Effectiveness of Short Term Percutaneous Tibial Nerve Stimulation for Non-neurogenic Overactive Bladder Syndrome in Adults: A Meta-analysis

Elita Wibisono, Harrina E. Rahardjo

Department of Urology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Correspondence mail:
Department of Urology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro 71, Jakarta 10430, Indonesia. email: drelitawibisono@gmail.com.

ABSTRAK

Tujuan: *menilai efektivitas stimulasi saraf tibia perkutaneus/percutaneous tibial nerve stimulation (PTNS) untuk OAB non-neurogenik pada orang dewasa secara sistematik dengan membandingkan prosedur semu (sham procedure) dan terapi lainnya.* ***Metode:*** *kami melakukan kajian sistematis atas penelitian kohort. Sumber data meliputi MEDLINE, EMBASE, CINAHL, National Library for Health, Cochrane dan google scholar dari tahun 2005 hingga 2015. Meta analisis dilakukan dengan menggunakan model efek acak (random effects model). Heterogenitas efek tersebut dinilai dengan menghitung statistik I2. Analisis statistik dilakukan menggunakan program Review Manager 5.3 untuk meta analisis uji klinis acak (RCT meta-analysis).* ***Hasil:*** *kami menganalisis 11 uji klinis acak terkontrol atau randomised controlled trial (RCT) dan lima penelitian prospektif non-komparatif dengan tingkat keberhasilan yang beragam. Berdasarkan persentase responden, hasilnya adalah 37,3% - 81,8% untuk kelompok PTNS, 0% - 20,9% untuk kelompok sham, 54,8% untuk kelompok anti-muskarinik dan 89,7% untuk kelompok multimodal. Berkurangnya episode gejala berkemih per hari ditemukan pada kelompok PTNS (0,7-4,5), sham (0,3-1,5) dan kelompok anti-muskarinik (0,6-2,9). Pada meta-analisis empat RCT, hasilnya menunjukkan bahwa PTNS lebih baik daripada prosedur sham dengan rasio risiko keseluruhan sebesar 7,32 (IK95% 1,69-32,16), p=0,09, I2=54%.* ***Kesimpulan:*** *terdapat bukti efektivitas PTNS jangka pendek sebagai terapi untuk OAB non-neurogenik. PTNS terbukti lebih baik secara bermakna dibandingkan prosedur sham.*

Kata kunci: *overactive bladder, percutaneous tibial nerve stimulation, sham, anti-muskarinik, gejala berkemih.*

ABSTRACT

Aim: *to evaluate the effectiveness of short-term PTNS for non-neurogenic OAB in adults systematically by comparing with sham procedure and other treatments.* ***Methods:*** *we performed a systematic review of cohort study. Data sources were MEDLINE, EMBASE, CINAHL, National Library for Health, Cochrane, and google scholar from 2005 through 2015. Meta-analysis was performed using the random effects model. Heterogeneity of effects was assessed by calculating I2 statistic. Statistical analysis was performed using Review Manager 5.3 for RCT meta-analysis.* ***Results:*** *we analized 11 randomised controlled trial (RCT) and five prospective non-comparative studies with variable success rate. Based on percentage of responders, the results were 37.3% - 81.8% in PTNS group, 0% - 20.9% in sham group, 54.8% in anti-muscarinic group, and 89.7% in multimodal group. The decrease of voiding symptoms episodes per day was found in PTNS (0.7-4.5), sham (0.3-1.5), and anti-muscarinic (0.6-2.9) groups. In meta-analysis of four RCTs, the results favour PTNS over sham procedure with overall risk ratio of 7.32 (95% CI of 1.69-32.16), p=0.09, I2=54%.* ***Conclusion:*** *there is an evidence of effectiveness of short term PTNS in treatment of non-neurogenic OAB. PTNS is proven significantly better than sham procedure.*

Key words: *overactive bladder, percutaneous tibial nerve stimulation, sham, anti-muscarinic, voiding symptoms.*

INTRODUCTION

Overactive bladder (OAB) is a common condition which refers to urgency with or without urgency incontinence, usually with frequency and nocturia in the absence of an underlying metabolic or pathological condition.[1] This problem is pervasive and has considerable effects on the quality of life. Around 455 million people (11% of the world population) are estimated to experience OAB symptoms during their life. The reported OAB prevalence in adult varies from 10.2% to 17.4% in males and 7.7 – 31.3% in females.[1-3] Urinary incontinence affects one-third of patients with OAB and thus associated with adverse effects on patients' health-related quality of life (HRQoL) as well as social interactions, sleep, depression and sexual health. Despite the high prevalence and impact of OAB, almost 60% of people with OAB do not seek medical assistance because of embarrassment of misconception of the disease.[4,5]

First line treatments of OAB are conservative treatment including bladder training, pelvic floor muscle training, and anti-muscarinic medication. Unfortunately, despite its effectiveness, only approximately 20% of OAB patients persist on medication therapy after 6 months. It is due to the fact of most commonly adverse events reported, such as dry mouth and constipation.[6,7] Then, patients with those conditions have treatment options like invasive surgery such as bladder augmentation, detrusor myomectomy, and urinary diversion or less invasive methods of treatment like botulinum toxin injection to the bladder and neuromodulation.

Percutaneous Tibial Nerve Stimulation (PTNS) is defined as a minimally invasive neuromodulation system delivering electrical stimulation to sacral nerve plexus through stimulation of posterior tibial nerve percutaneously. This nerve consists of mixed sensory motor nerve fibers originating from L4 through S3 which control modulation of innervation to the bladder, urinary sphincter, and pelvic floor. The system may have effect both on detrusor and micturition centers in the brain.[8] The stimuli is delivered by using a fine, 34-gauge needle electrode inserted just above the medial aspect of ankle. Commonly, PTNS cycles consist of 12-weekly treatment of 30 minutes with nocturia and urge incontinence, after 4 to 6 treatment as evaluated parameters.[9,10] The use of PTNS for OAB resistant to first line therapy is recommended by National Institute for Health and Clinical Excellence (NICE), European Association of Urology (EAU). In fact, the studies supporting guidelines really vary in terms of method, comparison, population, and outcome measured. Moreover, the success rates of PTNS use in OAB treatment have a great variation as well.

Therefore, this systematic review is necessary to solve this problem. The purpose of this study is to evaluate PTNS treatment for OAB systematically. Specifically, we limit the studies to non-neurogenic OAB only. The effectiveness of PTNS will be compared with sham procedure as well as other treatment like anti-muscarinic and combination therapy (PTNS and anti-muscarinic).

METHODS

Eligibility Criteria

All English language, prospective studies published on international journals in the last ten years were included in this review. Participants considered in the study were adults, with overactive bladder symptoms. Only studies describing effect of PTNS were included. Outcome measures were percentage of responders or patients with positive response and voiding diaries parameters including frequency, nocturia, urgency, incontinence, and voided volume.

Information Source

A literature search was performed using MEDLINE, EMBASE, CINAHL, National Library for Health, Cochrane and google scholar. The last literature search was run on January 2015.

Search

Search terms used were based on PICO formula. Related articles of relevant papers were also searched thoroughly.

Study Selection

Studies with randomized clinical trials and prospective study design about PTNS in

non-neurogenic OAB based on PICO criteria were included. The exclusion criterias were non-English articles, case reports or case series, studies about PTNS non reporting clinical results and retrospective studies.

Data Extraction and Quality assessment

Quality of study was assessed by reviewing papers titles and abstracts.

Statistical Analysis

Meta-analysis was performed using the random effects model. Heterogeneity was assessed by calculation the I2 statistic (low (25%-50%), moderate (50%-75%) and high (>75%)). Statistical analysis was performed using Review Manager 5.3 for RCT meta-analysis.

RESULTS

Evidence Synthesis

We included 16 studies in total. **Figure 1** summarizes the flow for study selection for this systematic review. There were 11 randomised clinical trial (RCT) studies and five prospective non-comparative studies which described effectiveness of PTNS (**Table 1**). Other studies were excluded as they did not meet inclusion and exclusion criterias.

Methodological Quality

Table 2 shows the methodological quality of the RCT included in this systematic review using Jadad scale. There were 5/11 studies with good

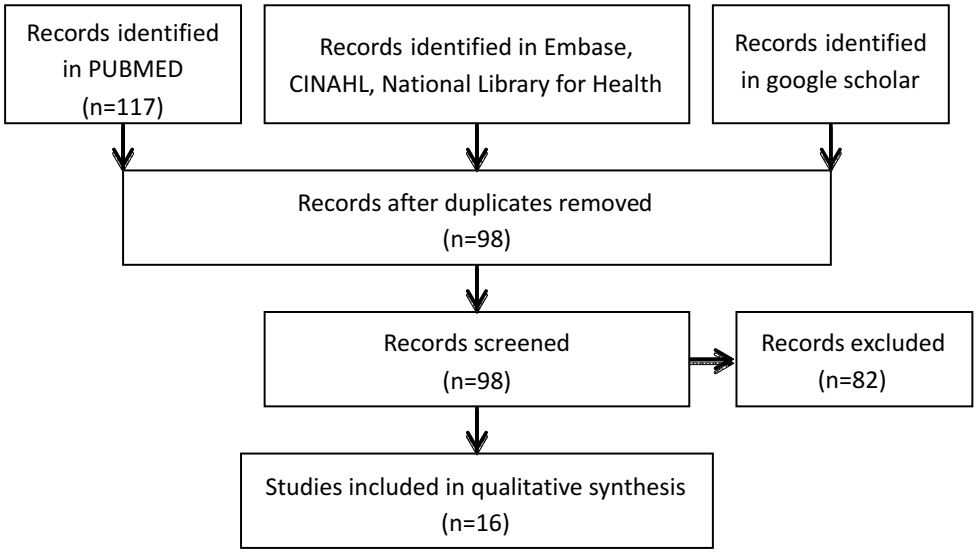

Figure 1. Search strategy used for systematic review of PTNS in OAB

Table 1. PICO formula

	Criteria	Search terms
Patients (P)	Adult patients with non-neurogenic OAB	"overactive bladder" or "detrusor overactivity" or "urgency"
Intervention (I)	Percutaneous tibial nerve stimulation (PTNS)	"neuromodulation" or "tibial nerve" or "percutaneous tibial nerve stimulation" or "posterior tibial nerve stimulation"
Comparison (C)	Sham nerve stimulation, anti-muscarinic medication, combination therapy, no comparison	"sham" or "placebo" or "anti-muscarinic" or "combination therapy" or "multimodal therapy"
Outcomes (O)	percentage of responders or patients with positive response and voiding diaries parameters including frequency, nocturia, urgency, incontinence, and voided volume	-

Table 2. Characteristic of the studies

No	Author, year	Randomized	Gender	Treatment groups	Age	N	Dosage	Duration
1	Souto et al, 2014[11]	RCT	females	PTNS	56.9 (33–77)	18	30 min; 2x/week	12 weeks
				Oxybutinyn	57.7 (34–79)	19	10 mg; daily	12 weeks
				PTNS + Oxybutynin	60.1 (33–77)	21	30 min; 2x/week (PTNS) and 10 mg; daily (Oxybutynin)	12 weeks
2	Vecchiolli et al, 2013[12]	RCT (crossover)	females	PTNS	63 (41-81)	16	30 min; 2x/week	6 weeks
				Solifenacin Succinate	61 (35-79)	14	5 mg; 1x/day	40 days
3	Polo et al, 2012[13]	NRCT	females	PTNS	60.8	14	8 weekly sessions, 4 sessions every 15 days, 2 monthly session	
4	Agro et al, 2010[14]	RCT	females	PTNS	44.9	17	30 min; 3x/week	4 weeks
				Sham	45.5	15	30 min; 3x/week	4 weeks
5	Peters et al, 2010[15] (SuMIT)	RCT	Mixed	PTNS	62.5	103	30 min; 1x/week	12 weeks
				Sham	60.5	105	30 min; 1x/week	12 weeks
6	Yoong et al, 2010[16]	NRCT	females	PTNS	55.3 (21-91)	43	30 min; 1x/week	6 weeks
7	Sancaktar et al, 2010[17]	RCT	females	Tolterodine	45.4-8.7	18	4 mg; 1x/day	12 weeks
				Tolterodine + PTNS	47.4-10.1	20	4 mg; 1x/day (Tolterodine) and 30 min; 1x/week	12 weeks
8	Peters et al, 2009[18] (OrBIT)	RCT	mixed	PTNS	57.5-15.2	44	30 min; 1x/week	12 weeks
				Tolterodine	58.2-11.3	42	4 mg; 1x/day	12 weeks
9	Agro et al, 2009[19]	RCT	females	PTNS	47-10.5	16	30 min; 3x/week	4 weeks
				sham	42-7	8	30 min; 3x/week	4 weeks
10	Preyer, 2007 (abstract)[20]	RCT	females	PTNS		16	30 min; 1x/week	12 weeks
				Tolterodine	59.4-10.9	15	2 mg; 2x/day	12 weeks
11	Van Balken et al, 2006[21]	NRCT	mixed	PTNS	54.1 (21-82)	83	30 min; 1x/week	12 weeks
12	Nuhoglu et al, 2006[22]	NRCT	females	PTNS	47.3±8.4	35	30 min; 1x/week	10 weeks
13	Van Der Pal et al, 2006[23]	NRCT	mixed	PTNS	51 (33-66)	11	30 min; 3x/weeks	4 week
14	Agro et al, 2005[24]	RCT	mixed	PTNS		17	30 min; 1x/week	12 weeks
				PTNS		18	30 min; 3x/week	4 weeks
15	Agro et al, 2005 (abstract)[25]	RCT	females	PTNS	43.5	8	30 min; 1x/week	12 weeks
				Sham	45.8	8	30 min; 1x/week	12 weeks
16	Karademir et al, 2005[26]	RCT	mixed	PTNS	40.3	21	60 min; 1x/week	8 weeks
				PTNS + Oxybutynin	43.1	22	5 mg; 1x/day	8 weeks

RCT=randomized controlled trial, NRCT = non randomized controlled trial

or excellent quality (Jadad score of 3 or more). Specifically, among 4 studies comparing PTNS with sham procedure, 3 studies had good quality.

Participants and Intervention

PTNS studies comprised a total of 787 adult participants, in which 480 patients treated with PTNS, 108 patients treated with anti-muscarinic, 63 patients treated with combination therapy, and 136 patients treated with sham treatment or placebo. In all studies the number of female patients was higher than male patients. Ten out of 16 studies were only on females. In the studies included, age ranges between 21 and 91 years old.

Comparison

Among 11 RCT included, there were four studies comparing PTNS with sham therapy, three compared PTNS with anti-muscarinic therapy, two compared PTNS with combination therapy (PTNS and anti-muscarinic), one compared anti-muscarinic with combination therapy, and one compared PTNS once a week with three times a week. In addition, there were five prospective studies with no comparative group.

Outcome

In **Table 3**, studies have reported variable success rates for treating OAB symptoms with PTNS (37.3% - 81.8%), sham procedure (0% - 20.9%), anti-muscarinic (54.8%), and multimodal therapy with PTNS and anti-muscarinic (89.7%). Success rate for each study varied depending on the criteria determined by each author. For example, there were some studies using criterias such as improvement on Global Response Assessment (GRA)[13-15,17], 50% or greater reduction in symptoms (urgency, frequency, incontinence episodes)[14,16-19,20-26], and subjective feelings of improvement.[13,21] **Table 4** shows objective parameters of studies included in this systematic review including voiding diaries parameters such as frequency, nocturia, urinary incontinence and urgency episodes, as well as voided volume.

PTNS vs Sham Procedure

When compared to sham procedures, the number or percentage of responders in PTNS group were statistically higher ($p<0.01$), not only in objective responses[14,19,25] but also in GRA improvement or cure.[15] Study by Agro et al[14] showed significant reduction of frequency episodes per day and urinary incontinence episodes per 3 days in PTNS group, but not in sham group. Two other studies by Peters et al[15] and Agro et al[25] showed significantly higher reduction of frequency and nocturia episodes per day in PTNS group compared to sham group. In the matter of voided volume, two studies comparing PTNS and sham procedure showed significant increase of voided volume ($p<0.001$)

Table 3. Methodological quality of studies

Study	Treatment	Randomization	Blinding	Withdrawal	Score
Souto et al, 2014[11]	PTNS vs anti-muscarinic vs combination	2	0	0	2
Vecchiolli et al, 2013[12]	PTNS vs anti-muscarinic	1	0	1	2
Agro et al, 2010[14]	PTNS vs sham	2	1	0	3
Peters et al, 2010[15]	PTNS vs sham	2	1	1	4
Sancaktar et al, 2010[17]	Anti-muscarinic vs combination	2	0	1	3
Peters et al, 2009[18]	PTNS vs anti-muscarinic	2	0	1	3
Agro et al, 2009[19]	PTNS vs sham	1	1	1	3
Preyer, 2007 (abstract)[20]	PTNS vs anti-muscarinic	1	0	1	2
Agro et al, 2005[24]	PTNS (1x/week) vs PTNS (3x/week)	1	0	0	1
Agro et al, 2005 (abstract)[25]	PTNS vs sham	1	0	0	1
Karademir et al, 2005[26]	PTNS vs combination	1	0	0	1

in PTNS group but not significant in sham group.[14,15] **Figure 2** shows the meta-analysis of four RCTs comparing PTNS to sham procedure. Number of responders, patients with successful treatment, was considered as "event" (outcome) and expressed in risk ratio with 95% confidence of interval. The results demonstrate that all of the studies favour PTNS over sham procedure with overall risk ratio of 7.32 (95% CI of 1.69-32.16). It means that patients in PTNS group were seven times more likely to be successful in treatment compared to sham procedure. Heterogeneity among studies was not significant as stated in p value (0.09) and I2 (54%). In addition, the number needed to treat (NNT) calculated was 4.28 (95% CI of 3.19-6.49).

PTNS vs Anti-muscarinic Therapy

In studies comparing PTNS and anti-muscarinic, there were variable results in changes of voiding diaries symptoms. Most of them showed significant reduction of symptoms in both groups with no significant difference. In studies comparing PTNS and multimodal therapy, there was one study by Sancaktar et al[17] showing the significant difference of symptoms

Table 4. Responders of PTNS studies

Author, year	Definition of responders	Number of responders (percentage)				p
		PTNS	Sham	Anti-muscharinic	Combination	
Polo et al, 2012[13]	Subjective improvement of symptoms	50%	-	-	-	-
Agro et al, 2010[14]	50% or greater reduction in incontinence episodes moderately or markedly improved on a 7-level global response assessment (GRA)	12/17 (71%)	0/15 (0%)	-	-	P<0.001
Peters et al, 2010[15]		60/110 (54.5%)	23/110 (20.9%)	-	-	<0.001
Yoong et al, 2010[16]	OAB symptoms no longer being bothersome, reduction by 50% in frequency episodes, reduction by 25% in Incontinence Impact Questionnaire (IIQ-7) outcomes	30/43 (69.7%)	-	-	-	-
Peters et al, 2009[18]	GRA improvement or cure	35/44 (79.5%)	-	23/42 (54.8%)	-	P=0.01
Agro et al, 2009[19]	Reduction >50% of urgency episodes	10/16 (62.5%)	0/8 (0%)	-	-	-
Van Balken et al, 2006[21]	>50% reduction in symptoms/24 hr (frequency, incontinence) Subjective response	31/83 (37.3%) 46/83 (55.4%)	-	-	-	-
Nuhoglu et al, 2006[22]	Complete recovery after treatment (<8 voids/24h, 0-1 urgency episodesday, no urinary incontinence	19/35 (54.2%)	-	-	-	-
Van Der Pal et al, 2006[23]	>50% fewer incontinence episodes and/or void	9/11 (81.8%)	-	-	-	-
Agro et al, 2005[24]	Reduction >50% of the micturition episodes/24h or of the incontinence episodes/24h	11/17 (64.7%) [1x/week] 12/18 (66.7%) [3x/week]	-	-	-	-
Agro et al, 2005 (abstract)[25]	50% reduction in urinary incontinence episodes	6/8(75%)	0/8 (0%)	-	-	-
Karademir et al, 2005[26]	Overall treatment response rate	61.6%	-	-	83.2%	P<0.0001

Table 5. Voiding diaries of PTNS studies

No	Outcome	Author, year	Treatment	Results			P change from baseline	Difference among group
				Before	After	Change from baseline		
1	Frequency/ 24h	Souto et al, 2014[11]	PTNS	12.7	8			P=0.75
			Oxybutynin	11	7.9			
			PTNS + Oxybutynin	11.2	7.6			
		Vecchiolli et al, 2013[12]	PTNS	11.4±1.4	9.4±1.9		0.0006	
			Solifenacin	11.6±1.2	10.0±2.1		0.0039	
		Polo et al, 201213	PTNS	12.64±6.8	10.21±6.13		0.05	
		Agro et al, 2010[14]	PTNS	13.6 (11.7-15.5)	9.5 (8.4-10.7)		<0.001	
			Sham	14.7 (11.9-17.4)	13.9 (11.3-16.5)			
		Peters et al, 2010[15]	PTNS	12.3±3.2	9.8±2.8	-2.4±2.5	<0.001	-0.9±2.5
			Sham	12.4±3.0	11.0±3.1	-1.5±2.4	<0.001	P=0.01
		Yoong et al, 2010[16]	PTNS (responders)	Median (IQR) 11.8(4)	Median (IQR) 6.9 (30)		<0.05	
		Sancaktar et al, 2010[17]	Tolterodine	12.8±1.3	6.4±0.6		<0.001	>0.05 (before)
			Tolterodine + PTNS	12.2±1.2	4.5±0		<0.001	<0.05 (after)
		Peters et al, 2009[18]	PTNS	12.1±3.1	9.8±3.0	-2.4±4.0	<0.001	0.44
			Tolterodine	12.5±3.7	9.9±3.8	-2.5±3.9	<0.001	
		Preyer, 2007 (abstract)[20]	PTNS	0.1 (-3.3-3.6)	0.1 (-3.3-3.6)		0.77	
			Tolterodine	0.7 (-2.3-3.7)	0.7 (-2.3-3.7)		0.77	
		Nuhoglu et al, 2006[22]	PTNS	11.2±2.9	7.4±1.5		<0.01	
		Van Der Pal et al, 2006[23]	PTNS	12.0 (6.5)	9.2 (2.9)			
		Agro et al, 2005[24]	PTNS (1x/week)	3 (1-5)	1 (0-3)		0.01	
			PTNS (3x/week)	3 (1-6)	1 (0-3)		0.01	
		Agro et al, 2005 (abstract)[25]	PTNS			-3.7		0.01
			Sham			-0.7		
		Karademir et al, 2005[26]	PTNS	11.7	7.4	36.7%		0.48
			PTNS + Oxybutynin	11.3	6.3	44.2%		
2	Nocturia /24h	Souto et al, 2014[11]	PTNS	94%	11%		<0.0001	P=0.24
			Oxybutynin	84%	5%		<0.0001	

			PTNS + Oxybutynin	95%	14%		<0.0001	
		Vecchiolli et al, 2013[12]	PTNS	2.6±1.4	1.7±0.9		0.0419	
			Solifenacin	2.7±1	1.9±1.4		0.0312	
		Polo et al, 2012[13]	PTNS	3.14±2.14	2.71±2.2		0.472	
		Peters et al, 2010[15]	PTNS	2.9±1.6	2.1±1.4	-0.7±1.2	<0.001	-0.4±1.3
			Sham	2.9±1.7	2.6±1.6	-0.3±1.4	0.02	p=0.04
		Yoong et al, 2010[16]	PTNS (responders)	Median (IQR) 4(2)	Median (IQR) 1(2)		<0.05	
		Peters et al, 2009[18]	PTNS	2.5±1.2	1.7±1.1	-0.7±1.0	<0.001	
			Tolterodine	2.5±1.4	1.9±1.6	-0.6±1.7	0.03	
		Van Der Pal et al, 2006[23]	PTNS	3.0 (3.2)	0.6 (0.7)		<0.05	
3	Urinary incontinence /24h	Souto et al, 2014[11]	PTNS	94% patients	11% patients		<0.0001	P=0.33
			Oxybutynin	100% patients	31% patients		<0.0001	
			PTNS + Oxybutynin	95%	19%		<0.0001	
		Preyer, 2007 (abstract)[20]	PTNS					
			Tolterodine					
		Van Der Pal et al, 2006[23]	PTNS	7.4 (12.0)	3.1 (4.)		<0.05	
		Agro et al, 2005[24]	PTNS (1x/week)	12 (8-22)	8 (5-15)		0.01	
			PTNS (3x/week)	11 (7-19)	8 (6-18)		0.01	
		Agro et al, 2005 (abstract)[25]	PTNS			-4.5		0.03
			Sham			-1.3		
	Urinary incontinence /3 days	Agro et al, 2010[14]	PTNS	4.1 (3.3-5.2)	1.8 (1.2-2.2)		<0.001	
			Sham	4.2 (3.2-5.2)	3.8 (3.0-4.5)		0.394	
	Urinary incontinence /week	Sancaktar et al, 2010[17]	Tolterodine	22.8±2.4	12.3±0.8		<0.001	>0.05 (before) <0.001 (after)
			Tolterodine + PTNS	22.4±2.8	6.4±0.5		<0.001	
4	Urge incontinence /24h	Polo et al, 2012[13]	PTNS	5.21±3.51	2.57±2.3		0.004	
		Yoong et al, 2010[16]	PTNS (responders)	Median (IQR) 3.5(3)	Median (IQR) 2.4(3)		<0.05	
		Peters et al, 2009[18]	PTNS	2.2±2.3	1.2±1.6	-1.0±2.2	0.007	
			Tolterodine	3.5±3.5	1.8±2.5	-1.7±3.8	0.006	
		Nuhoglu et al, 2006[22]	PTNS	2.3±1	0.8±0.7		<0.01	

		Karademir et al, 2005[26]	PTNS	3.7	3.9	70.2%		
			PTNS + Oxybutynin	1.1	0.4	89.7%		
5	Urgency/ 24h	Vecchiolli et al, 2013[12]	PTNS	3.44±1.41	1.7±1.5		0.0002	
			Solifenacin	3.7±0.9	2.6±1.6		0.0078	
		Polo et al, 2012[13]	PTNS	10.93±9.46	6.0±5.7		0.003	
		Sancaktar et al, 2010[17]	Tolterodine	12.7±1.1	7.6±0.9		<0.001	>0.05 (before) <0.05 (after)
			Tolterodine + PTNS	12.4±0.9	5.7±0.6		<0.001	
		Peters et al, 2009[18]	PTNS	6.0±4.1	3.9±2.8	-2.2±4.3	0.002	
			Tolterodine	7.4±4.8	4.5±3.6	-2.9±4.8	<0.001	
		Preyer, 2007 (abstract)[20]	PTNS					
			Tolterodine					
		Nuhoglu et al, 2006[22]	PTNS	3.5±1.8	1.9±1.3		<0.01	
		Karademir et al, 2005[26]	PTNS	6.3	3.4	46.1%		0.43
			PTNS + Oxybutynin	5.4	2.1	61.1%		
6	Voided volume (cc)	Vecchiolli et al, 2013[12]	PTNS	114.9±14.5	156.1±18.4		<0.0001	
			Solifenacin	121.6±26.4	147.4±27.5		0.0215	
		Agro et al, 2010[14]	PTNS	150.5 (126.8-174.3)	186.5 (160.9-212.0)		<0.001	
			Sham	146.0 (121.0-171.1)	150.4 (125.8-175.1)		0.0879	
		Peters et al, 2010[15]	PTNS	169.5±78.9	183.0±75.6	11.4±45.0	0.01	5.5±42.1
			Sham	168.7±84.0	172.6±90.6	5.9±39.0	0.13	p=0.35
		Peters et al, 2009[18]	PTNS	152.7-79.3	185.5-81.1	32.8±61.3	0.001	
			Tolterodine	141.2±76.2	158.7±99.8	17.6±58.4	0.06	
		Nuhoglu et al, 2006[22]	PTNS	148.3±49.1	178±53.2		<0.01	
		Van Der Pal et al, 2006[23]	PTNS	107.6 (51.5)	187.5 (100.6)		<0.05	

episodes between PTNS and multimodal therapy (PTNS and anti-muscarinic) favouring multimodal therapy. Karademir et al[26] also found significantly higher response rate of multimodal therapy group compared to PTNS only group. Among several studies comparing PTNS and anti-muscarinic, there was one study measuring significant reduction in percentage of patients having nocturia and urinary incontinence in both treatment ($p<0.0001$) with no significant difference between two groups.[11] In addition, in one study 35/44 (79.5%) patients in PTNS group reported a subjective improvement compared to 23/42 (54.8%) in anti-muscarinic group ($p=0.01$)18. Another study showed patients in both groups have significant increase of voided

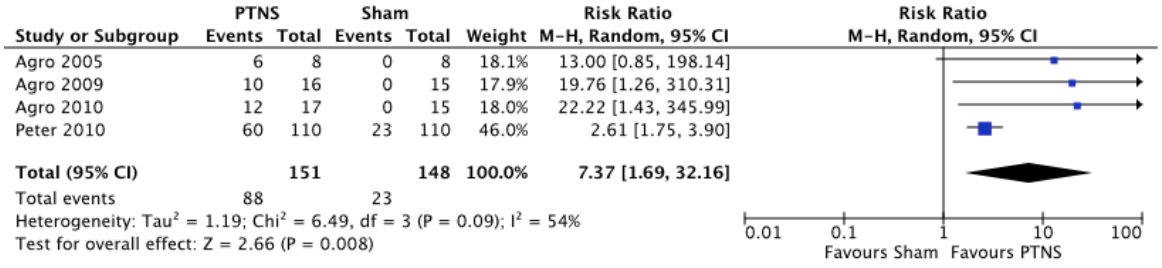

Figure 2. Meta-analysis of randomized control trials PTNS versus Sham procedure

volume ($p<0.05$) with higher changes in PTNS group.[12] Peters et al[18] also found that increase of voided volume was significant in PTNS group ($p=0.001$) and insignificant in anti-muscarinic group ($p=0.06$).

PTNS in Noncomparative Studies

In noncomparative studies, patients with PTNS treatment had significant reduction in frequency episodes per day 13,16,22,23, as well as in urinary incontinence episodes[23] and urgency episodes.[13,22] Among 3 studies evaluating nocturia, there was one study showing insignificant reduction in nocturia episodes per day[13], while the two others showed significant reduction of this symptom.[16,23] In a study by Agro et al[24] comparing frequency of PTNS treatment, there was no significant difference between them. The number of responders were 11/17 (63%) and 12/18 (67%) in once a week treatment and three times a week treatment, respectively.

DISCUSSION

Recently, there have been some systematic reviews published on the effectiveness of PTNS in adult patients with OAB.[27-31] However, more recent studies have not yet been included in those reviews. Therefore, it is necessary to analyze more data as the knowledge of PTNS in OAB is still evolving.

The studies included in this systematic review demonstrated variable success rate for treating OAB with PTNS, sham procedure, anti-muscarinic, and multimodal therapy (PTNS and anti-muscarinic). Based on percentage of responders, the results were 37.3% - 81.8% in PTNS group[21,23] and 0% - 20.9% in sham group.[14,19,25] Peters et al[18] showed that GRA improvement in those treated with anti-muscarinic therapy was 54.8%. Moreover, Karademir et al[26] showed high rate of overall treatment response in patients treated with combination therapy (89.7%). The decrease of voiding problems episodes per day was found in PTNS (0.7-4.5), sham (0.3-1.5) and anti-muscarinic (0.6-2.9) groups.[15,18,25]

Effectiveness of PTNS in OAB, specifically in non-neurogenic OAB, has been proven in sham controlled trials both in number of positive responders and also in voiding diaries parameters of the patients. It is supported in this systematic review that patients who received PTNS treatment were seven times more likely to have successful treatment compared to sham treatment. The number of patients needed to treat to get one additional successful outcome was 4 people.

When compared to anti-muscarinic treatment, there were no significant differences in reduction of symptoms and increase of voided volume. However, in one study, patients in PTNS group had significantly higher GRA improvement compared to anti-muscarinic group.[18] The possible explanation is that most of the studies included in this systematic review investigated patients who were already resistant to first line therapy of OAB, such as anti-muscarinic. On the other hand, multimodal therapy combining PTNS and anti-muscarinic therapy still had superior outcome compared to PTNS only.[17,26] Besides sham controlled and anti-muscarinic controlled trial, we also included non-comparative studies. From those studies, patients treated with PTNS had significant reduction in frequency episodes as well as high response rate.[13,16,21-24,26]

There were variable definitions of success among studies included in this systematic review. It might contribute to the wide results range obtained. The other things contributing to bias are variable gender of patients, dosage or frequency of PTNS and anti-muscarinic treatment, and tools used in voiding diaries outcome. For example there were episodes counted per day, per three days, and per week. Conclusively, there was no standardized protocol of PTNS treatment used in those studies. Therefore, to get better results, the future agenda is to reproduce RCT with one standardized protocol and more homogeneous patients. Since OAB is multifactorial, prognostic factor of successful response rate such as gender and age should be evaluated in the future. As an early finding, responder rate was found higher in females (66%) than in male patients (45%) receiving PTNS treatment.[32]

Studies included in this systematic review were RCTs and prospective non-comparative studies. Although non-comparative studies have lower level of evidence, they are the best available evidence to expand the information needed. Abstracts of scientific meeting were also included with exclusion of non-English language.

The effectiveness of short term PTNS therapy for OAB has been proven from the studies included. On the other hand, there is still lack of information on long term therapy of PTNS in OAB as it is needed to prevent deterioration of symptoms. Macdiarmid et al[33] evaluated the long term durability of PTNS in OAB by continuation of the second phase of The Overactive Bladder Innovative Therapy Trial (OrBIT) in which 33 responders of PTNS group received an additional 9 month of PTNS treatment. There were statistically significant OAB symptoms improvement achieved with 12 weekly PTNS that demonstrated good durability through 12 months. This conclusion was obtained from 12 months mean improvements from baseline in frequency, urge incontinence, nocturia, and voided volume.[33] Furthermore, there was Sustained Therapeutic Effects of PTNS (STEP) study which was the continuation from SuMIT study evaluating long term efficacy of PTNS. After successful 12 weekly treatments, patients continued with 14-week tapering protocol and personalized treatment plan. Improvements in frequency, urge incontinence, nocturia, and urgency episodes were statistically significant compared to baseline at 6, 12, 18, and 24 months.[34] At 3 years, they found 77% (95% CI, 64%-90%) of subjects with maintained or marked OAB improvements.[35] All in all, PTNS is durable and can be a long term treatment option for OAB.

From the studies reported, PTNS had no serious adverse event. The rare events found in PTNS treatment were ankle bruising, discomfort/pain at needle site, bleeding at needle site, tingling in leg, generalized swelling, worsening incontinence, headache, hematuria, inability to tolerate stimulation, intermittent foot/toe pain, and foot cramp.[15,18,23] They were found in a few number of patients and considered rare. In long term PTNS therapy (STEP study), the events reported were urinary tract infection (UTI), pulling feeling on feet, bladder pressure, pinched nerve, and slow stream, with no direct relationship to PTNS.[34] In patients receiving anti-muscarinic, the common adverse events were constipation, infection, dizziness, visual disturbance, and fatigue.[18]

In a study comparing PTNS and antimuscarinic, both treatments were well tolerated with no serious adverse events reported. It was stated that after 12 weeks of therapy, several symptoms were reported significantly less in the PTNS group compared to the antimuscarinic group, including dry mouth and constipation.[18] Peter et al[15] showed that there was no serious adverse events reported in PTNS group and sham group.

Although the studies included in this review provided evidence favouring PTNS, this systematic review has several limitations. First, the dosage, duration, frequency, cycle, and follow-up durations of PTNS varied among studies. The variations were also found in study design and baseline data (age, gender). Therefore, further large scale, RCT with consistent study design, criteria, and clinical outcome evaluation are strongly needed to attain the long-term effectiveness of the PTNS.

CONCLUSION

There is evidence of effectiveness of short term PTNS in treatment of OAB symptoms, especially non-neurogenic OAB. PTNS is proven significantly better than sham procedure and comparable to anti-muscarinic but with fewer systemic adverse events. On the other hand, multimodal therapy still gives higher effectiveness than PTNS alone. There is also an evidence of long term PTNS in OAB treatment indicating that PTNS may be an option for OAB maintenance treatment due to its durability and safety. Further studies are needed to evaluate this long-term effectiveness of PTNS in OAB and to find prognostic factor of successful response. Standardized protocol of PTNS prescription is needed to obtain homogeneous data, better result and analysis.

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