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ACUTE EFFECTS ON BLADDER CAPACITY USING AN IMPLANTABLE TIBIAL NEUROMODULATION DEVICE IN THE FULLY CONSCIOUS SHEEP

Hypothesis / aims of study

Tibial neuromodulation (TNM) is a clinically used therapy for patients with refractory, idiopathic overactive bladder [1]. TNM is currently delivered percutaneous using a needle electrode. Therapy sessions are commonly 30 minutes of stimulation once per week. There are questions regarding how often therapy should be delivered as well as optimal clinical and patient scheduling for delivery of therapy. A fully implantable tibial neuromodulation device will allow patient convenience as well as additional flexibility in terms of therapy delivery sessions. In this preclinical feasibility study using a fully conscious sheep model [2], acute effects of an implanted TNM device on bladder capacity and motor thresholds were quantified over an eight week period.

Study design, materials and methods

Two adult, female, polypay sheep were implanted with two separate neuromodulation devices (BlueWind Medical, Herzliya, Israel) on the same leg, targeting the tibial nerve. Each sheep received two devices implanted into the right hind leg, targeting the tibial nerve. To compare effects of differing device-nerve interface, devices were targeted to the tibial nerve with one more proximal (on-target) and one more distal (off-target) from the nerve. CT images were obtained immediately after implantation and at study term to confirm placement.

After one month of recovery, cystometry was performed weekly for eight weeks using repeated, single fill cystometry. Warmed saline was infused at 30 ml/min until the sheep moved into voiding posture with bladder pressure rising above 30mm Hg or until 350 ml had been infused. Ten trials were performed in each weekly cystometry session. The first five trials were conducted without stimulation (Baseline) followed by delivery of tibial neuromodulation for the remaining five trials (TNM). Stimulation parameters for urological testing were: unilateral, 20 Hz, 0.2 ms pulse width at maximum tolerable amplitude, as described previously [2]. Only one device was activated each week, alternating between the two devices (on- or off-target). TNM was turned off until the next week's session. Motor threshold was determined at 2 Hz by increasing current amplitude until motor response (flexion of the hoof) could be visually identified.

Urological data was examined comparing bladder capacity during baseline to trials with TNM. A mixed-effects regression model (R, Vienna, Austria) was used to control for repeated measurements in each sheep within each testing session as well as across multiple weeks. Urological data are shown as average ± 95% confidence intervals. Motor data ± standard deviation (SD) were analysed using a one-way ANOVA on Ranks. P value of <0.05 was considered significant.

Results

CT images confirmed stability of device location during the study. Motor thresholds were recorded for all four devices each week of the eight weeks of testing. Average motor threshold was 1.2±0.4 mA at week 1 and 0.8±0.2 mA at week 8 were not significantly different ($p > 0.6$). These data suggest minimal migration of the devices over the eight week period of the sheep's normal daily behaviours. There were also no observed changes in motor thresholds within the individual devices (Figure 1).

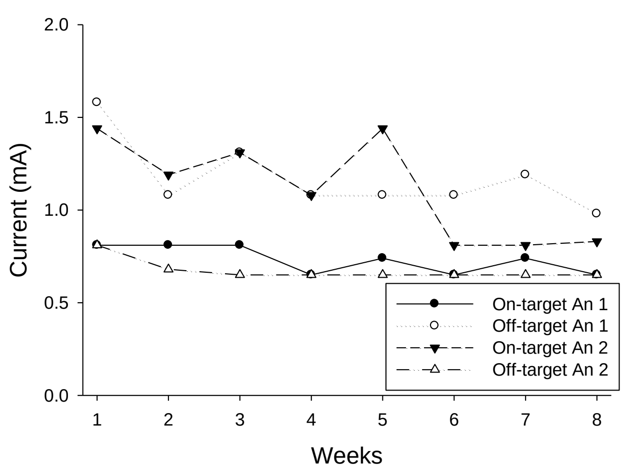

Figure 1. Motor thresholds were stable over eight weeks of testing. Average current (mA) to evoke a motor contraction was similar for each device over the eight weeks of testing. Each symbol represents either the on-target or off-target device in animal 1 (An 1) or animal 2 (An 2).

Effects of TNM on bladder capacity were examined with all data combined, which consisted of alternating weekly testing of the on-target (4 weeks) and off-target (4 weeks) devices. Over the eight weeks of testing, baseline bladder capacity in the two sheep was 198.2 ml and this increased to 242.3 ml in trials with TNM ($p < 0.0001$; Figure 2).

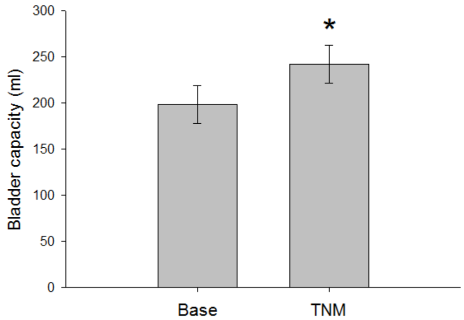

Figure 2. An implantable tibial neuromodulator significantly increases bladder capacity in the sheep. Average baseline bladder capacity was 198.2 ml and increased to 242.3 ml with TNM. N = 2 sheep with eight testing weeks, *: $p < 0.0001$.

Interpretation of results

Using an established fully conscious sheep model, these data demonstrate a significant and consistent effect of a fully implanted tibial neuromodulation device on urological and motor responses. Motor thresholds remained consistent over the duration of the study, suggesting no significant device migration away from the targeted tibial nerve. TNM significantly increased bladder capacity when applied acutely in cystometric trials.

Concluding message

An implantable tibial neuromodulation device significantly increases bladder capacity in the fully conscious sheep and motor thresholds were stable over an eight week period.

References

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Disclosures

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