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NEUROMODULATION FOR OVERACTIVE BLADDER WITH TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN ADULTS – A RANDOMIZED CLINICAL STUDY

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ABSTRACT

Neuromodulation has become a well-established treatment modality in OAB. Neuromodulation with Transcutaneous Electrical Nerve Stimulation (TENS) at sacral foramina (SF), Posterior tibial nerve (PTN) and combination of SF+PTN stimulation was being compared in a randomized assessor blinded prospective clinical study. 44 adult participants with OAB were randomly distributed into three groups (SF, PTN: n = 15 each and SF+PTN: n = 14). TENS was given daily for 20 minutes using standardized parameter for 4 weeks. An OAB Symptom Score (OABSS), Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) were recorded at baseline and at the end of 4 weeks of intervention. The results of the study show that all neuromodulation methods were significantly effective ($p<0.05$) in reducing symptoms of OAB. It was found that simultaneous stimulation at SF+PTN proves to be the most effective method compared to stimulation at SF and PTN alone. The study concluded that TENS is safe and acceptable with potential clinical effects in reducing symptoms of OAB in adult participants.

KEY WORDS: Overactive Bladder, Bladder training, Neuromodulation, Transcutaneous Electrical Nerve stimulation

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INTRODUCTION

Overactive bladder (OAB) syndrome is defined by the International Continence Society (ICS) as urgency (a sudden, compelling desire to urinate, which is often difficult to defer) with or without urge incontinence, usually with frequency and nocturia in the absence of proven infection or obvious pathology, and recognized OAB as a significant symptom complex syndrome affecting millions of people worldwide.[1] OAB may present as spontaneous, uninhibited contractions (over activity) of the bladder detrusor muscle which may be idiopathic or due to neurogenic dysfunction and age is the most important risk factor for the condition. In most of the cases of OAB the exact aetiology and pathogenesis is unknown.[2] OAB prevalence is thought to be underestimated because of various social and cultural factors in which most patients do not seek medical care, particularly when urinary incontinence (UI) is present.[3] In the last few years, many studies have provided evidence for the high prevalence of this condition with estimated prevalence rate of 20 to 30% in both genders and increases with advancing age.[4,5]The standard first line of treatment for OAB is administration of anticholinergic and symptomatic drugs.[6] However, the effectiveness of anticholinergic drugs still remains uncertain. Invasive treatment by neuromodulation has been proven effective in the management of OAB but reserved for severe cases who failed to respond to conservative treatment.[7] Non drug and non-invasive treatment methods includes behavioural therapy, bladder training, pelvic floor muscle training, biofeedback, electrostimulation etc.[8] Sacral neuromodulation was developed in the early 1980s and has now become a well-established treatment modality in OAB and has been shown in clinical trials, with a reported five year success rate of approximately 70%. The root S2 and S3 is stimulated and reflexes are neuromodulated by intravesicle, anal, vaginal, penile, perineal, sacral or tibial approach through minimally invasive percutaneous techniques.[9] The techniques involved in neuromodulation for treating the overactive bladder includes percutaneous stimulation at sacral foramina; percutaneous posterior tibial nerve stimulation (Stoller afferent nerve stimulation- SANS); and surface stimulations using interferential current; transcutaneous electrical nerve stimulation (TENS); and magnetic stimulation.[10] Neuromodulation treatment may fill the gap between conservative measures and invasive surgical treatments.[9,10] Non-invasive electrical neuromodulation delivered through surface electrodes using TENS have also been studied and found to be effective when stimulated at the sacral foramina (SF) or posterior tibial nerve (PTN) in children[11-13] as well as in adults.[14,15]The effectiveness of surface neuromodulation with TENS when applied at the SF (S2 and S3) was found to be more effective than percutaneous PTN stimulation in children.[12] Simultaneous stimulation at SF and PTN using TENS through surface electrodes has also been proven effective to relieve symptoms of OAB.[15] However no prospective study have compared the effectiveness of surface neuromodulation with TENS when stimulated at the SF, PTN and simultaneously at SF and PTN to reduce the symptoms of OAB. Hence the aim of this study is to compare the effectiveness of neuromodulation with TENS by three different stimulation methods (SF stimulation, PTN stimulation and SF+PTN stimulation). We hypothesized that there would be difference in the effectiveness of neuromodulation with TENS in reducing the symptoms of OAB when stimulated with three different methods. The result of this study may implicate the effectiveness of TENS in relieving symptoms of OAB in adults and also help the therapist in selecting an effective and appropriate method for neuromodulation with TENS in adult participants with OAB.

MATERIALS AND METHODS

The study was a single centred randomized prospective intervention study. The participants of the study were recruited through advertisement pamphlets circulated with the newspaper. Individuals who were interested to participate (n=137) were screened, out of which 44 participants were recruited who fulfils the selection criteria.

Participants were then randomly assigned (using a computer generated randomization method) into three groups (Figure 1). After randomization 15 participants each were assigned to SF group and PTN group and 14 participants in SF+PTN group. The study was blinded for the therapist who evaluated the outcome score at baseline and at post intervention and for the participants to the application of the neuromodulation techniques proposed in this study. The subjects were included if complains of urgency, with or without urge incontinence, frequency and nocturia with intact peripheral neurosensory system (OAB diagnosed with the help of Urologist); both males and females aged between 30 to 60 years; history of symptoms more than 6 months; and free from mechanical urethral obstruction. The subjects were excluded if they had an active urinary tract infection, a bladder stone, ankle injuries, injury to Tibial nerve, urodynamically proven instability secondary to a known neurologic cause (i.e. Stroke, Parkinsonism, Multiple Sclerosis), uncontrolled diabetes, diagnosed peripheral neuropathy such as diabetes with peripheral nerve involvement. The study was approved ethically by the Institutional Ethical Committee. All the subjects provided their demographic details (Table 1) and signed informed consent prior to collection of baseline data. Baseline pre-treatment evaluation consisted of symptoms evaluation of OAB and baseline outcome scores with Overactive Bladder Syndrome Score (OABSS) and short forms of Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7). OABSS consisted of four questions; one questions each for night time, frequency, daytime frequency, urgency and incontinence.The maximal score was defined as 2,3,5 and (total 15) for daytime frequency, night time frequency, urgency and incontinence, respectively.[16] UDI-6 consists of 6 questions and IIQ-7 consists of 7 questions assessing the symptom distress of urinary incontinence and quality of life respectively. Item responses are assigned values of “0” for “not at all”, “1” for “slightly”, “2” for “moderately” and “3” for “greatly” in both UDI-6 (total score 18) and IIQ-7 (total score 21).[17]Higher scores indicates poor outcome in all the three measures. All the participants in the entire group underwent TENS intervention with 10 Hz frequency with a pulse duration of 200 µsec biphasic waveform for 20 minutes daily (excluding Sundays) for 4 weeks.[13,14] Stimulation intensity was adjusted individually and increased to the maximum level tolerated by the participants. Two surface electrodes made of carbon conductive rubber were placed over the $S_{2\text{-}3}$parasacral region for SF stimulation (Figure 2). For the PTN stimulation TENS were provided via two surface electrodes, placed just proximal to the medial malleolus and another 10 cm proximally (Figure 3). In the simultaneous stimulation of SF+PTN, TENS were provided via two channels (Figure 4). In addition to the neuromodulation sessions, all the participants were also given general guidelines of bladder training and control strategies, pelvic floor muscle training, to avoid foods with caffeine, drink large volumes of fluids during the day and to urinate before going to sleep. Post intervention scores of OAB Symptom Score (OABSS) and Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) were recorded again at the end of 4 weeks intervention period by a therapist who was blinded to the intervention methods.

Table 1
Baseline Data

Variables	SF^ (N=15)	PTN^ (N=15)	SF+PTN^ (N=14)	P-value*
Demographic Detail				
Age (Year)	43.6±7.56	42.8±8.12	47.2±8.83	0.312
Height (cm)	173.8 ± 3.29	174.6 ± 3.24	173.7 ± 3.78	0.745
Weight (kg)	77.6 ± 5.66	78.4 ±4.7	77.2 ± 5.28	0.824
BMI	25.6 ±1.27	25.7 ± 1.05	25.5 ± 1.09	0.937
Female/Male	10/5	9/6	11/3	0.605
Outcome Measures				
OABSS	10.6±2.09	10.8±2.11	10.85±2.14	0.942
UDI-6	14.66±1.99	14.6±1.92	14.85±2.07	0.938
IIQ-7	16.27±1.79	15.87±1.88	17.21±1.52	0.117

^ Mean & Standard deviation; cm=centimetre; kg=kilogram; BMI=body mass index; N=number;
One Way ANOVA (* no significant difference = p>0.05);

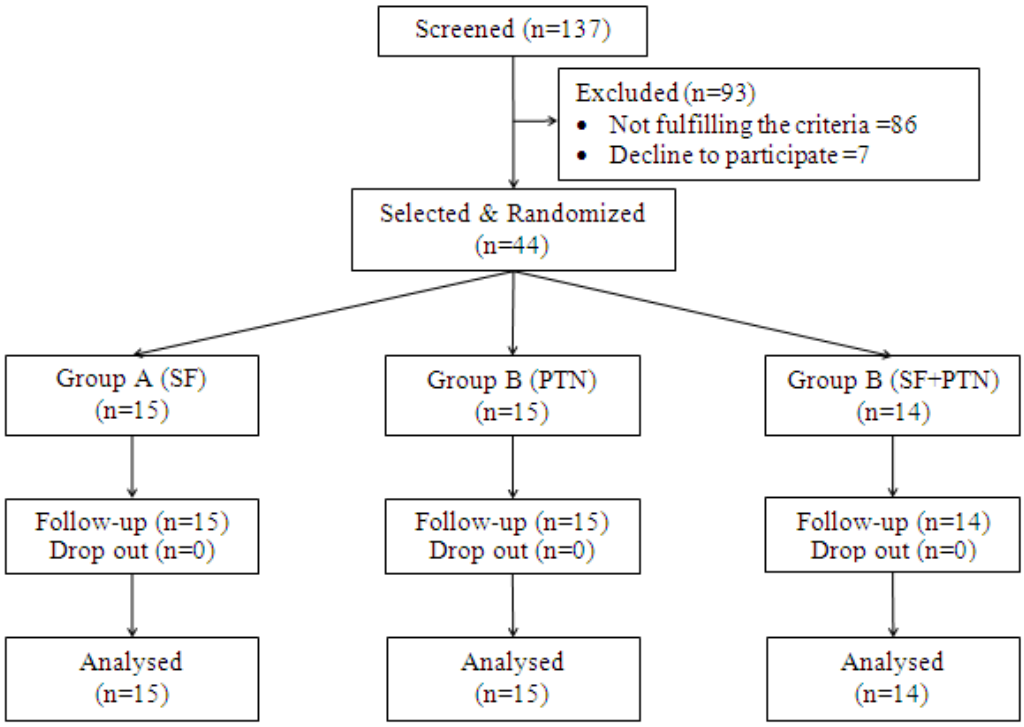

Figure 1
CONSORT Flow Diagram

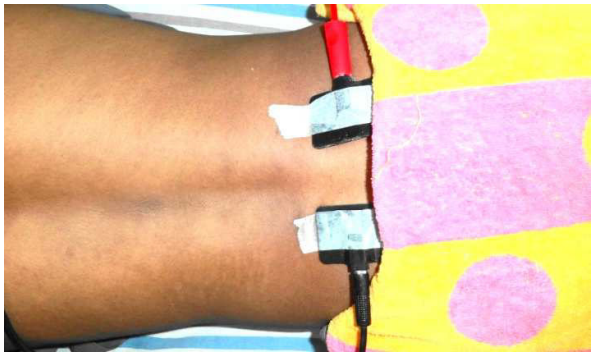

Figure 2
Stimulation at S_{2-3} Sacral Foramina (SF) with TENS

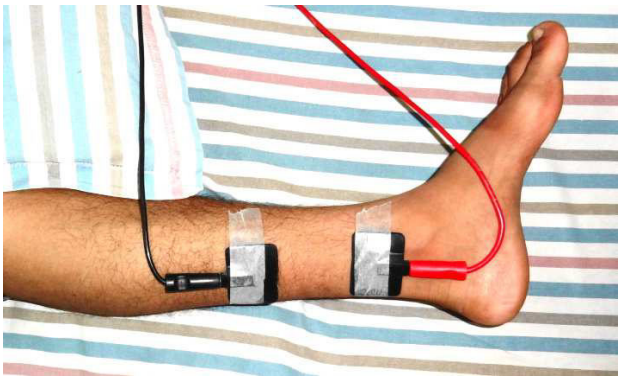

Figure 3
Stimulation at Posterior Tibial Nerve (PTN) with TENS

Figure 4
Simultaneous stimulation at $S_{2\text{-}3}$ Sacral Foramina (SF) and Posterior Tibial Nerve (PTN) with TENS

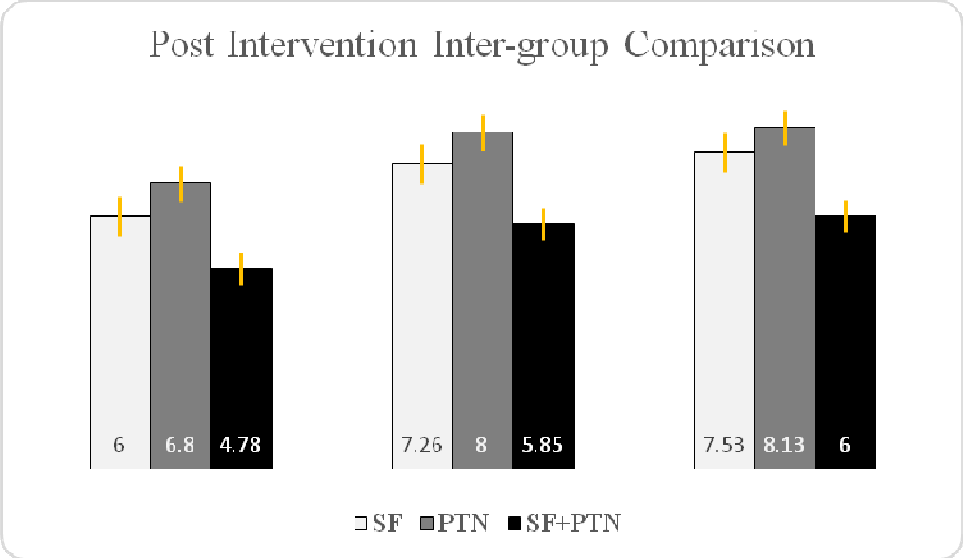

Figure 5
Post intervention intergroup comparisons

STATISTICAL ANALYSIS

All the analyses for obtained data were done using SPSS version 16 for windows. Descriptive analysis was used to calculate mean and standard deviation. Kolmogorov-Smirnov test was used to verify normality of data distribution (which was always present). ANOVA was used to determine baseline and intervention effect between the groups for the data. Analysis of OABSS, UDI-6 and IIQ-7 scores were done using student's t-test to show changes due to theintervention programs. Post hoc Tukey test was done to determine intergroup differences in the post intervention outcome scores. The level of significance was set at 95% (P=0.05). Clinically meaningful changeswereassessed by calculating effect size (Eta Squared and Cohen's d) in relation to the changes that occurred during the SF stimulation, PTN stimulation and SF+PTN simultaneous stimulation methods. Data were analysed using an intention-to-treat model.

RESULTS

The baseline demographic details of the groups were homogenous (age, height, weight, BMI) with p>0.05 (Table 1). The analysis to test initial differences between groups for baseline scores in OABSS, UDI-6 and IIQ-7 revealed no significant differences (p>0.05) in OABSS (p=0.942), UDI-6 (p=0.938) and IIQ-7 (p=0.117). Pre and post treatment intra group comparison was done using paired t-test which shows significant difference (p<0.05) in all the outcome scores (OABSS, UDI-6 and IIQ-7) in SF, PTN and SF+PTN groups (p=0.000) (Table 2). Post intervention inter group analysis for among group differences in the outcome scores shows significant difference (p<0.05) in all the outcome scores, OABSS p=0.042; UDI-6 p=0.048 and IIQ-7 p=0.038(Table 3, Figure 5). Post hoc analysis revealed greater significant improvement (p<0.05) in SF+PTN group with large effect size compared to SF and PTN group in all the outcome scores. Between SF and PTN group, no significant difference (p>0.05) was noted however SF group shows better improvements compared to PTN group in the entire outcome scores (Table 4) with medium effect size. Effect sizes of all significant changes were listed in Table 2, 3 and 4.

Table 2
Intra-group comparison

SF	Pre Treatment^	Post Treatment^	P value*	Effect Size**
OABSS	10.6±2.09	6±1.81		2.35
UDI-6	14.66±1.99	7.13±1.92	0.000	1.26
IIQ-7	16.27±1.79	7.53±2.19		4.36
PTN				
OABSS	10.8±2.11	6.8±2.27		1.82
UDI-6	14.6±1.92	8.07±2.31	0.000	3.07
IIQ-7	15.87±1.88	8.13±1.68		4.34
SF+PTN				
OABSS	10.85±2.14	4.78±2.12		1.84
UDI-6	14.85±2.07	5.86±2.71	0.000	3.72
IIQ-7	17.21±1.52	6.0±2.68		5.29

^ Mean & Standard deviation; Pair t-test (* significant difference = p<0.05); Effect size (Cohen's d) = Small – 0.2, Medium – 0.5, **Large - >0.8

Table 3
Post intervention Inter-group comparison

Variables	SF^	PTN^	SF+PTN^	p-value*	Effect Size**
OABSS	6±1.81	6.8±2.27	4.78±2.12	0.042	0.143
UDI-6	7.13±1.92	8.07±2.31	5.86±2.71	0.048	0.137
IIQ-7	7.53±2.19	8.13±1.68	6.0±2.68	0.038	0.147

^ Mean & standard deviation; One Way ANOVA (* significant difference = p<0.05); Effect size (Eta squared) = Small: 0.01, Medium: 0.059, **Large: >0.138

Table 4
Multiple Comparison of SF, PTN and SF+PTN Groups

Outcome Measure	Group		Effect size	Group		Effect size	Group		Effect size
	SF	PTN		SF	SF+PTN		PTN	SF+PTN	
OABSS^	6±1.81	6.8±2.27	-0.4*	6±1.81	4.78±2.12	0.64*	6.8±2.27	4.78±2.12	0.95**
UDI-6^	7.13±1.92	8.07±2.31	-0.45*	7.13±1.92	5.86±2.71	0.56*	8.07±2.31	5.86±2.71	0.91**
IIQ-7^	7.53±2.19	8.13±1.68	-0.31*	7.53±2.19	6.0±2.68	0.65*	8.13±1.68	6.0±2.68	0.99**

^ Mean & standard deviation; Post hoc (Tukey HSD) test (** significant difference = p<0.05; *no significant difference = p>0.05);
Effect size (Cohen's d) = Small – 0.2, Medium – 0.5, Large - >0.8

DISCUSSION

The short term effects of neuromodulation with TENS applied to the Sacral Foramina (S2-3), Posterior Tibial Nerve and simultaneously at Sacral Foramina and Posterior Tibial Nerve were demonstrated in relieving the symptoms of OAB. To our knowledge this is the first study showing and comparing the effects of surface TENS in adults with OAB when stimulated by three different methods. In this study all the participants of the entire group showed positive results irrespective of the stimulation site in all the outcome scores and the intervention methods were well tolerated by the entire participants.No major adverse effects were noted during and after the interventions with surface TENS. The efficacy of the parameters of TENS stimulation used in this study was well documented by other researchers in human as well as in animal studies.[13,14,18] After 4 weeks of surface TENS applied daily for 20 minutes, there was significant improvement in the OABSS, UDI-6 and IIQ-7 parameters in the entire group which is in accordance to previous studies.[13-15] It was also found that significant differences exists in the improvements among the three groups. Stimulation at SF and PTN simultaneously was found to be the most effective compared to that of the stimulation atSF or PTN alone and stimulation at SF was found to be superior compared to stimulation at PTN in relieving the symptoms of OAB. The later finding is in accordance with earlier studies conducted in children with OAB.[11,12] This may be due to the effect of parasacral neuromodulation which directly stimulate spinal reflexes and reach supraspinalcenters at a more effective intensity than stimulation of PTN, which is more peripheral.[19]The exact mechanism of neuromodulation, whether it works only in the spinal level or supra-spinal pathways are involved is still uncertain.[20] However it is believed that the sacral nerve stimulation works via the efferent rather than the efferent nerves and affects the supra-spinal level of the nervous system.[21,22] And stimulation of the sacral roots inhibits bladder activity by stimulating large diameter somatic afferent fibres, which in turn evokes a central inhibition of the micturition reflex pathway in the spinal cord or the brain. Neuromodulation is believed to treat OAB by restoring and maintaining the balance between the peripheral and central inhibitory and excitatory control systems.[20,23-26] Transcutaneous electrical nerve stimulation of sacral foramina and posterior tibial nerve is a physiotherapeutic method and an alternative for the treatment of overactive bladder, which is effective and without side effects. Despite the fact that pharmacological treatment is currently the first line of treatment of OAB in adults, adherence to treatment is low, especially due to side effects.[27,28]Overactive bladder is a chronic condition and may require a lifelong treatment to control symptoms. With this fact, neuromodulation using surface TENS may be considered as an easier, non-invasive, effective and more affordable form of treatment that is well tolerated by the participants.[29] Various types of treatment for OAB (Pharmacological, Surgical, Neuromodulative) are available in the literature, with different mechanisms of action. But it is always important to choose the optimal treatment for each individual based on several factors, including co-morbidities, mental status, age, motivation and mobility, considering the chronicity of the disease and that therapy must be adapted over the life of each patient.[29] Neuromodulation through the sacral and the tibial approach seems to be an effective therapeutic approach for relieving the symptoms of OAB in adults. And hence may be considered as an effective first-line of

treatment for overactive bladder. The study has certain limitations as it was conducted in a small sample size of a selected age group, the result could not be generalized to all the age groups but restricted to adults diagnosed with non-neurogenic OAB. The absence of a control group in this study made us unable to comment on the additional effects of bladder training and control strategies over surface TENS in non-neurogenic OAB. The study has not demonstrated the long term benefits of TENS on OAB. Future studies with a control group and a wider age range can be considered with lower weekly sessions and with a different type of stimulating current or different parameters of TENS. The study may also be conducted in hypereflexic neurogenic bladder (e.g. Stroke, Parkinsonism, Multiple sclerosis etc.).

CONCLUSION

The study found that simultaneous stimulation of sacral foramina and posterior tibial nerve is the most effective in relieving the symptoms of OAB when compared to sacral foramina stimulation or posterior tibial nerve stimulation alone using surface TENS. Moreover TENS seems to be a safe, acceptable and an effective physiotherapeutic practice with evidence of potential clinical effects for OAB in adults. The results support the feasibility of TENS as a first line intervention of OAB in adults.

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CONFLICT OF INTEREST

None declared.

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