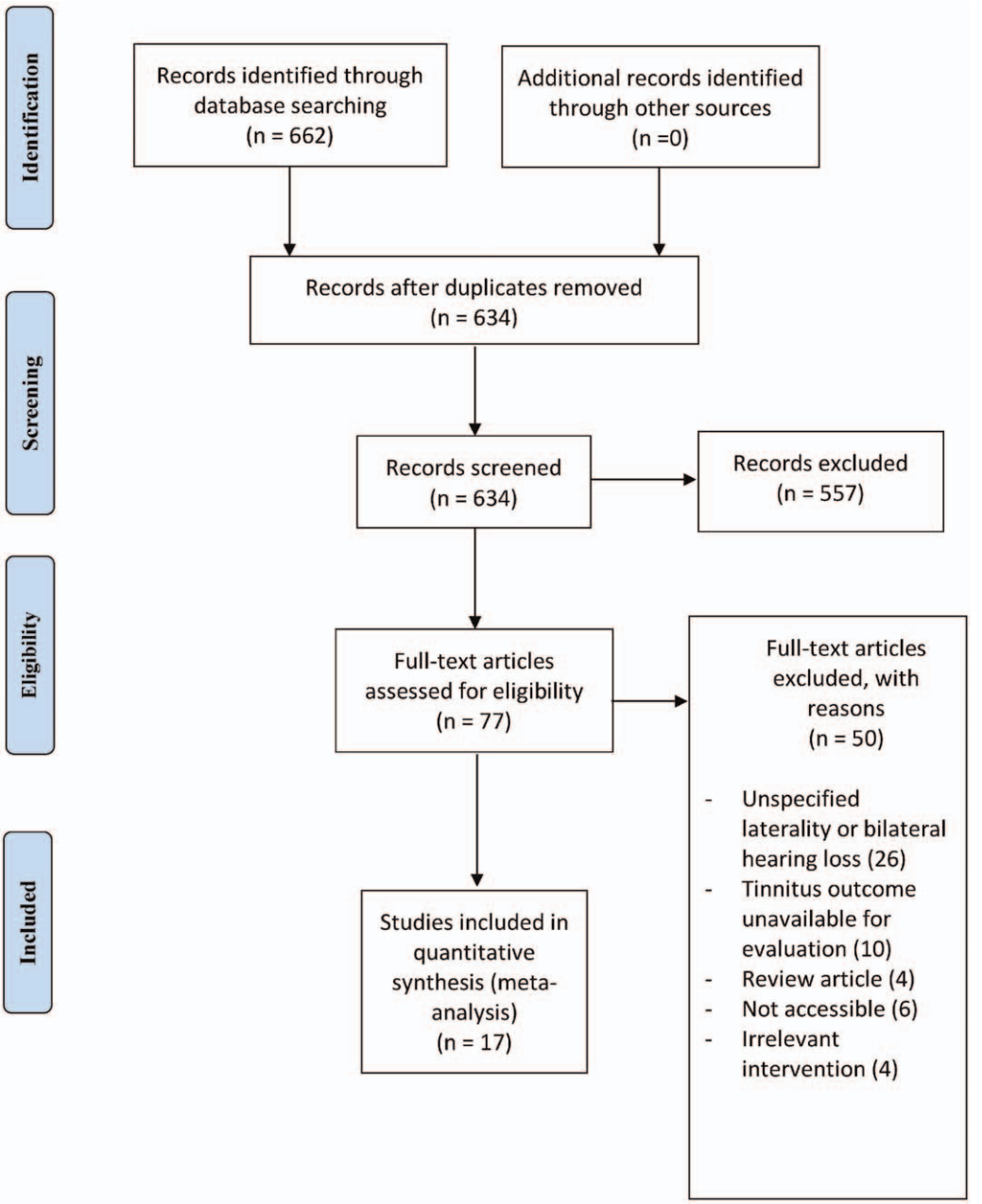

FIG. 1. PRISMA diagram.

robust measures and high-quality prospective evidence to determine the efficacy of CI in these patients. Therefore, analyzing treatment characteristics and subjective outcomes in this population through meta-analysis might offer insight into the role of CI for tinnitus amelioration. Unlike previous reports (33,34), the present study provided a weighted analysis of available data and analyzed multiple time points to determine the longitudinal benefits of this intervention.

The main findings of the present study demonstrate that both THI and VAS decrease substantially after CI in both the SSD and AHL populations. THI is a validated PROM composed of 25 questions to determine the disturbance to daily life associated with tinnitus. Original interpretation of these scores is used to determine gradation of tinnitus-related handicap severity in 18-point increments (35). Although the nature of this meta-analysis does not enable the specific reporting of the distribution of Grades 1–4 between pre- and post-intervention measures, the average reduction of 35 points for all patients represents a substantial difference which translates into an improvement of at least one severity grade. Furthermore, Zeman et al. (36) determined that a reduction of only six points on the THI scale represents the

TABLE 1. *Study characteristics*

Author (yr)	Country	OLE	Study Design	n Overall	Mean Age (yr)	Males (%)	Tinnitus-Related Measure	Cochlear Implant Device
Ahmed (2016)	Egypt	4	R	13	40 (24–60)	61.5%	THI, TRS	CI24RE (4), Concerto (6), HiRes90K (3)
Arndt (2010)	Germany	4	P	11	45.2 (23–68)	NR	VAS (loudness)	Nucleus Freedom Implant (11)
Buechner (2010)	Germany	3	P	5	50 (42.2–56)	NR	None	HiRes 90k (5)
Dillon (2017)	USA	3	P	20	50 (23–66)	NR	THI	MED-EL Concert (29)
Dorbeau (2018)	France	3	P	18	58.9 (47–71)	44.4%	THI	CI422 (1), CI24RECA (2), CI 512 (10), Oticon EVO (4), AB MIDSCALA (1)
Finke (2017)	Germany	4	P	19	48.4 (22–69)	NR	None	NR
Galvin 2019	USA	3	P	10	57.6 (45–71)	50.0%	TFI, VAS (loudness)	MED-EL Concerto Flex 28 (10)
Harkonen (2016)	Finland	3	P	7	48 (36–61)	28.6%	VAS (loudness)	Cochlear Nucleus CI24RE (7)
Holder (2017)	USA	4	R	12	51.6 ± 15.5	83.3%	THI	Cochlear CI24RE (1), MED-EL Synchrony Flex 28 (5), MED-EL Concert Standard (1), MED-EL Concert Flex28 (1), Cochlear Nucleus 422 (1) and Cochlear Nucleus 522 (1), Cochlear Nucleus 512 CA (1), AB HiFocus MidScala (1)
Kitoh (2016)	Japan	4	R	5	52.2 (26–71)	20.0%	THI[a]	Med-El Concerto Flex28 (5)
Mertens (2013)	Belgium	3	P	15	54.5 (28–66)	40.0%	TQ, VAS[a], TLM	MED-EL SONATATI 100 (8), MED-EL PULSARCI 100 (5), MED-EL COMBI 40 + (2)
Punte (2011)	Belgium	3	P	26	NR	NR	VAS (loudness), TQ	NR
Ramos-Macias (2018)	Spain	3	P	16	52.8 (31–70)	50.0%	THI, VAS (loudness)	CI24RE (CA) (10), CI422 (6)
Seo (2016)	South Korea	4	R	16	51.94 ± 13.73	62.5%	THI, VAS (loudness)	CI 24RE, CI422, and MED-EL Sonata
Sladen (2017)	USA	4	R	23	40.6 ± 20.1	NR	None	NR
Tavora-Vieira (2013)	Australia	4	R	9	57 (45–70)	NR	TRQ	MED-EL Flex (9)
Van de Heyning (2008)	Belgium	3	P	22	51.1 (12.4)	54.5%	VAS (loudness), TQ	COMBI 40+ M (10), PULSAR CI100 FLEX SOFT (12)
Mean				247	50.2 ± 5.5	52.2% ± 14.2%		–

Means presented with ± SD or range (). R indicates retrospective study;P, prospective study; THI, Tinnitus Handicap Inventory; TFI, Tinnitus Functional Index; TLM, Tinnitus Loudness Match; TRQ, Tinnitus Reaction Questionnaire; TRS, Tinnitus Rating Scale; TQ, Tinnitus Questionnaire; VAS, Visual Analogue Scale.

[a]Data not evaluable.

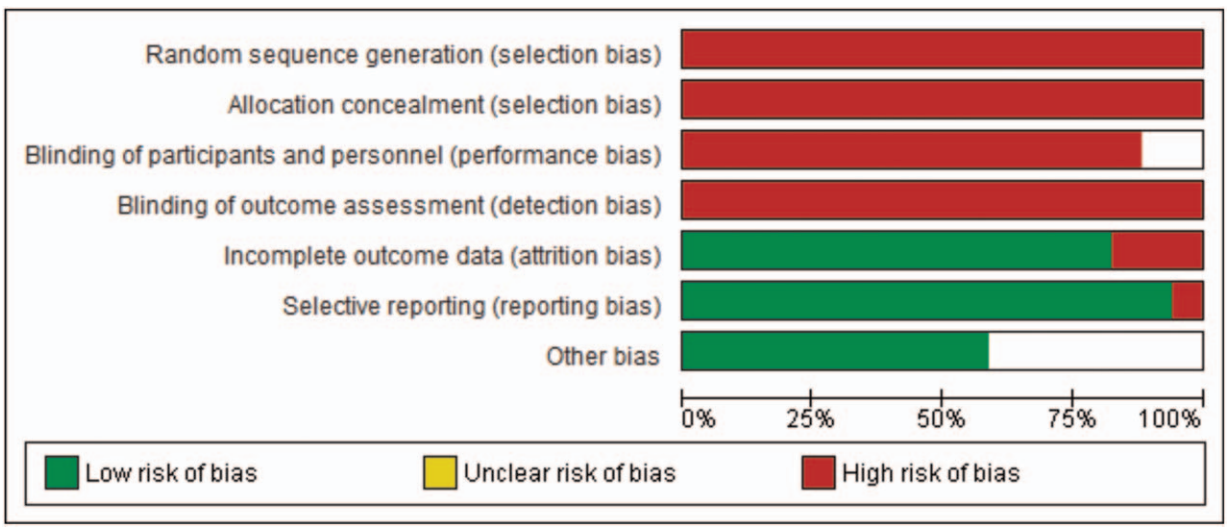

FIG. 2. Risk of Bias Graph: a review of authors' judgments about each risk of bias item presented as percentages across all included studies.

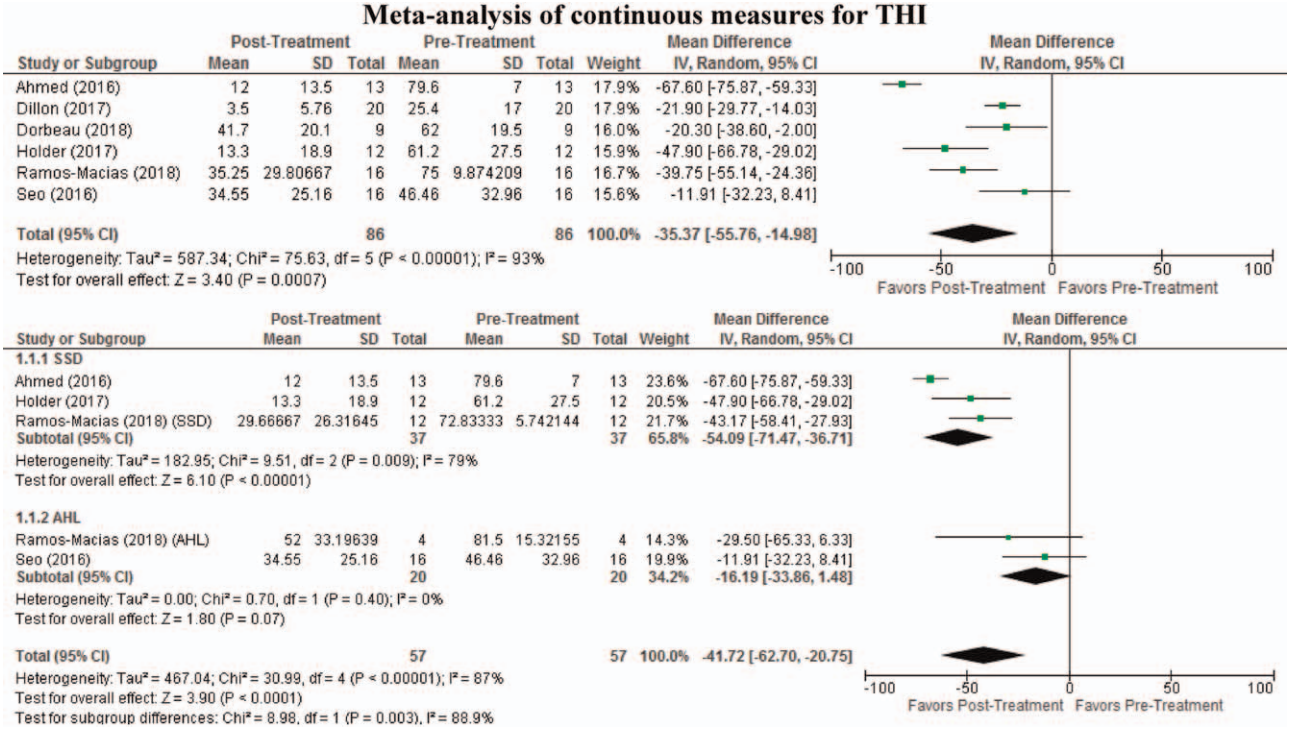

FIG. 3. Posttreatment improvement in THI overall (*top*) and by subgroup (*bottom*). Available data provided from six studies. THI indicates Tinnitus Handicap Inventory.

minimal clinically important difference (MCID) for tinnitus handicap. As the average baseline THI in our cohort was 56, this average reduction is likely to be clinically significant.

VAS for loudness is a simpler tool for assessing the impact of tinnitus on patients with SSD, but nevertheless represents an important self-reported measure of disturbance that is commonly employed in research of subjectively perceptible symptoms (37). By marking a point on a 10-cm line anchored by extreme values (e.g., 0 = no tinnitus at all, 10 = worst tinnitus imaginable), patients can easily quantify their symptom severity. In the present study, we identified a substantial reduction in VAS of roughly 4.6 points. Previous research revealed that a difference of 15 points on a VAS scale of 100 indicates a MCID for chronic tinnitus (38). When categorizing responses to CI, we found that approximately 16% of patients achieved complete tinnitus resolution and approximately three in every four patients received partial resolution. Furthermore, less than 8% of patients

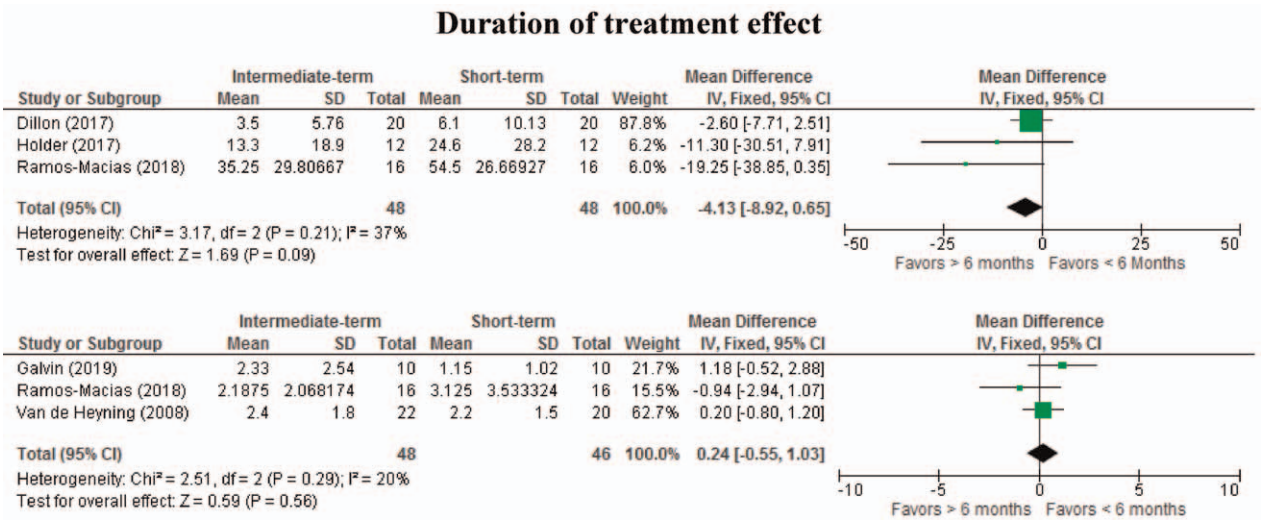

FIG. 4. Comparison of short-term versus intermediate-term effects on THI (*top*) and VAS (*bottom*). Available data provided from five studies. THI indicates Tinnitus Handicap Inventory; VAS, Visual Analogue Scale.

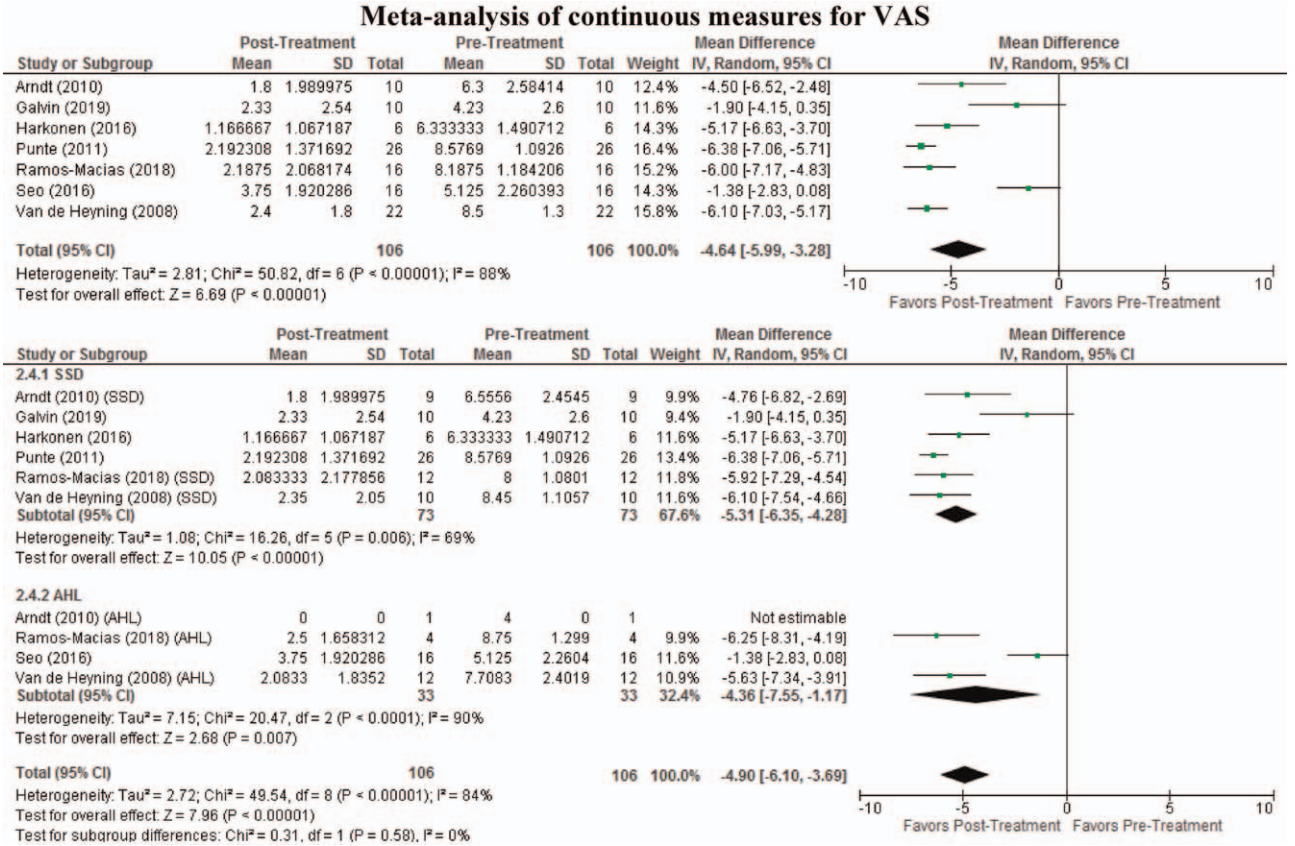

FIG. 5. Posttreatment improvement in VAS overall (*top*) and by subgroup (*bottom*). Available data provided from seven studies. VAS indicates Visual Analogue Scale.

received no benefit, and approximately 3% of patients experienced worsening of their tinnitus. Thus, CI appears to effectively reduce tinnitus severity for a substantial proportion of patients with SSD.

Reductions in THI and VAS indicate the potential for not only improving symptomatic severity but also improving quality of life. This latter measure carries particular relevance to patients with tinnitus as they often suffer psychosocial consequences from their condition (39). Hearing loss experienced by this population can further exacerbate quality of life (1,40). As such, by improving both hearing and tinnitus, CI likely provides

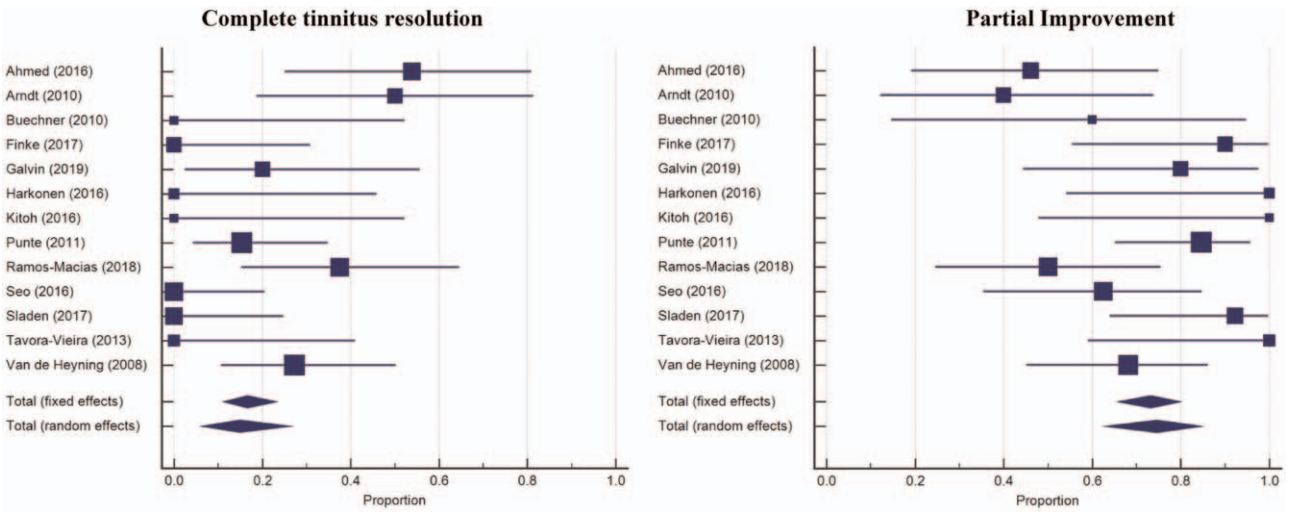

FIG. 6. Meta-analysis of proportions. *Left*: pooled proportion of patients who achieved complete tinnitus resolution. Right: pooled proportion of patients who achieved partial improvement. Available data provided from thirteen studies.

substantial multidimensional benefit for these patients. Additionally, our study found no difference between short- and intermediate-term improvement of THI and VAS, suggesting that these benefits can be sustained without diminishing over time. Future studies with extended follow-up periods might further elaborate the longitudinal potential of this intervention.

The post-hoc subgroup analysis also revealed interesting differences in outcomes between patients with SSD compared with patients with AHL. Specifically, patients with SSD appeared to experience a greater reduction in THI and VAS compared with patients with AHL. Although these differences were only significant for THI, differences measured by VAS approached statistical significance. With a larger dataset, advantages for patients with SSD are likely to be seen across tinnitus measures. This finding reveals the possibility that hearing loss in the contralateral ear contributed to the perception of tinnitus and therefore remained unaddressed by CI in the deaf ear. Ultimately, our results suggest that hearing loss in the contralateral ear might diminish tinnitus relief following CI. Nevertheless, CI appears to have effectively reduced the burden of tinnitus in both groups.

Limitations

There were several limitations to the present study. First, we did not have a complete set of individual patient data, thus limiting our analysis on important patient characteristics such as tinnitus etiology. There might have also been substantial variations in patient selection or implant programming that could not be accounted for. Using mostly retrospective data, we were also subjected to significant selection bias within individual studies. Furthermore, while we used any reduction in VAS to indicate partial improvement, it is impossible for us to confirm whether minimal changes were clinically significant. The degree of baseline tinnitus severity in this population is yet another limitation, as several studies only selected for patients with severe tinnitus. As a result, caution must be taken when extrapolating these findings to patients with mild or moderate tinnitus. Lastly, there are additional reports pertaining to tinnitus reduction in this patient population that use other measurement scales such as Tinnitus Functional Index (TFI) (7), Tinnitus Questionnaire (10,24,41,42), Tinnitus Rating Scale (43), and Tinnitus Reaction Questionnaire (44). Similar to VAS and THI, patients in these studies typically showed improvement in these measures. However, data were insufficient to be included in these quantitative analyses. The heterogeneity in tinnitus measures encountered by this systematic review identifies the need for a standardized tinnitus assessment tool, such as the TFI which was designed specifically to measure tinnitus reduction in response to intervention (45). If promoted effectively, unified reporting will enable more meaningful cross-study comparisons going forward. Despite these limitations, a balancing strength of this study was that the included articles represent a diverse multinational population of patients that have received various models of implants from presumably different surgeons. Ultimately, the present study demonstrated the promising role of CI in reducing tinnitus for patients with SSD.

CONCLUSION

The present study reports the pooled effect of CI on tinnitus for individuals with SSD, as measured by THI and VAS. On both measurements, patients experienced significant reduction in their scores, representing an overall improvement in tinnitus severity that likely translates to improvement in patient quality of life. Nearly three-quarters of patients are likely to experience partial improvement in tinnitus, while approximately 16% of patients experience complete resolution. These findings beg the question as to whether tinnitus severity should be taken into account when determining CI candidacy. Future prospective research with a unified method for determining tinnitus severity will further help delineate the role of CI for tinnitus reduction in this population.

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