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REVIEWS

Efficacy of Transcutaneous Vagus Nerve Stimulation in Patients with Drug-Resistant Epilepsy: Systematic Review and Updated Meta-Analysis Based on Randomized Controlled Trial

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Abstract

Background: Approximately thirty percent of epileptic patients have drug-resistant epilepsy (DRE), which severely reduces their quality of life (QoL). Transcutaneous vagus nerve stimulation (t-VNS) has become a noninvasive alternative to invasive vagus nerve stimulation (i-VNS), which has been proven to be a neuromodulatory treatment for seizure reduction.
Objective: In this meta-analysis, we investigate the effectiveness of t-VNS in people with DRE by looking at four key outcomes: seizure frequency, responder rate, adverse events, and quality of life.
Methods: A systematic review and meta-analysis were conducted following the PRISMA guidelines. PubMed, Cochrane, and Scopus were used for literature searches (December 2024). Included were randomized controlled trials (RCTs) that evaluated t-VNS in DRE patients. Reduction in seizure frequency, responder rate (≥50%), adverse events, and quality of life as assessed by the QOLIE-31 and Liverpool Seizure Severity Scale (LSSS) were the outcomes that were examined. Review Manager 5.4.1 was used to perform the meta-analysis, and odds ratios (OR) and standardized mean differences (SMD) were computed.
Results: The inclusion criteria were met by four RCTs with 359 patients. There was no significant difference in responder rates (p=0.16), but the meta-analysis showed a significant decrease in seizure frequency favoring t-VNS (p=0.008). Three studies reported improvements in QoL, but there were no notable differences. Sleep disturbances, lightheadedness, and local discomfort were among the mild to moderate adverse events.
Conclusion: t-VNS demonstrated significant seizure reduction with fewer adverse effects. Further high-quality trials are needed to establish the efficacy of t-VNS.

Keywords: Drug-Resistant Epilepsy, Meta-Analysis, Quality of Life , Seizure Frequency, Vagus Nerve Stimulation

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INTRODUCTION

Epilepsy is a neurological condition that impacts around 51 million individuals globally.[1,2] Approximately 30% of these patients are categorized as drug-resistant epilepsy (DRE), defined by the failure to achieve seizure control despite sufficient trials with at least two well-tolerated, adequately chosen, and correctly delivered antiepileptic medications (AEDs).[1-3] Individuals with DRE endure a considerable detriment to their quality of life (QoL) that transcends the immediate effects of seizure frequency and kind.[4]

Moreover, their quality of life deteriorates due to supplementary medical and psychological issues, along with anxiety around social occasions, which disrupt their regular routines.[4]

Epilepsy surgery may enhance the quality of life in people with drug-resistant epilepsy.[5] Surgical intervention for drug-resistant epilepsy (DRE) can be categorized into three primary methodologies: (1) total excision of the epileptogenic focus, (2) disconnection procedures such as corpus callosotomy or hemispherectomy, and (3) stimulation therapy.[6] In this particular patient cohort, the application of stimulation therapy may enhance quality of life.[7] Among the stimulation options are vagus nerve stimulation (VNS), deep brain stimulation, and responsive neurostimulation.[8] These stimulation options are typically considered when resection or disconnection is not viable due to unclear seizure focus, involvement of critical brain regions, or contraindications arising from significant comorbid conditions.[8,9]

Unlike resective surgery, VNS is reversible and features adjustable parameters, allowing for improved efficacy with minimal side effects.[10] The specific mechanism of VNS is not yet clear, but evidence suggests it impacts both subcortical and cortical brain regions. The phenomenon probably engages the noradrenergic and serotonergic systems, given that the nucleus tractus solitarius (NTS) is linked to the locus coeruleus (LC), responsible for norepinephrine production, and the raphe nuclei, which synthesize serotonin,both of which have anti-seizure characteristics.[11]

To avert any effect on cardiac function, VNS is generally administered on the left side, as the right vagus nerve is linked to the sinoatrial node.[11] The conventional invasive VNS (i-VNS) treatment necessitates the implantation of a device akin to a pacemaker; nevertheless, it may be inappropriate for individuals with additional severe health conditions.[12,13]

However, transcutaneous auricular VNS (t-VNS) offers a non-surgical alternative for treating various neurological and psychiatric disorders.[14] Instead of directly stimulating the vagus nerve, t-VNS works by placing electrodes on the cymba conchae of the ear, which in turn activates the sensory fibers of the nerve's auricular branch (ABVN).[12,13] t-VNS is another form of VNS, which presents less invasiveness and broadens its applicability.[15]

These modalities present advantages and broaden treatment choices for patients with DRE. Recent studies on t-VNS show that its success is not always the same, as it can be influenced by factors like co-existing medical issues and how long the patient has had epilepsy. As research continues to evolve, t-VNS presents an integral component of managing DRE patients, particularly seeking improvement in patients' QoL and seizure frequency. In this meta-analysis, we investigate the effectiveness of t-VNS in people with DRE by looking at four key outcomes: seizure frequency, responder rate, adverse events, and quality of life.

METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in the conduct of this systematic review and meta-analysis.[16]

Search Strategy

We conducted a literature search using PubMed, Scopus, and the Cochrane Controlled Register of Trials (CENTRALS) to locate studies that evaluated efficacy t-VNS as a treatment for DRE. The search terms used for each database are listed as supplementary data. We conducted the search of the literature in December 2024.

Eligibility Criteria

The inclusion requirements, encompassing participants, interventions, comparisons, outcomes, and studies (PICOS), are outlined in Table 1. Only randomized controlled trials (RCTs) with t-VNS on patients with DRE in English were included, with concrete comparison of outcomes between the intervention and control groups or baseline. Differences in technical parameters regarding t-VNS and i-VNS were not raised as a point of exclusion for further analysis regarding differences

Table 1. Population, Intervention, Comparion, Outcomes (PICOS)

Criteria	Inclusion	Exclusion
Participants	Studies with drug resistant epilepsy subjects of any age and gender	Studies with other subjects
Interventions	t-VNS. All technical parameters of stimulation were accepted.	Invasive vagus nerve stimulation intervention
Comparison	Control groups or baseline.	Studies without comparison group
Outcomes	Seizure frequency reduction compared with the control group.	Studies not reporting any quantitative data on either primary or secondary outcomes.
	Seizure frequency reduction to baseline.	
	Technical parameters of stimulation (Site of placement, Intensity, Frequency, pulse width, stimulation periods, duration of sessions).	
	Quality of life measured by QOLIE-31 and LSSS score compared to baseline or control group.	
	Any reported adverse effects.	
Study design	RCTs	Observational studies including cohorts, case reports, case series, cross-sectional, case control, in vitro and in vivo studies, reviews, editorials, and commentaries.

T-VNS; transcutaneus vagus nerve stimulation, QOLIE-31; Quality of Life in Epilepsy Inventory, LSSS; Liverpool Seizure Severity Scale, RCTs: Randomized Controlled Trials

in outcome, with key outcomes for this analysis were the change in seizure frequency, the responder rate (patients with a 50% seizure reduction), and quality of life, evaluated using the QOLIE-31 and LSSS scales. Observational studies, that is, cohorts, case controls, cross-sectional studies, case reports, case series, and in vivo studies involving animal in vitro experiments were excluded, as well as reviews, editorials, and commentaries.

Data Extraction and Quality Assessment

Initial review of titles and abstracts to determine the relevance of the studies was performed independently by R.I and F.W, after which detailed review of full-text articles was commenced. Data extracted included patient demographics, duration of epilepsy, seizure characteristics, t-VNS stimulation parameters, changes in seizure frequency, quality of life measurements, adverse events, and complications. To assess the quality and potential for bias in the studies, both authors independently used the Cochrane risk-of-bias (RoB) tool for RCTs, resolving any differences of opinion through discussion.

Outcome Measures and Statistical Analysis

The primary outcome measures were the percentage decrease in seizure frequency following t-VNS application, compared to control or baseline values, along with responder rate defined as the number of individuals with ≥50% seizure frequency reduction. Data on seizure frequency post-treatment were acquired from the most recent follow-up periods, during which the comparison between t-VNS and the control group was preserved. In trials where the difference in seizure frequency was not expressed as a percentage, the following formula was employed: percentage of seizure frequency reduction = [(seizure frequency recorded during intervention) / baseline seizure frequency] × 100%. Standardized mean differences (SMD) were computed for each study, and high heterogeneity was defined as >50% of I^2 statistical value.

Secondary measures included assessments of quality of life through the QOLIE-31 for general measures and LSSS. specifically for seizure severity, along with the identification of adverse events and complications, to assess the safety of t-VNS. The outcomes were unsuitable for meta-analysis; therefore, descriptive analysis was employed instead.

For studies lacking means and standard deviations (SDs), these metrics were calculated using medians and ranges (minimum to maximum) utilizing the methodologies proposed by Hozo and Wan, in conjunction with the Meta-analysis accelerator tool created by Abbas et al.[17-19]

We calculated summary SMDs for continuous data and odds ratios (OR) for binary data, both with 95% confidence intervals (CI). Review Manager (version 5.4.1) was used for all statistical analyses, and a p-value of less than 0.05 was deemed significant.

RESULTS

Study Selection

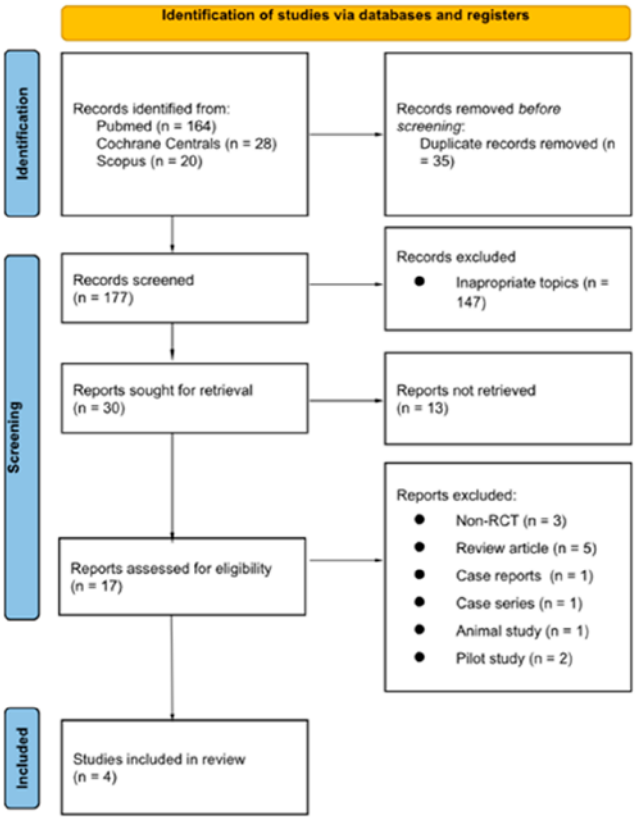

Figure 1. Prisma flow chart displaying included studies selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Based on the search strategy used the initial search returned 212 articles. Once 35 duplicates were removed, 177 were screened by title and abstract. This led to 30 articles being selected for full-text retrieval, though 13 of these could not be accessed. However, we were unable to access the full text for 13 of these. After reviewing the full text of the 17 available studies, we ultimately included four randomized controlled trials (RCTs),[20-23] hich together involved 359 patients, in our final analysis (Fig. 1).

Study Characteristics

The characteristics of the four studies published from 2014 to 2023 are described in Table 2. Most of this research were carried out in China (75%, n = 3) and the age of the participants ranged from 27.9 (1–57) years. Baseline seizure frequency is 53.34 ± 27.0 (per month). The duration of epilepsy was 12.95 ± 6.5 per years. The intervention length varied from 5 to 12 months, and the AED regimens were consistently upheld throughout all studies.

Three trials featured two arms (treatment and control), with Bauer et al.[5] and Yang et al.[33] utilizing low-frequency VNS as the control arm. One study by Aihua et al.[20] used earlobe stimulation as the control group. Four studies (350 patients) reported seizure frequency, 2 studies Bauer et al.[23] and Rong et al.[22] (191 patients) reported treatment response, 3 studies (Aihua et al.[21], Bauer et al.[23], and Yang et al.[20]) (217 patients) reported QOL, and 3 studies (Rong et al.[22], Aihua et al.[21], and Yang et al.[20]) (292 patients) reported adverse effects in 292 patients.

Technical Parameters

Table 3 is here.

The table 3 summarizes the key parameters of vagus nerve stimulation (VNS) interventions in various studies. The devices included the tVNS TENS from Suzhou Medical Appliance Co. Ltd., tVNS-200 from Hua Tuo, tVNS NEMOS from Cerbomed GmbH, and TVNS-100 from Xinzhlie, Jiangxi, China. Stimulation settings vary across studies, with frequencies ranging from 1 to

Table 3. Technical Parameters

Author	Vagus Nerve Stimulator	Stimulation periods	Pulse width	Frequency (Hz)	Intensity	Electrodes Site of Placement
Rong, P et al. 2015	tVNS TENS, Suzhou Medical Appliance Co. Ltd	Twice a week, 1 time/ day, 30 minutes per session	<1 m/s	20–30	1.0 mA	Bilateral; Triangular fossa
Liu, A et al. 2014	tVNS TENS-200, Hua Tuo	3 times/ day, 20 minutes per session	0.2s	20	Increased 2 mA gradually. Median stimulation intensity: 6.0 mA	Bilateral; Ramsay Hunty Zone
Bauer, S et al. 2016	tVNS NEMOS, Cerbomed GmbH	4 hours/day, at minimum 1 hour per session	250 μs	1 and 25	1 Hz group mean intensity is 1 mA; 25 Hz group mean intensity is 0.5 mA	Left; Ear Conch
Yang, H et al. 2023	TVNS-100, Xinzhile, Jiangxi	2 hours/day, divided into 4 sessions/day at 30 minutes each	250 μs	1 and 25	N/A	Left; Ear Conch

NA, not available

Table 2. Study Characteristics

Author, Year	Country	Study Design	Duration of Study (Month)	Number of Participants		Frequency (Hz); Pulse Width (ms)	Age (Year)	Sex		Duration of Epilepsy (Year)	Seizure Frequency (/Month)	LSSS	QOLIE-31	Side Effects
				t-VNS Group	Control Group			Male	Female					
Rong P et al, 2015	China	RCT	6	93	40	t-VNS Group: 20-30; ≤ 1	t-VNS Group: 24.4 ± 12.1	30	20	t-VNS Group: 12.0 ± 8.1	t-VNS Group: 85.2 ± 14.4	N/A	N/A	Discomfort, Redness, Swelling, and Dizziness
						Control Group: 20-30; ≤ 1	Control Group: 22.40 ± 15.4			Control Group: 11.4 ± 11.1	Control Group: 66.4 ± 12.3	N/A	N/A	
Liu et al, 2014	China	RCT	12	26	21	t-VNS Group (Ramsay Hunt Zone): 20; 200 ms	t-VNS Group: 34.5 (26.5-41.3)	N/A	N/A	t-VNS Group: 19.7 ± 11.1	t-VNS Group: 6.0 (4.8-25.0)	t-VNS Group: 13.9 ± 3.9 (*baseline*); significant decrease (p < 0.001)	t-VNS Group: 105.2 (*baseline*); 212.15 (after t-VNS)	Discomfort, Dizziness, and Daytime Drowsiness
						Control Group (ear lobe): 20; 200 ms	Control Group: 29.0 (24.5-42.0)			Control Group: 17.6 ± 9.6	Control Group: 7.0 (4.0-11.5)	Control Group: 14.8 ± 4.4 (*baseline*); no significant decreaase (p = 0.421)	N/A	
Bauer S et al, 2016	Germany	RCT	5	27	31	t-VNS Group: 25; 0.25	t-VNS Group: 40.1 ± 12.7	31	45	t-VNS Group: 23 ± 15.4	t-VNS Group: 62.1 ± 14.8	t-VNS Group: 36.9 ± 4.7 (*baseline*); 38.46 (after t-VNS)	t-VNS Group: 56.2 ± 14.3 (*baseline*); 58.88 (after t-VNS)	Redness and Dizziness
						Control Group: 1; 0.25	Control Group: 37.5 ± 12.2			Control Group: 24.2 ± 13.8	Control Group: 50.4 ± 10.2	Control Group: 37.1 ± 5 (*baseline*); 37.9 (after t-VNS)	Control Group: 57.5 ± 13 (*baseline*); 62.15 (after t-VNS)	
Yang H et al, 2023	China	RCT	7	76	36	t-VNS Group: 25; 250	t-VNS Group: 33.25 ± 11.32	62	88	t-VNS Group: 15.05 ± 10.2	t-VNS Group: 9.91 ± 12.4	N/A	t-VNS Group: 164.64 (*baseline*); 167.39 (after t-VNS)	Pain, Sleep Disturbances, Influenza, Skin Discomfort, Mild Sinus Bradycardia
						Control Group: 1; 250	Control Group: 34.02 ± 10.78			Control Group: 16.53 ± 10.7	Control Group: 15.10 ± 29.2	N/A	Control Group: 170.53 (*baseline*); 181.16 (after t-VNS)	

t-VNS; transcutaneus vagus nerve stimulation, QOLIE-31; Quality of Life in Epilepsy Inventory, LSSS; Liverpool Seizure Severity Scale, RCTs: Randomized Controlled Trials, N/A; Not Available

30 Hz and intensities between 1.0 mA and 6.0 mA. Pulse widths range from 0.2 ms to 250 μs, with most studies targeting bilateral or left-ear electrode placements, commonly at the concha or triangular fossa. Stimulation durations ranged from 20 minutes to 4 hours per session, applied 2–4 times daily or weekly. These heterogeneous protocols reflect the variability in stimulation parameters and placement to optimize VNS efficacy.

Risk of Bias Analysis of RCTs

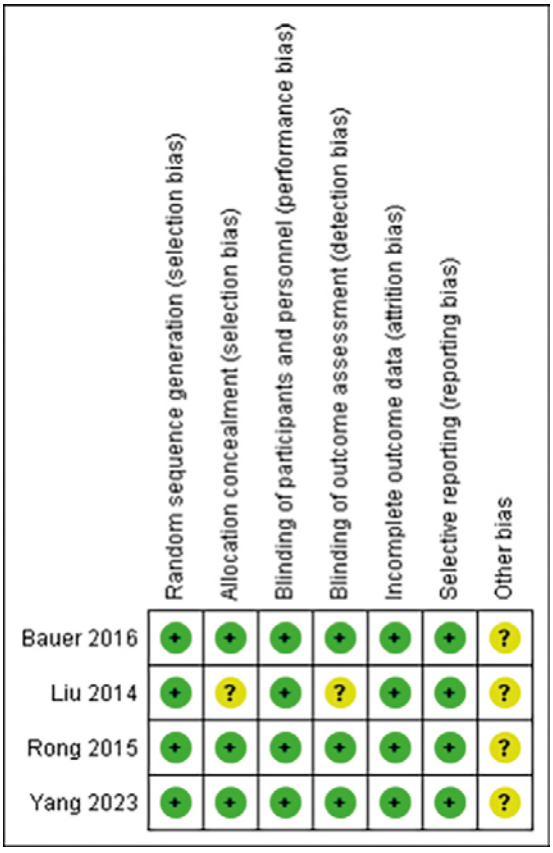

Figure 2. Risk of Bias assessment of included studies

The risk of bias for all included papers was assessed utilizing Cochrane's RoB 2.0 methodology. The instrument examined the risk of bias across six domains: selection, performance, detection, attrition, and reporting biases, along with a section addressing other biases. Allocation concealment and random sequence creation were assessed as potential sources of selection bias. Participants and personnel blinding was assessed as a performance bias indication, whereas outcome assessment blinding was assessed as a detection bias indicator. The incompleteness of outcome data was evaluated as an indicator of attrition bias, whereas selective reporting was evaluated as an indicator of reporting bias.[36]

A moderate risk of bias was found in all four of the RCTs that were part of this review. Since the study by Aihua et al.[2] was single-blinded, attention was warranted regarding allocation concealment and blinding of outcome assessment, with further attention towards no available data regarding mean initial seizure frequency for all subjects assessed as a part of other bias. In the study by Bauer et al.[5] the intervention group had a higher seizure frequency than the control group, whereas the study by Rong et al.[26] found the opposite to be true. provided inadequate data regarding tVNS intervention, focusing on other biases in both studies. Initial assessment of patient demographics from all studies revealed heterogeneity in terms of initial seizure frequency as in addition to Aihua et al not reporting the aforementioned data, median with standard deviation was chosen as measure by Rong et al to report initial seizure frequency - leaving the studies by Bauer and Yang as the only two studies included to report initial seizure frequency through mean. Bauer et al. reported a higher seizure frequency among subjects in the intervention group than among controls, while Rong et al. reported otherwise.

Seizure Frequency and Responder Rate

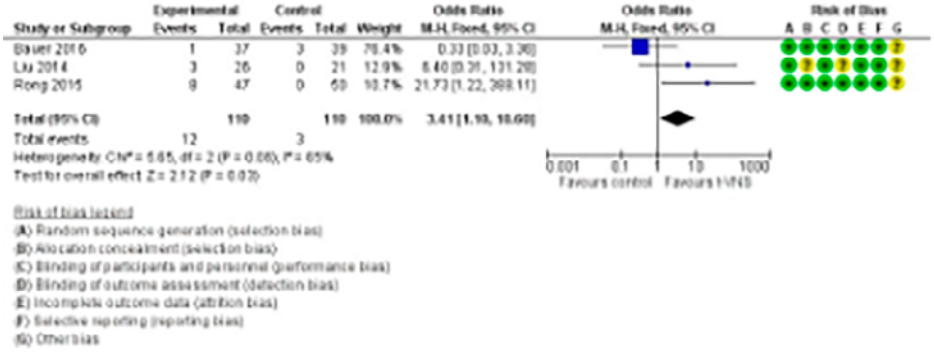

Figure 3. Forest Plot Comparison Regarding Seizure-Free Rate

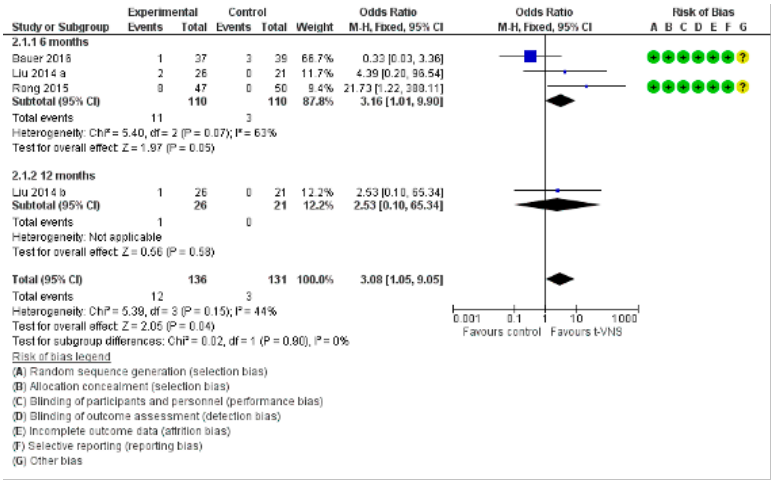

Figure 4. Forest Plot Comparison Regarding Subgroup Seizure-Free Rate

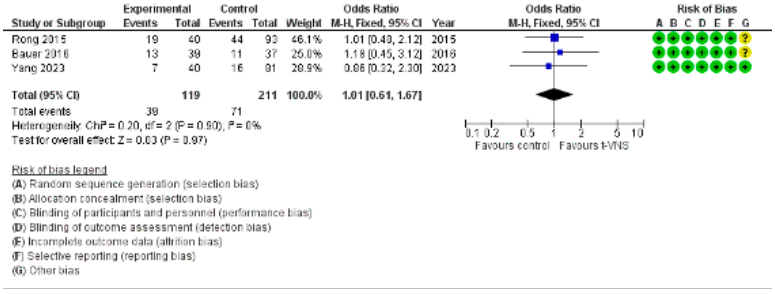

Figure 5. Forest Plot Comparison Regarding Responder Rate

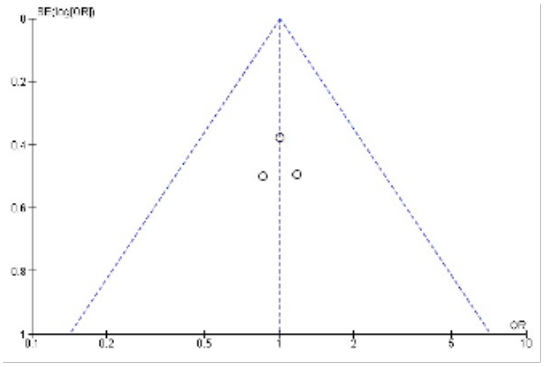

Figure 6. Funnel Plot Regarding Responder Rate

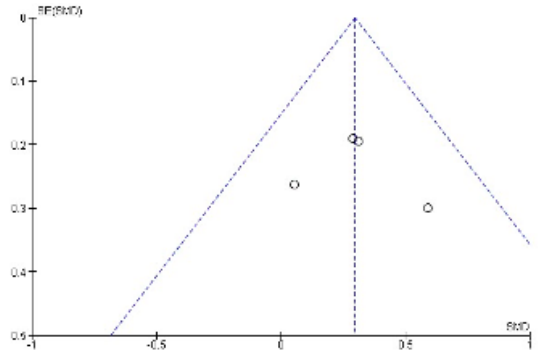

Figure 6. Funnel Plot Regarding Seizure Frequency

Seizure frequency was evaluated in four investigations encompassing 359 participants at the conclusion. The meta-analysis demonstrated a statistically significant difference, as illustrated in Figure 3, indicating that patients who underwent t-VNS experienced a better positive outcome with Z = 2.65 (p = 0.008) following the assessment of overall effect (95% CI 0.08–0.52; I2 = 0%, p = 0.61). This outcome signifies an improvement in individuals administered t-VNS treatment. All studies demonstrated substantial disparities in seizure reduction (Table 2).

Only three trials reported seizure-free rates for patients in both the treatment and control groups. Bauer et al. determined that 2.70% of patients in the therapy group were seizure-free, in contrast to 7.70% in the control group. Rong et al. presented a noteworthy finding: 15.10% of patients undergoing the treatment attained seizure-free condition, in contrast to merely 5% of those in the control group. The response rate was assessed in three investigations. Bauer et al. indicate that around 29.70% of patients treated with t-VNS are classified as responders, but Rong et al. claim a response rate of 47.40%, and Yang et al. disclose that 44.7% of participants reacted to the treatment. Figure 3 illustrates that there was no significant difference in responder rates between the treatment group and the control group following comprehensive analysis (Z = 0.03, P = 0.97, 95% CI (OR) 1.01(0.61–1.67); I2 = 0%). Sensitivity analysis indicated the absence of research with results beyond the funnel plot, signifying no publication bias.

A significant difference was found in the number of seizure-free subjects between the treatment and control groups (Z = 2.12, P = 0.03, 95% CI (OR) 3.41(1.10 – 10.60); I^2 = 65%). Due to the high heterogeneity (I^2 = 65%), subgroup analyses were performed in which the results from Liu et al. were divided into 2 timelines, the amount of seizure free during 6 and 12 months after treatment. (Z = 2.05, P = 0.04, 95% CI (OR) 3.08 (1.05 – 9.05); I^2 = 0%).

Quality of Life

Three studies reported improvement in quality of life. Liu, A et al. only mentioned the improvement of QOLIE-31 score in t-VNS group. Studies conducted by Bauer et al. and Yang et al., improvements in QOLIE-31 scores were seen in both the t-VNS group and the control group. Bauer et al.[23] showed an increase of 2.68 points in the t-VNS group and 4.65 points in the control group. Meanwhile, Yang et al.[20] showed an improvement of 2.75 points in the t-VNS group and 10.63 points in the control group. None of the three studies found a statistically significant difference between the t-VNS and control groups when it came to QOLIE-31 scores.

Seizure severity was assessed using LSSS in two studies. There was a conflict in the findings on seizure severity: Aihua et al. reported a significant improvement for those receiving t-VNS, but Bauer et al. found no significant difference and noted that severity actually increased.

Adverse Events

Of the three studies, the most common adverse event was local discomfort at the t-VNS site. Other adverse events reported by Rong et al.[22] were rash and swelling in the skin of the t-VNS site and one drop out due to severe dizziness. Yang, et al.[20] reported sleep disturbance, flu-like symptoms, and pain. Aihua et al.[21] reported 1 patient suffering from dizziness after t-VNS stimulation.

Discussion

This review presents a comprehensive analysis of existing RCTs, highlighting the advantages of t-VNS in decreasing seizure frequency and enhancing treatment efficacy. By combining data from four RCTs (n=359), our meta-analysis uncovered a moderate effect size that was statistically significant and favored t-VNS (SMD = 0.30; 95% CI: 0.08–0.52; p = 0.008), with no observed heterogeneity (I^2 = 0%). These clinical findings support t-VNS as a promising adjunctive therapy for DRE, particularly given its noninvasive nature.

While the specific mechanism of action is still not completely clear,[17] it has been proposed that afferent vagal input activates the STN, which subsequently projects to the LC, which is the main source of norepinephrine in the brain. Supporting this, a study by Berger et al.[37] observed a trend toward a significant association between clinical response to VNS and increased contrast in the caudal portion of the right LC (p = 0.03, pFDR = 0.08), suggesting a neurophysiological correlation to treatment efficacy. Even though this connection wasn't statistically significant after being corrected, it does point to a possible link between LC activation and the positive effects of VNS, which deserves more research.

In line with this, t-VNS is thought to modulate limbic system activity, including the posterior cingulate gyrus and hippocampus, and may exert anticonvulsant effects through these pathways.[24] Anatomically, t-VNS does not directly stimulate the vagus nerve, but rather activates it through its auricular branches—most effectively via the cymba conchae, which has demonstrated superior activation of both the NTS and LC compared to sham stimulation.[32]

Among the studies reviewed, three out of four reported that the placement of t-VNS electrodes in the cymba conchae, while the remaining study utilized the triangular fossa of the auricle.[20-23] In the most cases, t-VNS applied in the left ear unilaterally as it prefers to avoid interference with cardiac function.[20-24] Due to insufficient data across studies, it was not possible to establish a correlation between the choiceof unilaterallor bilaterall VNS placement and specific types of epilepsy. However, Barbella et al. demonstrated that epilepsy with falls was a significant predictor of better outcomes with t-VNS treatment. Among patients, the number of seizures involving falls was reduced, and they became less disabling, especially when an aura happened beforehand.[25] The stimulation frequencies employed in the studies ranged from 20 to 30 Hz. The intensity level was generally adjusted to fit each patient's comfort and tolerance, with the final stimulation intensity in the reviewed studies averaging 1–2 mA. From 20 minutes to continuous stimulation, the length of the stimulation sessions varied greatly. Despite this, there is no agreement in the scientific literature about the ideal features for stimulation.[14,26] The studies examined in our study lasted from 20 weeks[20] and 12 months[21].

In this review, the frequency of seizures in the treatment group was significantly lower than in the control group. These results point to t-VNS as a promising option for controlling seizures. The mean seizure reduction across the four studies was approximately 30%, with about 33.6% of patients classified as responders, which, according to Kulju et al.[38], is determined if an epilepsy patient gained >50% seizure frequency reduction over the course of neurostimulation therapy. The

results are analogous to those seen in individuals undergoing VNS, with a 50.6% response rate and a mean seizure reduction of 44.6%.[27] However, a significant difference in responder rates could not be conclusively determined due to limitations in the quality and consistency of the study data. Compared to the other three studies, Bauer et al.'s[5] study found a lower mean seizure reduction rate, which could be explained by variations in the patient selection criteria. The study indicated a diminished mean seizure reduction rate compared to the previous three studies, potentially due to variations in patient selection criteria. Bauer et al. specifically.[23] included patients who had utilized less antiepileptic drugs (AEDs) and were in a more stable condition, whereas the other three studies involved patients with more refractory seizure onsets and a higher number of prior AEDs.[23] This implies that in patients receiving t-VNS therapy, the intensity of seizure frequency may be a potential predictor of treatment success.

A significant difference in seizure-free subjects was found between the treatment and control groups. Although the duration of seizure free was found to be reduced in 12 month post treatment due to the difference of the stimulation intensity given between these subjects, this revealed t-VNS to be able to provide a longer duration which patient would be able to live without experiencing any seizure if t-VNS is provided while also increasing the stimulation intensity during the treatment instead of using the same amount of intensity throughout the treatment.[2]

Ghani et al. found that raising the stimulus frequency in the 1–30 Hz range is an improved approach to lower the number of seizures in people with epilepsy who don't respond to medication or surgery.[28] On the other hand, study by Jiao et al. indicates that high-frequency VNS (130–180 Hz) may be superior to 30 Hz in reducing seizure activity.[29]

Because the right vagus nerve sends signals to the heart, transcutaneous vagus nerve stimulation (tVNS) is only safe when it is given to the left ear.[30] This occurs because The right vagus nerve connects to the sinoatrial (SA) node, and the left vagus nerve connects to the atrioventricular (AV) node.[31] Gentile et al. conducted a study demonstrating that acute right-sided tVNS enhances cardiovagal baroreflex in individuals with congestive heart failure (CHF) and diminished left ventricular ejection fraction (LVEF).[32]

Quality of Life

This topic was only suitable for descriptive analysis, as not all of the included RCTs provided a quantitative assessment of quality of life and seizure severity. The QOLIE-31 is a recognized instrument for assessing many health-associated aspects of life dimensions, including social functioning, emotional well-being, energy or weariness, and cognitive functioning in individuals with epileps [39]. QOLIE-31 was used to evaluate these aspects in the studies by Aihua, Bauer and Yang et al. [5, 26, 33] However, QOL was only evaluated among subjects receiving t-VNS by Aihua et al - showing an increase of 106.95 points while all subjects were assessed accordingly by Bauer and Yang et al - who reported better QOLIE-31 scores in terms of final endpoint assessment and increase by control compared with the t-VNS group, albeit not significant. This presented yet another discrepancy that strengthened the unsuitability for this topic to be meta-analyzed.

As with general quality of life, not all of the included RCTs provided quantitative assessment of seizure severity; only Aihua and Bauer et al. assessed seizure severity quantitatively using the Liverpool Seizure Severity Scale (LSSS). LSSS is one of the recommended tools for quantifying the perception of seizure severity in adults with epilepsy.[40]

Although a significant decrease was reported by Aihua et al. in the t-VNS group, significance was not reported by Bauer et al., who instead showed increasing seizure severity among subjects receiving t-VNS compared to controls. The discrepancy shown by RCTs included in this study regarding the reporting of quality of life and seizure severity in a standardized, quantitative measure brought a limitation for this study, warranting further attention in engaging further studies to better assess this point of contention for better understanding regarding efficacy of t-VNS as a whole.

Adverse Events

Most patients in the study did not experience adverse events related to t-VNS. T-VNS can induce both anti-nociceptive and pro-nociceptive effects.[33] The response to t-VNS varies based on individual susceptibility, influencing whether the stimulation relieves or worsens pain perception. Laqua et al. documented a severe vasovagal reaction in a participant, reinforcing the hypothesis that sensitivity to t-VNS varies among individuals.[33] However, the adverse events reported in our review were modest to moderate in intensity; an

ECG examination revealed mild sinus bradycardia in one patient in the active stimulation group[20] exhibited asymptomatic mild sinus bradycardia, whichwas detected on ECG examination. Compared with i-VNS, t-VNS is associated with fewer adverse events. Frequent adverse effects of i-VNS encompass voice modification, paraesthesia, cough, headache, dyspnoea, pharyngitis, and discomfort.[34] However, further research is needed to fully evaluate the benefits of t-VNS as a non-invasive therapeutic approach.

Study Limitations

It is important to note that this review has several limitations, one of which is the relatively small number of participants in the four included RCTs, which constrained the pooling of seizure frequency and treatment response outcomes and precluded meta-regression analysis of covariates influencing these outcomes. In relation to seizure frequency, three out of the four included RCTs reported responder rates, warranting caution in approaching this particular topic, as the result presented in this study may be statistically undermined. Additionally, the number of studies reporting QOL in patients undergoing t-VNS was limited–all the more so regarding seizure severity, as this study presented the non-standardized reporting of QOL and seizure severity in a quantitative fashion. Consequently, owing to the scarcity of data, it is challenging to conclude whether t-VNS significantly improves patient QOL. Furthermore, a number of studies found a moderate to high risk of bias, and clinical disparities among the studies, such as differences in the underlying conditions of the patients, institutional expertise with t-VNS, treatment duration, and stimulation parameters, constrained our review. It was not possible to analyze the genesis of epilepsy and the placement of unilateral or bilateral electrodes since this review lacked sufficient information on the etiology of epilepsy. Finally, the consumption of AEDs varied considerably across studies, which may have influenced the outcomes to differing degrees.

Despite these limitations, our review showed favorable outcomes in the treatment arm compared to the control arm, indicating that t-VNS has comparable outcomes to controls in patients with DRE.

CONCLUSIONS

In conclusion, the findings of this meta-analysis indicate that t-VNS exerts a significant influence on seizure control and is associated with mild-to-moderate adverse effects. However, the interpretation of certain critical outcomes, including epilepsy etiology, treatment parameters, and treatment duration, was constrained by the high heterogeneity observed across studies. This limitation precluded us from drawing definitive conclusions regarding these factors. Furthermore, it is important to note that no RCT has been conducted to directly compare the efficacy of t-VNS and i-VNS. Such a study would be valuable for fully elucidating the comparative potential of t-VNS in relation to i-VNS.

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Authors' contributions

R.I: Conceptualization, methodology, data – extraction, data – analysis, writing – original draft; F.W: Conceptualization, methodology, data – extraction, writing – original draft; Y.B Conceptualization, methodology, data – extraction, data – analysis, writing – original draft, writing – review and editing; I.N.S.S: data – extraction, data – analysis, data – visualization, writing – original draft; M.T.A: Conceptualization, methodology, data – extraction, data – analysis, writing – original draft, writing – review and editing.

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