Use of Electrical Stimulation of the Posterior Tibial Nerve in Patients with Bladder Hyperactivity as a Substitute for Pharmacological Therapy based on Solifenacin Succinate and Oxybutynin Hyloridrate

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Abstract: In a previous paper, we proposed a technique for the therapeutic use of Transcutaneous Electrical Nerve Stimulation (TENS) of the posterior tibial nerve. The goal was to treat patients with signs of urinary incontinence (UI) due to detrusor overactivity (DO). We now conduct a comparison between our proposed TENS technique and the most commonly used treatment against DO, namely the pharmacological therapy based on solifenacin succinate and oxybutynin hydrochloride. Our goal is to show that the TENS of the posterior tibial nerve treats UI associated with DO, as well or better than the pharmacological treatment, but without the adverse side effects of the drugs (the so-called cholinergic syndrome). Method: we applied the proposed posterior tibial nerve TENS in 21 patients, including the TENS Burst anaesthetic current. We treated each patient in 10 sessions, 2 times per week, for 20 minutes each session. Each patient could control the current intensity, in order to keep it at comfortable levels, and in order to still be able to move the halux, thus simulating the Babinski reflex. Results: we observed that with the proposed TENS approach and with the removal of the pharmacological treatment, the cholinergic syndrome symptoms disappeared after 3 days without drugs, whereas we attained the modulation of the non-inhibited detrusor contractions. Conclusion: this research provides evidence of the proposed TENS technique's efficiency in eliminating the effects of the hyperactive bladder, while avoiding the symptoms of cholinergic syndrome associated to the more common pharmacological treatment. The statistical tests showed that the reductions of DO symptoms and of the cholinergic syndrome were significantly improved over the pharmacological treatment ($p < 0.01$). This improves patients' life quality by reducing or eliminating the social discomfort and hygiene problems associated to UI while avoiding the cholinergic syndrome.

1 INTRODUCTION

Detrusor hyperactivity is a type of urinary incontinence, associated to severe social discomfort and hygiene problems. It also leads to important changes in urinary frequency (including an increased number of enuresis cases) and to the need for using urinary-loss protection devices (Coyne et al., 2003; O'Conor et al., 1998).

Among the possible treatment modalities, pharmacological therapy is a common approach (Diokno and Ingber, 2006), based for example on solifenacin succinate and oxybutinin hydrochloride. However, this approach usually leads to strong side effects, such as dry mouth, blurred vision, and intestinal constipation, which are jointly called the *cholinergic syndrome*.

In this context, we propose and evaluate a different type of treatment based on electrical stimulation of the posterior tibial nerve, with the purpose of reducing the detrusor hyperactivity while avoiding the cholinergic syndrome. We applied the proposed protocol in 10 sessions and with 21 patients, and our results suggest that the treatment reduces the effects of detrusor hyperactivity without the side effects of the pharmacological treatment.

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2 BACKGROUND

In pharmacological therapy applied to disorders of the detrusor and external urhetral sphincter, it is important to analyze the neurophysiology of urination, and its physio-pathological disorders. The injury or illness of the nervous system is an important complication of the urinary tract (UT). Specially, the neurogenic bladder has several possible causes such as spinal cord injury, stroke, brain stem injury, lesions in the cerebral cortex, peripheral nervous system injury, multiple sclerosis, quadriplegia and paraplegia.

2.1 Urination Control

The urination control is a neural-physiological process which is controlled by the sympathetic and the parasympathetic systems. The continence phase is controlled by the sympathetic system with the alpha 1 and beta 2 adrenergics receptors. These are responsible for the contraction of the external sphincter ureter and the perineum and detrusor muscles. The parasympathetic system, on the other hand, controls the urination itself based on a different mechanism, using the perineum muscle and urethral sphincter to relax and the detrusor muscle contract. Figure 1 illustrates this process.

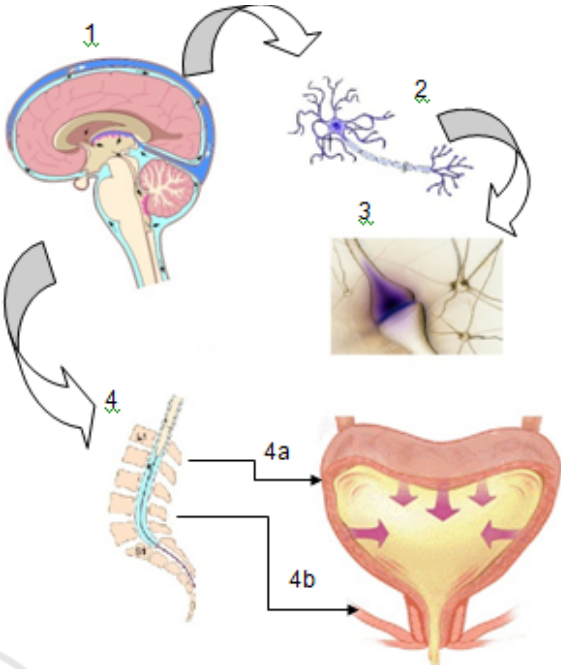


Figure 1: Neurophysiology of urination: 1) Motor cortex; 2) afferent nerve; 3) Parasympathetic ganglion; 4) Pontine "continence" center (L-region) – 4a: Nerve impulses stimulate contraction of muscle-hypogastric nerve and 4b: Nerve impulses stimulate relaxation of internal urethral sphincter muscle-pudendal nerve.

2.2 Bladder Hyperactivity

Involuntary loss of urine is a problem of social order and hygiene, causing embarrassment and changes in behavior such as social isolation, low self-esteem and psychosocial disorders (Oliveira et al., 2007). The most common etiology of urinary incontinence is neurogenic (Monteiro et al., 2009; van der Pal et al., 2006; Coyne et al., 2003; Fischer-Sgrott et al., 2009).

The four handles or neurological pathways in the control of urination, and which are related to each other, are: the core trunk detrusor cerebral cortex (loop I), the core detrusor muscle spinal / sacral brainstem (loop II)-sacral urethral sphincter of the bladder (loop III), and the sacral-brain (loop IV). Pathways I and IV are responsible for voluntary control of urination. Pathways II and III, on the other hand, regulate the contractions of the detrusor bladder emptying to promote and coordinate efforts between the detrusor and urethra (Stephenson and O'Conor, 2004).

The neurogenic bladder dysfunction is defined as a neurological disease produced by nerve damage that interferes with the mechanisms of voluntary and involuntary urination, thus causing changes in normal bladder function. The neurogenic bladder corresponds to the overactive and/or underactivity of the detrusor (Azevedo et al., 1990).

The underactive bladder retention or overflow is characterized by urinary loss that occurs when intravesical pressure exceeds urethral pressure. This is associated with bladder distention, but in the absence of detrusor activity. This overflow happens when one reaches the limits of distensibility or compliance of the bladder (Miltrano, 2009).

According to the International Continence Society, the overactive bladder is defined as a neurogenic injury due to the presence of involuntary detrusor contractions during the filling phase (Coelho, 2009). This is characterized by urinary incontinence, urinary frequency, nocturia and urgency (Fischer-Sgrott et al., 2009; Jones III et al., 1988; O'Conor et al., 1998; Guidi et al., 2005).

3 PHARMACHOLOGICAL TREATMENT

Several drugs have been developed for treating the overactive bladder. However, in our clinical practice we observed that most become innocuous at the end, leading to a symptom reduction that only lasts during

drug usage. Other drugs with proven clinical effects, on the other hand, must be used for long periods and show severe adverse effects, resulting in high dropout rates.

3.1 Anticolinergics: The Most Used Drugs

Stimulation of muscarinic receivers M2 and M3 cause bladder contractions. Anticholinergic drugs inhibit these receivers, causing the decrease of contractions' amplitude and the increase of the first contraction volume, thus resulting in a higher bladder functional capacity.

These drugs' parasympatholytic action occurs selectively on these receptors. Yet, they have uncomfortable system effects, since the inhibition of muscarinic receivers do not occur only in the bladder, where M2 and M3 receivers predominate. In the bladder, the M2 muscarinic are predominant, but the M3 receivers are more functionally important, mediating direct contraction of detrusor muscle (Chapple et al., 2002).

This prevents the interaction of acetylcholine with receptors and inhibits the release of this neurotransmitter in the synaptic cleft post-ganglionic.

There are two types of anticholinegic: (i) I-Mixed (antispasmodics) — combine action antimuscarinic with relax direct muscule (receiver independent) and local anesthetic. The main representative of these groups and cloridrat oxibutina. (ii) II-Pure — represented by tolterodine, propantelina, darifenacin, and vamicamide. They are classified also with aminoterciarios or aminoquaternarios. The difference between the two groups refers to the ability of the blood brain barrier crossing aminioterciarios.

The use of anthicholinergic is not free of side effects. Its major side effects are: dry mouth, constipation and blurred vision, headache, dyspepsia and even diarrhea, which corroborates with a dropout rate of treatment during the first three months around 25,5% (Diokno and Ingber, 2006).

A survey showed that only 18% patients remained taking anticholinergic by one period exceeding six months. The activation of M3 receivers is due to the detrusor contraction, but also to the contraction of the smooth muscles of the gut and salivary glands (Diokno and Ingber, 2006; Chapple et al., 2002).

The ability of the blood brain barrier to cross the antimuscarinic agents can lead to cognitive alterations, especially in the elderly. These side effects occur by the relative loss of selectivity for the bladder over other organs (Appell, 2003).

Other central effects include dizziness, memory loss and drowsiness, the presence of receptors M1 in the neocortex, hippocampus and neostratum (Appell, 2003).

Muscarinic receptor antagonists are formally not recommended for patients with closed angle glaucome and should be used with care in case of infravesical obstruction, dur to the possibility of precipitating urinary retention.

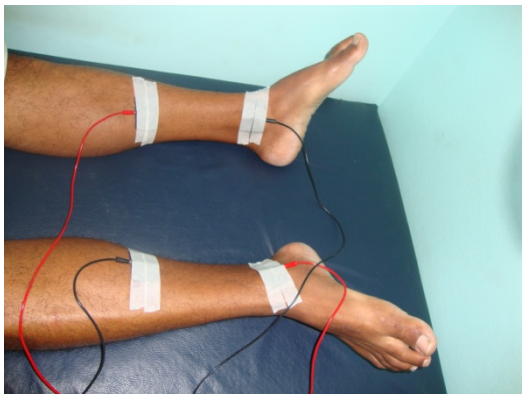
4 TREATMENTS BASED ON ELECTRICAL STIMULATION

The existing electrical stimulation techniques for UI treatment are based on applying electrical current directly over the perineum muscle. This approach uses, in the case of male patients, internal anal electrodes and, in the case of female patients, internal or surface vaginal electrodes. These techniques are embarrassing, invasive (in the case of internal electrodes), and may cause discomfort and burns in patients with abnormal sensibility (Marques, 2008).

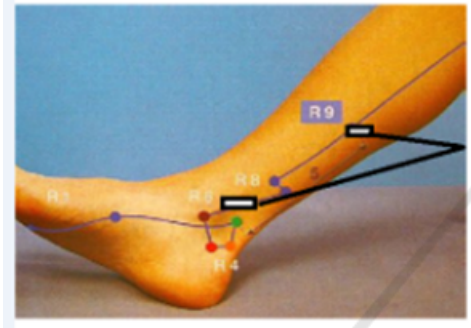
Treatments with transcutaneous electrical stimulation in the posterior tibial nerve aim at reducing UI and assume that bladder neural projections exist in that nerve's path (Fischer-Sgrott et al., 2009).

The TENS current is used for the treatment of urinary incontinence by bladder hyperactivity (BH). The electrodes are placed bilaterally in the medial region of the legs, causing motor and sensory stimulation as the current is applied (Fischer-Sgrott et al., 2009). During each session, the patient's neurological physiotherapist or urological physiotherapist observes the stimulation caused by the motor current, and the sensory way is not changed to modulate the current flow. This technique promotes the reduction of involuntary detrusor contractions (Marques, 2008). Regarding the TENS current for the treatment of BH, some researchers propose a sequence of pulses with a frequency of around 20 Hz and with a duration of around 200 milliseconds per pulse (Amarenco et al., 2003). The therapies based on electrical currents can be used in neurological patients with abnormal sensitivity, because applying electrical stimulation results in rhythmic flexing of the hallux, thus indicating the correct placement of electrodes and confirming this to be intact innervation (Maciel and Souto, 2009; Fischer-Sgrott et al., 2009). However, in individuals with Babinski's reflex, it is difficult to apply the current therapeutic modulation due to incorrect motor response from these individuals, so it becomes impossible to control the current intensity and the electromotor response (Perez, 2011).

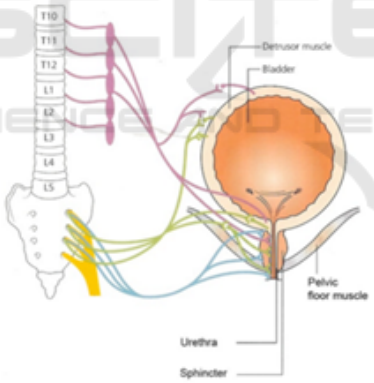
In the case of hyposensitivity, the dose should be



(a)



(b)



(c)

Figure 2: (a) Positioning of the 4 electrodes, two for each channel, used to apply the electrical currents during the TENS sessions. (b) Detail of the electrode positioning. Source: (Marques, 2008). (c) The connection between the posterior tibial nerve and the detrusor muscle; source: http://www.bladderclinic.com.au/images/bladder-conditions/neurogenic-bladder.png.

applied until it causes rhythmic inflections of the big toe, and it should then be reduced until the motor action disappears. The provided dose agrees with several studies arguing that the ideal intensity must be maintained according to the threshold of each patient and below the motor threshold (Fischer-Sgrott et al., 2009; Maciel and Souto, 2009; Amarenco et al., 2003; C.Kabay et al., 2009).

The use of TENS in the current technique of posterior tibial nerve can reduce the uninhibited detrusor contractions and improve the quality of life of patients with DO due to a reduction of urinary incontinence and of the number of times that the patient urinates. This can result in a better quality of sleep, humor, and personal relationships, as well as in less embarrassment and in reduction of stress. It can also potentially reduce the use of medication while reducing or eliminating the sings of anticholinergic syndrome.

5 METHODS

In order to collect preliminary data, we started with an assessment of patient's urological history, using validated questionnaires applied at Unifesp. The patients' selection and inclusion criteria included overactive bladder and concomitant use of anticholinergics.

We then performed the Babinski test in the case of patients with hyposensitivity and hyperreflexia (a prerequisite for patients to remain in the study was the presence of a neurological dysfunction such as multiple sclerosis). We only started the Electrotherapy in the case of patients with absence of the Babinski reflex in at least one lower limb.

The patients who were selected to participate in the study were then submitted to a physio-therapeutic protocol. The main procedure consisted in applying in an electrical current to the posterior tibial nerve, according to the following steps.

On the first evaluation day, we applied the physiotherapy assessment protocol forms, which the patient completed in the Urogynecology laboratory at Unifesp. We instructed the patient to complete a voiding diary for three days after treatment.

During the neurological assessment, a physical examination showed no sensory deficit and bilateral Babinski's reflex. Given that no pathological reflex existed, we positioned the electrodes in the path of the posterior tibial nerve, to detect whether innervation was intact, by using electrical stimulation (we used the TENS NEURODYN/FES portable device, by Ibramed Ltda). This stimulation was based on a sequence of 200-millisecond pulses, with a frequency of 20 Hz, following the recommendation in (Amarenco et al., 2003).

The treatment protocol consisted of 10 sessions, twice a week and lasting 20 minutes each. We applied the TENS current through two channels, using four electrodes positioned transcutaneously and bilaterally in the lower limb (2 electrodes per channel). For each

channel, one electrode was fixed to the posterior medial malleolus and the other 10 cm above. The intensity parameter due to hyposensitivity was measured through the signal engine rhythmic inflections of the hallux. A maximum intensity of 30 mA was applied, for safety reasons. In the case of patients with normal sensibility, the current intensity was adjusted for comfort.

6 RESULTS AND DISCUSSION

This paper presents the results of 21 case studies monitored by descriptive assessments from the Unifesp Physiotherapeutic Protocol in Urogynecology and the voiding diary for three days. The patients were submitted to physiotherapeutic treatment with transcutaneous electrical stimulation in order to attenuate urological clinical complaints. This justifies the choice of a treatment by elective electrostimulation separated from other techniques such as kinesiotherapy. We applied both evaluation procedures before treatment and after 10 TENS sessions.

According to (C.Kabay et al., 2009), when applied to people suffering from multiple sclerosis, the technique noticeably decreased nocturia in 75% of patients. Marques reports decrease in nocturia with 38% of symptoms relief (Marques, 2008). Another study found improvement in nighttime urination in 21% of cases (F. E. Govier et al., 2001). Tables 1 and 2 show that before and after 10 sessions of electrical stimulation of the posterior tibial nerve, there was a decrease in the signs of enureses, as well as a reduction in the need for urine-loss protection, and of symptoms associated to the cholinergic syndrome.

We can explain the improvement of urinary urgency conditions based on a study in which urodynamic evaluation with electrical stimulation of the posterior tibial nerve revealed that the maximum bladder capacity can increase together with a decrease of involuntary detrusor contractions during standard cystometry (Amarenco et al., 2003).

This research aimed at verifying the efficacy of the electrical stimulation as applied to the posterior tibial nerve in order to control the detrusor hyperactivity (while reducing the symptoms related to the non-inhibitted detrusor contractions and the anticholinergic syndrome).

We analyzed five conditions and symptoms before and after applying the proposed electrical stimulation protocol: i) number of enuresis cases per night; ii) number of needed urine-protection devices (UPD) per day; iii) dry mouth; iv) intestinal constipation; and v) blurred vision. Tables 1 and 2 describe the obtained results.

We then conducted a statistical analysis of the measured conditions and symptoms. The null hypotheses refer to each condition or symptom being the same or even worse after the stimulation sessions, as compared to the values measured before them. The preliminary normality tests we performed indicated that the measured values do not follow a normal distribution, and therefore we used the non-parametric Wilcoxon test in order to evaluate the main null hypotheses.

Table 3 shows the p-values obtained for the null-hypothesis associated to each of the considered condition or symptom. Note that the low values ($p < 0.1$) indicate that the null hypothesis can be rejected. This suggests that the applied electrical stimulation protocol significantly reduces the corresponding condition or symptom.

Hence, the applied electrical stimulation can inhibit or reduce the adverse effects of the anticholinergic drugs. This conservative and non-invasive technique was hence beneficial to the evaluated patients suffering from detrusor hyperactivity.

These results are the beginning of an intense planned study of the use of electrical stimulation of the posterior tibial nerve in patients with bladder hyperactivity as a substitute for pharmacological therapy based on solifenacin succinate and oxybutinin hydrochloride. By increasing the sample size and by evaluating the patients for longer periods, we want to further evaluate other impacts of the proposed protocol, including long-term effects.

7 CONCLUSION

Patients with hyperactive bladder that use anticholinergic drugs may present the cholinergic syndrome, characterized by dry mouth, intestinal constipation, and blurred vision. These symptoms add to the problems caused by the non-inhibited detrusor contractions, including loss of urine and enuresis. By replacing the pharmacological approach by the electrical stimulation of the posterior tibial nerve, we observed an improvement of the hyperactive bladder condition ($p < 0.01$), without the inconvenience associated to the cholinergic syndrome.

We also emphasize that the proposed approach is noninvasive, does not cause pain, and is cheaper than the continuous use of solifenacin succinate and oxybutynin hydrochloride. It therefore has an important effect on the patients' quality of life, in terms of social and economical aspects.

Table 1: Cases of enuresis per night and number of used urine-loss protection per day for all male and female participants, as measured before and after the electrical stimulation (ES) sessions. We interrupted the pharmacological treatment (medication A or B) in all cases, after the ES started.

Patient ID	Genre	Age	NIC	Medication type	Before Electrical Stimulation		After Electrical Stimulation	
					Enuresis/night	ULP/day	Enuresis/night	ULP/day
1	Female	46	NO	A	3	1	0	0
2	Female	55	YES	A	4	3	3	0
3	Male	22	YES	A	6	0	0	0
4	Female	67	YES	A	3	4	0	1
5	Male	25	YES	A	3	3	0	1
6	Female	76	CE	A	3	6	1	1
7	Female	56	YES	B	2	5	0	0
8	Male	64	CE	B	2	6	0	1
9	Male	79	YES	B	3	3	0	0
10	Female	50	CE	A	1	0	0	0
11	Female	67	YES	A	4	0	0	0
12	Male	72	YES	–	3	8	1	3
13	Male	67	YES	A	0	3	0	0
14	Male	63	YES	A	1	4	0	1
15	Female	43	YES	B	2	2	0	0
16	Male	70	CE	B	7	1	2	0
17	Female	41	YES	B	0	0	0	0
18	Female	57	YES	–	3	2	0	0
19	Female	52	YES	B	1	0	0	0
20	Female	41	YES	A	0	0	0	0
21	Male	89	YES	A	4	3	1	0

Table 2: Symptoms of the cholinergic syndrome.

Patient ID	Before Electrical stimulation			After Electrical Stimulation		
	Dry mouth	Intestinal constipation	Blurred Vision	Dry mouth	Intestinal constipation	Blurred Vision
1	NO	YES	NO	NO	NO	NO
2	NO	YES	NO	NO	NO	NO
3	YES	YES	NO	NO	YES	NO
4	YES	NO	NO	NO	NO	NO
5	YES	YES	NO	NO	NO	NO
6	YES	NO	YES	NO	NO	NO
7	NO	YES	NO	NO	NO	NO
8	YES	NO	NO	NO	NO	NO
9	YES	NO	NO	NO	NO	NO
10	YES	NO	NO	NO	NO	NO
11	YES	YES	NO	NO	YES	NO
12	NO	NO	NO	NO	NO	NO
13	YES	YES	NO	NO	NO	NO
14	YES	YES	YES	NO	YES	NO
15	NO	YES	NO	NO	NO	NO
16	YES	NO	NO	NO	NO	NO
17	YES	YES	YES	NO	NO	NO
18	NO	YES	NO	NO	NO	NO
19	YES	NO	NO	NO	NO	NO
20	YES	NO	NO	NO	NO	NO
21	YES	YES	YES	NO	NO	NO

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Table 3: Results, in terms of p-values, of the statistical tests regarding the null hypothesis that each symptom or condition after the electrical stimulation (EE) is equal or worse than before the EE.

Condition or symptom	p-value
Enuresis	$7.9 \cdot 10^{-6}$
Need for urine-loss protection	$2.9 \cdot 10^{-4}$
Dry mouth*	$9.8 \cdot 10^{-7}$
Intestinal constipation*	0.002
Blurred vision*	0.021

*Symptoms associated to the cholinergic syndrome.

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