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UNILATERAL VERSUS BILATERAL NEUROMODULATION IN A RAT MODEL OF THE BLADDER RHYTHMIC CONTRACTION

Hypothesis / aims of study

Electrical stimulation of one side of the S3 sacral nerve using Interstim® Therapy produces an effective therapy in 40 to 80% of patients with overactive bladder. Bilateral stimulation has been reported to increase efficacy of neuromodulation therapy. In a preclinical porcine model, bilateral stimulation was found to be more effective for attenuating hyperactive detrusor contractions induced by formalin infusion (1). Using the rat bladder rhythmic contraction (BRC) model, we have demonstrated that bilateral electrical stimulation of the L6 spinal nerve (SN), through which most mechanosensitive bladder afferent fibers pass in the rat, at 10 Hz for 10 min inhibits bladder contractions (2, 3). In this study, we compare the relative effectiveness of unilateral vs bilateral neuromodulation by stimulating the L6 SN.

Study design, materials and methods

In anesthetized female rats (urethane, i.p. 1.2g/kg), an electrode of teflon-coated stainless steel wire was placed under the L6 SN in three ways, 1) a bared portion of wire electrode under the left side of the SN *unilaterally*; 2) two bared portions of a single wire placed under each of the SN serially and bilateral stimulation was achieved by passing current in a parallel circuit *uncontrolled*, and 3) two electrodes were placed bilaterally under the SN and current was controlled *independently*. A cannula was placed into the bladder via the urethra and the urethra was ligated to ensure an isovolumetric bladder. The urethral cannula was linked with a pressure transducer and the signal was amplified through a DC amplifier. Saline infusion induced the BRC. Effect of SN stimulation on the BRC was evaluated at the highest intensity of 0.6 mA or motor threshold intensity which was adjusted for each animal as a function of hind-toe twitches and pelvic floor muscle contraction. Mean motor threshold for the animals in this experiment was 0.12 ± 0.02 mA; n=62.

Results

There was no significant change in the isovolumetric bladder contractions during a 45 min recording when no electrical stimulation was applied (n=7). Stimulation at a supra-threshold intensity of 0.6 mA, 10 Hz for 10 min completely abolished bladder contractions which sustained for 10 min (*prolonged inhibition*) and was equally potent using either bilateral stimulation (uncontrolled or independently controlled) or unilateral stimulation (Fig 1A). The time course of the response (bladder contraction frequency during and following stimulation) was very similar for both bilateral and unilateral stimulation. Using 0.5 Hz stimuli of the same intensity (a stimulus that does not induce maximum bladder quieting), uncontrolled bilateral stimulation reduced contraction frequencies during stimulation to 20±10% of controls (n=8) which was significantly larger than reductions produced by unilateral stimulation (to 58±16% of controls, n=7, $p<0.05$, Student's t-test, Figure 1B, 1B *inset*). Independently controlled bilateral stimulation reduced contraction frequencies to 30±12% of controls (n=7).

We also tested bilateral and unilateral stimulation using lower stimulation intensities equivalent to the motor threshold at 10 Hz for 10 min. Independently controlled bilateral stimulation decreased the frequency of the BRC to 29±14% of controls during stimulation. Uncontrolled bilateral stimulation failed to significantly change bladder contractions during stimulation, but produced a significant *post-stimulation inhibition* with maximum bladder inhibition at 10 min post-stimulation. Stimulation decreased the frequency of the BRC to 45 ± 14% of controls (n=11, v.s. control, n=7, $p<0.05$, two-way ANOVA). Unilateral stimulation for 10 min (n=9) or sequential 10 min periods of stimulation of both spinal nerves (e.g. 10 min per side for a total of 20 min stimulation, n=9) failed to attenuate bladder contraction frequency (data not shown).

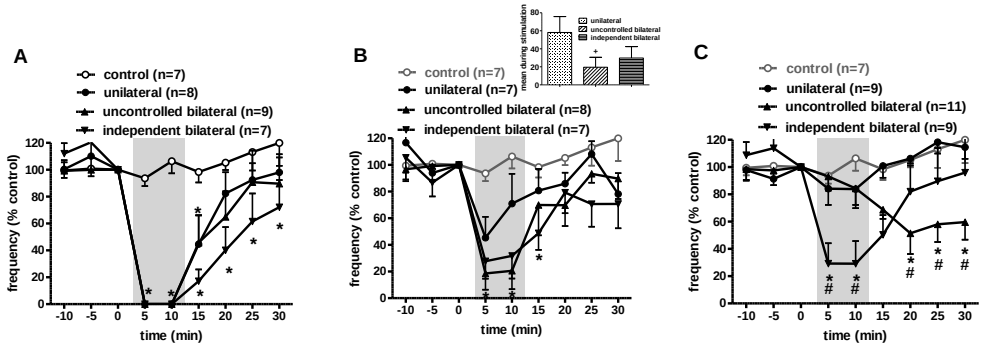

Figure 1. Time course effect of the bladder rhythmic contraction by unilateral or bilateral spinal nerve stimulation at 0.6 mA, 10 Hz (**A**), 0.6 mA, 0.5 Hz (**B**) and motor threshold stimulation, ~0.12mA, 10 Hz (**C**). **B** *inset*, mean responses during 10 min stimulation. Responses are as a percentage of control where the baseline response before stimulation is defined as 100%. A value of $P<0.05$ was considered statistically significant, determined by ANOVA test followed by Bonferroni post test (*, vs control; #, vs unilateral) or Student t-test (+, vs unilateral, figure **B** *inset*). The shaded areas are responses during electrical stimulation.

Interpretation of results

Consistent with our previous studies (2, 3), stimulation at high intensity (0.6 mA, 10 Hz) abolished bladder contractions during electrical stimulation and the inhibition was sustained for 10 min following discontinuation of the stimulation (*prolonged*

inhibition). Since unilateral stimulation of spinal nerve at 10 Hz, 0.6 mA totally abolished bladder contractions, enhanced inhibition by bilateral stimulation was not observed. Using 0.6 mA, 0.5 Hz or motor threshold intensity, bilateral neuromodulation produced a stronger inhibition on the BRC than unilateral stimulation. For our test of uncontrolled bilateral stimulation, absolute current intensity may not be equally delivered to the two nerves. Using this configuration, bilateral but not unilateral stimulation produced a moderate reduction of the frequency of the BRC and this inhibition was maximal 10 min post-stimulation (*delayed inhibition*). Furthermore, independently controlled bilateral stimulation reduced bladder contractions during stimulation. Such enhanced actions of bilateral neuromodulation may be caused by spatial summation of bladder afferents during the simultaneous bilateral neuromodulation. Temporal summation over the 20 min we tested here (e.g. 10 min each side) was not observed. The spatial summation of bilateral stimulation is superior to stimulation with a high current intensity which may also activate more afferent fibers to produce a stronger bladder quieting response. These higher intensities of current stimulation ultimately activate small afferent fibers, which in turn competes with or reduces the inhibitory effects of stimulation. The spatial summation utilized by bilateral stimulation may allow the use of lower stimulation intensities to achieve higher efficacy for Interstim® Therapy.

Concluding message

The enhanced inhibitory effects by bilateral neuromodulation may be due to the additive or synergizing effects of simultaneous stimulation of both L6 nerve roots. These results prompt further investigation and potential applications of bilateral Interstim® Therapy in the treatment of patients with urinary bladder dysfunction.

References

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2. Su X, Nickles A, Nelson, DE. Interstim® therapy in a rat model of rhythmic bladder contraction. ICS Annual Meeting, 2010a.
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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**The Institutional Animal Care and Use Committee of Medtronic (Minneapolis, MN).**