Pooled analysis of the efficacy and safety of tibial nerve stimulation versus antimuscarinic agents in the management of overactive bladder syndrome

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Abstract

Objectives: The purpose of this meta-analysis was to evaluate the efficacy and safety of tibial nerve stimulation (TNS) versus antimuscarinic agents in the management of overactive bladder (OAB) syndrome.

Methods: The databases MEDLINE, EMBASE, the Cochrane Controlled Trial Register of Controlled Trials from 2000 to May 2021 were searched to identify randomized controlled trials that referred to the use of TNS and antimuscarinic agents for the treatment of OAB syndrome. A systematic review and meta-analysis was conducted.

Results: Eight publications involving 420 patients were included in the meta-analysis. In the analysis, we found TNS had a comparable effect with antimuscarinic agents on micturition per day, nocturia, urge incontinence, and voided volume (P = .9; .4; .78; .44, respectively). Scores measured by questionnaires Overactive Bladder Symptom Score and Overactive Bladder questionnaire Short Form items also indicated no statistical difference between 2 groups. TNS group had a significantly less discontinuation rate and adverse events (P = .003; .0001).

Conclusions: TNS is as effective as antimuscarinic agents for the treatment of OAB. Moreover, TNS appears to be more tolerable and safer than antimuscarinic agents.

Abbreviations: AEs = adverse events, CIs = confidence intervals, MDs = mean differences, OAB = overactive bladder, OAB-qSF = Overactive Bladder questionnaire Short Form 6 items, OAB-qSF 13 = Overactive Bladder questionnaire Short Form 13 items, OABSS = Overactive Bladder Symptom Score, PTNS = percutaneous tibial nerve stimulation, QoL = quality of life, RCTs = randomized controlled trials, TNS = tibial nerve stimulation.

Keywords: antimuscarinic agents, meta-analysis, overactive bladder syndrome, randomized controlled trials, tibial nerve stimulation

1. Introduction

Overactive bladder (OAB) is a symptom complex defined as urinary urgency, usually accompanied by frequency and nocturia with or without urge incontinence in the absence of pathologic or metabolic conditions that might explain these symptoms. The prevalence of OAB has been reported to be about one-sixth of the population in the United States and up to one-fifth of the population in Asia. With such a prevalence, OAB can have a significant negative impact on quality of life (QoL). According to the 2019 American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction guidelines, the management of OAB includes conservative treatment with behavior and pharmacological therapies and surgical treatment.

Currently, the antimuscarinic agents are the first-line medications for the treatment of OAB including oxybutynin, darifenacin, solifenacin, tolterodine, fesoterodine, and trospium. Though they have pronounced ability to improve the symptoms of a big amount of patients with OAB, the drug discontinuation is high with a mean rate of 58.8% at 6 months, as a result of its systemic anticholinergic side effects, insufficient response, and enduring costs.

Given the limitation mentioned above, there is a growing requirement for other therapy methods that had less side effect,
less costs, and same therapeutic effect as anticholinergic drugs. Neuromodulation seems to be that very alternative therapy option which is efficient in the treatment of lower urinary tract syndromes with less undesirable side effects.[10,11] Although the specific mechanism of neuromodulation has not been explained clear totally, 2 potential mechanisms are considered to be possible: activate the afferent fibers and lead to inhibition at a spinal or supraspinal level; and activate the efferent fibers to the striated urethral sphincter which releases detrusor reflexively.[12] Tibial nerve stimulation (TNS) is one sort of neuromodulation which was approved for refractory OAB by Food and Drug Administration in 2010. Percutaneous tibial nerve stimulation (PTNS) is performed via placement of a peripheral needle that stimulates the posterior tibial nerve. Electrical impulses are delivered along the tibial nerve to the S2/S3 segment of the pelvic sacral plexus which contains the spinal center of bladder control.[13,14] In a systematic review of the available studies, PTNS showed a therapeutic success rate ranging from 54% to 59%.[15]

Nowadays, some randomized controlled trials (RCTs) compared the efficiency of TNS and antimuscarinic agents for the treatment of OAB but their outcomes varied a lot.[16–23] And there has been no systematic meta-analysis of assessing the efficacy and safety of TNS versus antimuscarinic agents in treatment of OAB. Therefore, we performed this meta-analysis to compare the efficiency and tolerance between TNS and antimuscarinic agents for the treatment of OAB.

2. Materials and methods

2.1. Inclusion criteria and exclusion criteria

RCTs were required to meet the following inclusion criteria: RCTs studied the efficacy of TNS and antimuscarinic agents for the treatment of OAB; provided sufficient data for analysis, including the mean values and the standard deviations for the OAB, Overactive Bladder questionnaire Short Form items, micturition, nocturia, urge incontinence, and voided volume; English was the publish language of the articles; and the full text of the study could be accessed. If the above inclusion criteria were not met, the studies were excluded from the analysis. Articles with the following exclusion criteria were eliminated: duplicate articles; the reported data were clearly erroneous or incomplete; conference abstract; pediatric and obese patients; and did not meet the inclusion criteria.

2.2. Search strategy

MEDLINE, EMBASE, the Cochrane Controlled Trail Register of Controlled Trials, and the reference lists of retrieved studies were searched to identify RCTs that referred to the efficacy and safety of TNS and antimuscarinic agents for the treatment of OAB. The following search terms were used: tibial nerve stimulation (TNS), percutaneous tibial nerve stimulation (PTNS), transcutaneous tibial nerve stimulation (TTNS); antimuscarinic agents, anticholinergic drugs solifenacin, tolterodine, oxybutynin, darifenacin, fesoterodine, trospium, and overactive bladder. Abbreviations (TNS, PTNS, TTNS, OAB) were also searched.

2.3. Trial selection

The authors independently identified potentially relevant studies and trials. Together, we discussed each of the RCTs that was included and excluded. We excluded studies that either failed to meet the inclusion criteria or had discrepancies that could not be resolved. The study selection process is presented by a diagram in Figure 1.

2.4. Quality assessment

All the identified RCTs were included in the meta-analysis regardless of the quality score. The quality levels of the enrolled RCTs were assessed according to the Cochrane Collaboration bias appraisal tool.[24] The methodological quality of each trial was assessed based on the following items: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Each item was assessed with low risk, high risk, or unclear. Differences were resolved by discussion among the authors.

2.5. Data extraction

We independently performed the data extraction for the meta-analysis, which included the following: the name of the first author and the publication year, the design of the study, the therapy that the patients received, the number and gender of the patients, the duration of follow-up, the outcome measurements of the study, the inclusion criteria, the incidence of side effects, the discontinuation because of adverse events (AEs), the baseline and outcome micturition per day, nocturia per night, urge incontinence per day, Overactive Bladder Symptom Score (OABSS), Overactive Bladder questionnaire Short Form 6 items (OAB-qSF 6), and Overactive Bladder questionnaire Short Form 13 items (OAB-qSF 13).

2.6. Statistical analysis

The pooled effects were expressed as the mean differences (MDs) for continuous outcomes and odds ratios for dichotomy vary with 95% confidence intervals (CIs). Heterogeneity of the
enrolled studies was assessed according to Higgins I² and the Cochrane Q-statistic test. When there was no conspicuous heterogeneity (P > .1 or I² ≤ 50%), a fixed model (Mantel-Haenszel method) was used; otherwise, a random model (DerSimonian-Laird method) was applied. A 2-sided P < .05 was considered statistically significant. By removing each study sequentially, sensitivity analyses were performed to evaluate the stability of the final results. All these are dealt with Review Manager 5.3 (The Cochrane Collaboration, London, UK).

3. Results

3.1. Characteristics of individual studies

Based on the inclusion and exclusion criteria, 8 RCTs involving 420 patients were included in the analysis. The characteristics of the individual studies are listed in Table 1.

3.2. Quality of individual studies

Among the trials in the analysis, all the 8 studies are RCTs and were included for the meta-analysis. All of the included RCTs were not blinded. The quality of all the identified studies that we searched shows in Table 2.

3.3. Efficacy assessment

As revealing in Figure 2, 5 studies assessed the micturition per day. The pooled MD for micturition was -0.14 (95% CI -2.29 to 2.01, P = .9), which indicated that TNS had no significantly better effect on reducing micturition. Three studies assessed the nocturia per night. The pooled MD was -0.72 (95% CI -2.39 to 0.94, P = .4), indicating no significant difference in reducing nocturia. Four studies reported urge incontinence per day. The pooled MD for urge incontinence was 0.09 (95% CI -0.55 to

Table 1
Characteristics of individual study.

| Study | Design | Experimental group | Control group | Sample size | Follow-up | Outcome measurements | Inclusion criteria |
|-------|--------|--------------------|---------------|-------------|-----------|----------------------|-------------------|
| Kızılyel 2015 | RCT | PTNS once/week for 30 min | Tolerodine 4 mg/d | 10 | 10 | Female | 12 wks | Micturition, nocturia, urge incontinence, and OABSS | Women with OAB at least 6 months |
| Manríquez 2016 | RCT | TTNS twice/week for 30 min | Oxybutynin 10 mg/d | 34 | 30 | Female | 12 wks | Micturition, urge incontinence, and AEs | Women with OAB |
| Peters 2009 | RCT | PTNS once/week for 30 min | Tolerodine 4 mg/d or 2 mg/d | 41 | 43 | Mixed | 12 wks | Micturition, nocturia, urge incontinence, voided volume, and AEs | Patients with OAB |
| Preyer 2015 | RCT | PTNS once/week for 30 min | Tolerodine 2 mg/day | 16 | 16 | Female | 3 mos | Micturition, urge incontinence, and AEs | Women with OAB |
| Souto 2014 | RCT | TTNS twice/week for 30 min | Oxybutynin 10 mg/d | 18 | 19 | Female | 12 wks | OABSS | Women with OAB |
| Vecchioli 2013 | RCT | PTNS twice/week for 30 min | Solifenacin 5 mg/d | 16 | 14 | Female | 6 wks | Micturition, nocturia, urge incontinence, voided volume, AEs, OAB-qSF 6, and OAB-qSF 13 | Women with OAB |
| Vecchioli 2018 | RCT | PTNS twice/week for 30 min | Solifenacin 5 mg/d | 34 | 27 | Female | 12 wks | OABSS, OAB-qSF 6, and OAB-qSF 13 | Women with OAB |
| Zonč 2019 | RCT | TTNS every day for 30 min | Oxybutynin 5 mg twice/d | 30 | 30 | Mixed | 3 mos | Micturition, nocturia, and AEs | Multiple sclerosis patients with OAB |

AEs = adverse events, OAB = overactive bladder, OAB-qSF 6 = Overactive Bladder questionnaire Short Form 6 items, OAB-qSF 13 = Overactive Bladder questionnaire Short Form 13 items, OABSS = Overactive Bladder Symptom Score, PTNS = percutaneous tibial nerve stimulation, RCT = randomized controlled trial, TTNS = transcutaneous tibial nerve stimulation.

Table 2
ROB for included randomized controlled trials.

| Study | Sequence generation | Allocation concealment | Blinding | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|-------|---------------------|------------------------|----------|-------------------------|---------------------------|----------------------|
| Kızılyel 2015 | ? | ? | – | + | + | + |
| Manríquez 2016 | + | + | – | + | + | + |
| Peters 2009 | + | + | – | + | + | + |
| Preyer 2015 | + | + | – | + | + | + |
| Souto 2014 | + | + | – | ? | + | + |
| Vecchioli 2013 | ? | ? | – | + | + | + |
| Vecchioli 2018 | + | + | – | + | + | + |
| Zonč 2019 | ? | ? | – | + | + | + |

+, indicates low risk of bias; ?, unclear risk of bias; –, high risk of bias. ROB = risk of bias.
indicating no significant difference in reducing urge incontinence. In terms of voided volume, only 2 studies were included in the analysis, the pooled MD was 6.05 (95%CI −9.24 to 21.34, \(P = .44\)), which indicated that TNS had a comparable effect with antimuscarinic agents on increasing voided volume.

Regarding the outcomes measured by questionnaires, the OABSS (MD: \(−2.23\); 95%CI, \(-6.49\) to 2.03; \(P = .3\)), the OAB-qSF 6 (MD: \(-0.23\); 95%CI, \(-0.57\) to 0.11; \(P = .19\)), and OAB-qSF 13 (MD: \(-0.34\); 95%CI, \(-0.71\) to 0.03; \(P = .07\)) also indicated that TNS had a comparable effect with antimuscarinic agents on improving OABSS, OAB-qSF 6, and OAB-qSF 13 (Fig. 3).

### 3.4. Safety assessment

With regard to safety profile, there was no severe AE in the current study. Most of the side effects were mild or moderate, including dry mouth and constipation in the antimuscarinic agents group and puncture pain in the TNS group. As showed in Figure 4, the incidence of AEs and discontinuation because of AEs was compared between the TNS group and antimuscarinic agents group. The relevant odds ratios were 0.08 (95%CI 0.02–0.26, \(P < .0001\)) and 0.13 (95%CI 0.03–0.51, \(P = .003\)), indicating that TNS had significantly fewer incidence of AEs and less discontinuation because of AEs than antimuscarinic agents.

### 4. Discussion

OAB is a prevalent and distressing symptom complex which is known to increase with age and has a significant effect on QoL.[28] Whilst antimuscarinic agents remain integral in the management of OAB, their side effects commonly limit ongoing use and include dry mouth, dry eyes, constipation, blurred vision, dyspepsia, urinary retention, and impaired cognitive function.[29] Besides, there is increasing evidence to suggest that these drugs may act on the central nervous system and may lead to a long-term reduction of cognitive function and dementia.[30] Sometimes OAB and underactive bladder syndrome can coexist in the same patient and, if so, need a specific approach beyond treatment of the single and apparently opposing syndromes.[31] Botulinum toxin A, sacral nerve stimulation, and PTNS are established treatments for idiopathic OAB refractory to oral drug therapy. Further research is required to optimize these procedures and to better understand which patients will benefit from the various options available in managing refractory OAB.[32] Several systemic reviews have demonstrated the efficiency and safety of TNS in the treatment of OAB.[14,33,34] Generally, TNS had rare side effects and common side effects contain puncture pain, swelling, hematuria, headache, leg cramps, vasovagal response, and intermittent foot/toe pain.[16,35,36] Over the past decade, 2 meta-analyses have shown that TNS had significantly better improvements on the symptoms of OAB comparing with sham treatment.[37,38] However, due to the lack of enough studies,
these 2 meta-analyses had not sufficient efficiency to show any superiority on improving OAB symptoms between TNS and antimuscarinic agents.

In our meta-analysis, we found that TNS had a comparable effect on the improvement of micturition, nocturia, urge incontinence, and voiding volume compared with antimuscarinic agents. Except for comparing the improvements of symptoms, we also included commonly used questionnaires, involving OABSS, OAB-qSF 6, and OAB-qSF 13, to assess the impact of OAB symptoms on patient’s QoL and the patient impression of improvement. Our meta-analysis found that TNS had a comparable effect on improving OABSS, OAB-qSF 6, and OAB-qSF 13 than antimuscarinic agents. Tolerance of antimuscarinic agents was poor for patients with OAB. In our meta-analysis, the incidence of side effect and the discontinuation because of AEs in the antimuscarinic agents group was significantly higher than that of the TNS group. In other words, the tolerance of TNS is better than that of antimuscarinic agents, and this tolerance could even be much better if we adopt transcutaneous TNS, which abandons the traditional needle and uses the superficial electrode to stimulate the nerve, making it less invasive and more tolerable.[21] After a comprehensive analysis of all results, our meta-analysis suggested the equal efficacy and more safety of TNS in treating OAB compared with antimuscarinic agents.

All of the included RCTs have demonstrated that short term TNS had a significant effect on the improvement of OAB. MacDiarmid et al.[39] offered an additional 9 months of TNS treatment for the patients, who were randomized to TNS group in

Figure 3. Forest plot for the OABSS, OAB-qSF 6, OAB-qSF 13, and PGI-I. OAB-qSF 6 = Overactive Bladder questionnaire Short Form 6 items, OAB-qSF 13 = Overactive Bladder questionnaire Short Form 13 items, OABSS = Overactive Bladder Symptom Score, PGI-I = Patient Global Impression of Improvement questionnaire.

Figure 4. Forest plot for adverse event and discontinuation because of an adverse event.
Overactive Bladder Innovative Therapy Trail and have already received 12 weeks of TNS therapy, to evaluate the sustained therapeutic efficacy. They found evidence that TNS a durable and long-term effect on OAB symptoms from 12 weeks to 12 months. The pathophysiology of TNS with OAB has not been clearly proved yet, but there is a study proposing that the plastic reorganization of the cortical network induced by the peripheral stimulation might be responsible for it.[90]

Compared with previous systematic reviews and meta-analyses, our research has several advantages. All of the included studies were RCTs, which had a relatively higher level of evidence comparing with non-RCTs. And most of the included patients were not refractory patients with OAB and some of them were naïve treatment, the outcomes might slightly be influenced by the resistance to antimuscarinic agents. In addition to bladder diary parameters and success rates, we also summarize the questionnaire score.

Although the studies included in this meta-analysis provided evidence favoring TNS, our meta-analysis has several limitations. Firstly, the sample size was not large. Secondly, all of the included RCTs were not blinded, which may lead to some unavoidable biases influencing the results of this meta-analysis. Thirdly, the dosage, variety, frequency, duration, and cycle of TNS and antimuscarinic agents varied a lot in different studies and these variations could also be found in the baseline information and measurement parameters which may lead to bias. Besides, all of the studies only assessed the short-time efficiency of TNS and antimuscarinic agents and the long-term effect needs to be assessed in the subsequent follow-up. Therefore, more high-quality RCTs with large scale and long-time follow-up are strongly necessary to evaluate the efficiency of TNS and antimuscarinic agents.

5. Conclusions
In this meta-analysis, we confirm that TNS has comparable therapeutic effects on the improvement of OAB symptoms including micturition, nocturia, urgency, and voiding volume compared with antimuscarinic agents. Compared with patients receiving antimuscarinic agents, those receiving TNS have a similar improvement of OABSS, OAB-qSF 6, and OAB-qSF 13 but had a better impression on the improvement of OAB in terms of Patient Global Impression of Improvement. Besides, we also found that PTNS, with less side effects and less discontinuation, was more tolerable compared with antimuscarinic agents. PTNS can be an alternative option of antimuscarinic agents for the treatment of OAB.

Author contributions

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