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Efficacy of peripheral lidocaine application (neural therapy) in the treatment of neurogenic detrusor overactivity in multiple sclerosis patients

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AIMS: Many agents and treatments are used in the treatment of neurogenic detrusor overactivity (NDO) in MS patients, but no study has been conducted on the use of peripheric lidocaine (neural therapy—NT) on MS patients. We evaluated the effects of local administration of lidocaine on NDO in Multiple Sclerosis (MS) patients.
METHODS: For each patient local anesthetic lidocaine was injected at each session. Sessions were held once a week for 5 weeks. At each session, Th 10-L1, urogenital segment intradermal injections, Frankenhauser, and sacral epidural injections were given. The patients had clinical and urodynamic assessment 1 month before and 3, 9, and 12 months after NT. In addition, multiple sclerosis quality of life inventory (MSQL-54) and bladder control scale (BLCS) was performed for patients.
RESULTS: Twenty-eight patients were included in the study (8 males, 20 females). The patients' average age was 31.7 ± 8.1 years. The injection therapy significantly improved volume at first involuntary bladder contraction (FCV), maximal detrusor pression during filling (P det. max.), maximal cystometric bladder capacity (MCC) after 3 months. Also, the MSQL-54 and BLCS scores were improved with treatment. However, these improvements reached a maximum 3 months after treatment, but from the 9 month a regression was seen in the parameters, and after 12 months the findings were seen to be slightly above their basal levels.
CONCLUSIONS: These results suggest that NDO treatment in MS patients could be an effective treatment which is easy and has very few side effects, and is cost effective.

KEYWORDS
incontinence, lidocaine, multiple sclerosis, neural therapy, neurogenic detrusor overactivity

1 | INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease leading to demyelination and progressive neuronal loss within the central nervous system.[1] Multiple sclerosis-related lower urinary tract dysfunction is common in patients and is a major negative influence on the quality of life of these patients. Multiple sclerosis can affect brain structures and spinal pathways involved in sphincter control, and this may cause lower urinary tract symptoms.[2] Neurogenic detrusor overactivity (NDO) is the most frequently reported urodynamic abnormality.[2] Detrusor overactivity is often associated with an overactive bladder, defined by urgency, possibly associated with urge incontinence, daytime frequency, and nocturia.[3] Also, these patients have preserved sensation and compliance of the bladder as well as normal urethral closure pressure and relaxation to facilitate voiding.

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Anticholinergic agents are the first line of treatment for NDO but they can cause side effects that avoid their use, both on the central nervous system and on the heart.[4,5] NDO is considered as refractory, and the use of bladder botulinum toxin-type A (BTX-A) injection is currently recommended therapy.[6] Local anesthetic agents have been used for topical analgesia intravesically, with or without an electromotive drug administration in the case of painful procedures, to produce mucosal anesthesia for bladder biopsy.[7] Lidocaine is a common local anesthetic agent that is also used in a variety of chronic and persistent pain syndromes, including treatment of interstitial cystitis. Intravesical lidocaine therapy is one of the evolving treatment options in selected patients with functional disorders of an overactive bladder in addition to standard anticholinergic therapy or the newer generation of therapies using BTX.[8]

Neural therapy (NT) is a treatment modality using injections with local anesthetics for diagnosis and therapy (indications include functional disorders, inflammatory diseases, and acute or chronic pain).[9] The generation of targeted stimuli (through the needle) and the selective extinction of other stimuli (through the local anesthetic) affect both the organization of the nervous system and tissue perfusion.[10] NT can be divided into a local therapy (eg, infiltration of trigger points) and a segmental therapy (eg, sympathetic ganglia, nerve roots, and peripheral nerves).[9,11] Recent studies have shown that NT is effective in many neurogenic diseases.[12,13]

There are studies showing the effectiveness of lidocaine in the bladder, but the main problems with this treatment are its limited effectiveness and its difficulty of application. However, there are no studies in the literature showing the peripheral effectiveness of lidocaine in NT treatment in MS patients. This is the first study on this topic. In this study, we evaluated the effects of local administration of lidocaine using a new technique on NDO in MS patients.

2 | MATERIALS AND METHODS

2.1 | Patients

This study was conducted retrospectively in the Neurology Department of Dicle University, Diyarbakir, Turkey. Local ethical committee approval (Dicle University Faculty of Medicine Local Ethics Committee [clinical registration number 2016-197]) was obtained. Forty two patients suffering from MS who were complaining of urgency, daytime frequency, and urge incontinence due to NDO, and who were receiving NT were approached for the study. Among these eight patients were excluded from the study due to exclusion criteria defined below. Exclusion criteria included a history of hysterectomy, vaginal surgery, or stress urinary incontinence, a history of antidepressant, anticonvulsant, anticoagulant, and anxiolytic drug use, nitrite-positive urinary tract infection, previous surgical treatment for benign prostatic obstruction, or severe benign prostatic obstruction. Thirty four remaining patients were enrolled in the study. However, only 28 consecutive patients were included in the final evaluation as six patients did not complete required sessions (four did not come after first session for personal reasons, two lost in follow up after second and third sessions). The MS patients underwent their first urodynamic examination between January 2010 and January 2015. Diagnosis of MS was made according to the McDonald Revised criteria.[14]

Evaluation of medical files of 28 cases revealed that 24 of them used some kind of anticholinergics (oxybutynin [10-15 mg/day], solifenacin [5-10 mg/day], tolterodine [2-4 mg/day]) during their disease process. To avoid any possible interference, anticholinergic medications were stopped at least 1 week before NT. A period of 1 week cessation seems reasonable when the biological half lives of these anticholinergic drugs are considered. None of the cases were started anticholinergics after the end of the study by authors.

2.2 | Technique

For each patient a total dose of 40 mL of local anesthetic mixture (5:1000 mixture of 20 mg/mL Lidocaine HCl (Jetokain simplex® and saline) was injected at each session. A total of five once weekly sessions were held. All cases received this protocol only for one time. At each session, Th 10-L1, urogenital segment intradermal injections, Frankenhauser, and sacral epidural injections were applied. Th10-L1 segment injections were applied intradermally to each spinous process, and 2 cm laterally on each side. Urogenital segment injections were applied at the points shown in Fig. 1a and b.

For the Frankenhauser technique, a 22-gauge, 4-6 cm (varying from person to person) needle was used. The patient was placed in a prone position. Following prepping, the symphysis pubis midpoint was palpated. Referring the midline of the symphysis pubis, three fingers (approximately 5 cm) laterally, the needle entered vertically was withdrawn after bone contact and advanced aiming towards the anus of the patient at a depth of 4-6 cm (varying from person to person). Five milliliter of the anesthetic mixture was injected to and around the outer wall of the bladder. (Fig. 2).[12,15]

For sacral epidural injection, the patient was placed in a prone position, and following prepping and draping, the sacral hiatus was palpated (bordered by the sacral cornua), and the needle advanced at approximately 45 degrees to the midline. A pop can sometimes be felt as the needle passes through the sacrococcygeal ligament and into the hiatus. Once reached, 5 mL of anesthetic mixture is injected.[16]

As a summary, of the total amount of 40 mL local anesthetic mixture, 5 mL is injected in the sacral epidural

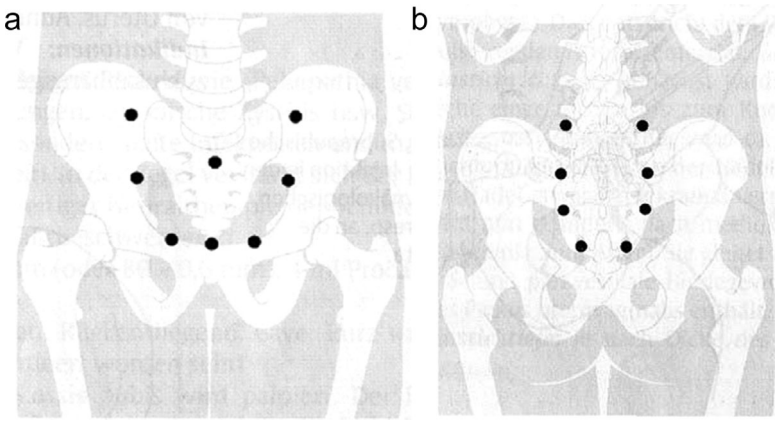

FIGURE 1 (a and b) Urogenital segment injections[13]

space, and 5 mL used while applying Frankenhauser technique. Remaining 30 mL is injected to 24 injection sites (approximately 1.25 mL per injection site) indicated above. Although it seems like an extensive protocol, its application is quite rapid and easy in experienced hands.

2.3 | Evaluation

Demographics, age, sex, clinical features, expanded disability status scale (EDSS), disease duration, MR findings, subtype, and treatments were assessed. Also, urination frequency, frequency of micturition during the night, urodynamic examination, and pelvic ultrasound were evaluated.

The patients had clinical and urodynamic assessment 1 month before and 3, 9, and 12 months after NT. Urodynamics were carried out according to the ICS and manufacturer's recommendations.[17] In addition, multiple sclerosis quality of life inventory (MSQL-54) and bladder control scale (BLCS) was performed for patients.[18,19]

Urodynamic data were collected: volume at first involuntary bladder contraction (FCV), maximal detrusor pression during filling (P det. max.), maximal cystometric bladder capacity (MCC).

2.4 | Statistical analysis

The statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Continuous data are presented as mean ± standard deviation (SD). Differences in the continuous variables between groups were determined by Student *t*-test or the Mann Whitney *U*-test, for variables with or without normal distribution, respectively. To test the normal distribution, the Kolmogorov Smirnov test was used. Significance was set at $P < 0.05$.

3 | RESULTS

Twenty-eight consecutive patients were included in the study. Twenty women and eight men were studied, with a mean age of 31.7 ± 8.1 years. The patients' characteristics are summarized in Table 1.

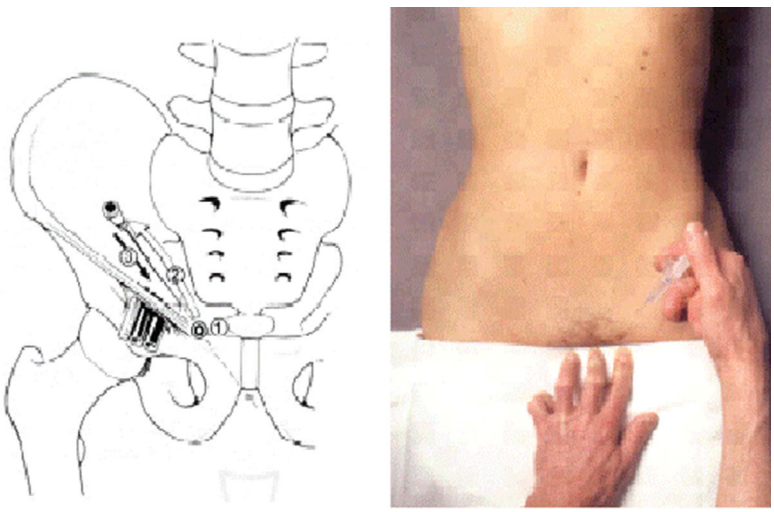

FIGURE 2 Frankenhauser technique[13]

TABLE 1 Characteristics of patients

Patients' characteristics	Mean ± standard deviation
Age (years)	31.7 ± 8.1
Age of onset of multiple sclerosis (years)	24.4 ± 5.4
Disease duration (years)	7.2 ± 4.6
EDSS	3.6 ± 1.4

EDSS, Expanded Disability Status Scale.

The injection therapy improved FCV, MCC, and P det. (Table 2). Also, the frequency of urination, urinary frequency at night and MQoL-54 scores were improved with treatment (Table 2). These improvements reached a maximum 3 months after treatment, but from the 9th month on a regression was seen in the parameters, and after 12 months the findings were seen to be slightly above their basal levels.

In one patient mild hematuria that continued for 3 days was observed, but no other relevant side effect was seen. None of the patients had any progression of the MS during study period.

4 | DISCUSSION

We showed in this study that lidocaine with NT applied to MS patients with NDO gave clear improvements in objectively measurable bladder function. In addition, this treatment was also observed to bring about an improvement in patients' daily life activities.

Bladder control is under the control of the parasympathetic and sympathetic systems. The sympathetic division arises from the thoracolumbar spinal cord (T12-L2) and the parasympathetic division arises from cell bodies in the intermediolateral horn spinal cord (S2-S4).[20–22] NDO treatments partly have their effect by modulating these two systems.

NT with lidocaine is based on normalizing a dysfunctional autonomic nervous system, the part of the peripheral nervous system that is responsible for involuntary actions in the body such as the immune system, the cardiovascular system, the endocrine system, and also the healing process.[12,13,15]

Lidocaine alters signal conduction in neurons by blocking the fast voltage-gated Na^+ channels in the neuronal cell membrane responsible for signal propagation.[23] With sufficient blockage, the membrane of the postsynaptic neuron will not depolarize and will thus fail to transmit an action potential. This creates the anesthetic effect by not merely preventing pain signals from propagating to the brain, but by stopping them before they begin. Careful titration allows for a high degree of selectivity in the blockage of sensory neurons, whereas higher concentrations also affect other modalities of neuron signaling.

Beside the action on sodium ion channels, additional molecular mechanisms in NT have been revealed. Local anesthetics induce Gq-protein-complex mediated intracellular anti-inflammatory mechanisms deactivate overactive granulocytes, inhibit the signaling of human N-methyl-D-aspartate (NMDA) receptors, and affect the synthesis and release of inflammatory mediators as eicosanoids, histamine, prostaglandins, and cytokines.[24–28]

The longstanding effect of local anesthetics cannot only be explained by their pharmacological effect, but pleiotropy (ie, the "alternative effects") of local anesthetics.[28]

These other mechanisms can be listed as;

1. By indirectly reducing long term potentiation.[29,30]
2. By decreasing sympathetic sprouting.[31–34]
3. By decreasing the sympathetically mediated activity of wide dynamic range neurons.[35]
4. By temporarily disrupting the positive neuronal feedback loops ("reset") and subsequently re-organizing the systems involved.[36,37]

Local anesthetics also induce vasodilatation, reduce a pathologically increased capillary permeability, have antimicrobial properties, and exhibit a sympatholytic effect.[26,28,39,40]

Empirically, the number of sessions is decided according to the patients' reply to treatment, changing from three to seven sessions. In current study, we applied five sessions to the patients, in order to standardize our protocol and achieve optimized results. The interval in-between sessions should be 3-7 days in order to treatment can take effect. In his review, Weinschenk proposed that, NT works best if it is repeated several times with increased intervals as complaints are decreasing.[27] Our protocol included 7 Day interval in-between sessions.

Studies have shown that lidocaine delivered intravesically has an anti-inflammatory effect, that it reduces inflammation in the urinary system and that it is effective in intestinal cystitis.[41] Local anesthetics have also been shown to play a significant role in the treatment and prevention of neuropeptide-induced peripheral sensitization.[42] It was shown by Yokoyama et al that intravesical lidocaine was effective in overactive detrusor treatment.[43] It has been stated that lidocaine spreads around the bladder and is absorbed by the mucosal barrier, and may be effective in treatment by affecting the protein and lipid canals of the non-ionized substrata.[23]

One of the technique we used for intrapelvic injection was Frankenhauser injection technique. The aim of Frankenhauser injection is to regulate both the parasympathetic and sympathetic nerves which is present in the targeted Frankenhauser ganglion, a ganglion located approximately 1 cm lateral to cervix within the inferior hypogastric plexus.[15,44] Thus we apply it into perivesical space. However, there are different techniques of Frankenhauser injection described in literature[44]; intravaginal technique in women and perianal technique in men, which are too painful and may not be

TABLE 2 Changes in clinical and urodynamic assessments of cases

	Before NT	3th month	9th month	12th month
Mean FCV (mL)/SD	167.8 ± 21	270.3 ± 53.0*	232.6 ± 56*	168.7 ± 22
Mean MCC (mL)/SD	237.8 ± 24	298.7 ± 27*	269.2 ± 28*	238.5 ± 24*
Mean P det. max. (cm H2O)/SD	70.0 ± 4.6	62.00 ± 5.3*	53.0 ± 4.7*	62.8 ± 4.7*
MSQL- mental health	49.8 ± 8.6	61,5 ± 7.3*	57,1 ± 7.2*	53,8 ± 7.8*
MSQL- physical health	50.0 ± 7.8	55.3 ± 7.4*	53.0 ± 7.7*	51.0 ± 8.6
BLCL	21.8 ± 2.9	15.3 ± 3.2 *	17.8 ± 3.5*	21.0 ± 4.1*
Daily urination frequency	12.2 ± 2.3	8.2 ± 1.3*	8.4 ± 2.1*	11.4 ± 2.4 *

MSQL, Multiple Sclerosis Quality of Life Inventory; BLCS, Bladder Control Scale; FCV, Volume at first involuntary bladder contraction; P det. Max, maximal detrusor pression during filling; MCC, maximal cystometric bladder capacity; NT, neural therapy.
Data is expressed as mean ± standard deviation.
Values of $P < 0.05$ are taken as significant.
*Means that there was a significant difference from the control.

accepted by the patient because of cultural bias. The technique we used in this manuscript is easy to apply, acceptable by the patients and standardized for both men and women.

Adverse drug reactions (ADRs) are rare when lidocaine is used and administered correctly. Most ADRs associated with lidocaine relate to administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia, and allergic reactions only rarely occur.[45] Systemic exposure to excessive quantities of lidocaine mainly result in central nervous system (CNS) and cardiovascular effects. It is available as a generic medication and is not very expensive.[46] In the current study, one patient had mild hematuria that continued for 3 days.

It is known that in NDO treatment the effectiveness of neuromodulatory treatment is long-lasting. Percutaneous electrical stimulation of the tibial nerve, sacral neuromodulation, and magnetic stimulation are used in the treatment of NDO and overactive bladder.[47,48] The mechanism of neuromodulation for overactive bladder has been reported to be the reflex inhibition of detrusor contraction by the activation of afferent fibers by three actions: activation of the hypogastric nerve, direct inhibition of the pelvic nerve within the sacral cord, and supraspinal inhibition of the detrusor reflex.[48] It has been shown in previous studies that neuromodulatory treatment by repeated electrical stimulation of the plexus has been effective in NDO. It is known from a number of studies that lidocaine is effective in NDO treatment in intravesical applications. In addition, there are publications which report the effectiveness of NT in NDO treatment. [12,13,15]

In our study we chose lidocaine for NT. We applied peripheral lidocaine to the sympathetic derived hypogastric nerve and pelvic nerves, and to the region of the sacral canal and parasympathetic nerve regions. Maximum effect was observed at 3 months. This effect lasted until the 9 month, and regressed by degrees so that in the 12th month it was observed to have returned approximately to its starting values. The quality of life inventory applied within this period showed a clear improvement for the first 9 months in urination frequency and BLCL problems consistent with these parameters. At the end of 1 year, they had returned to slightly above their basal levels.

The current study has some limitations. It was a retrospective preliminary study with a short follow-up time in a small group of MS patients. Another limitation was the lack of a control group.

NT is a regulation therapy based on normalizing a dysfunctional autonomic nervous system. The technique is easy and applicable, with minimum adverse effects. The complications may be hematuria and pain due to inappropriate injection technique. It is also cost effective compared with other treatments.

Our findings may be related to the neuromodulatory or anti-inflammatory effects of lidocaine, or its effect in correcting peripheral sensitization. No study was found in the literature assessing the effect of NT with lidocaine in the treatment of NDO in MS patients. We are of the opinion that the effectiveness of NT should be evaluated more clearly with studies comparing different treatments in wider populations.

POTENTIAL CONFLICTS OF INTEREST

Nothing to disclose.

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