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Resarch Article

Effect of Early Sacral Neuromodulation using Different Frequencies on Bladder Function in a Rat Model of Neurogenic Bladder

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Abstract

Purpose: This study utilized a Neurogenic Bladder (NB) Sprague-Dawley (SD) rat model induced by T10 Spinal Cord Injury (SCI) to investigate the effects of Sacral Neuromodulation (SNM) at different frequencies on bladder function recovery.

Materials and Methods: Twenty healthy adult female SD rats were randomly divided into 4 groups: the control group, 5 Hz group, 14 Hz group, and 35 Hz group. The NB model was established using T10 SCI. After 2 weeks of SNM therapy at different frequencies, bladder function recovery was evaluated among the groups using urodynamics.

Results: The maximum bladder capacity (MCC) in the 35 Hz group was 2.02±0.144 ml, which was significantly lower than that in the 14 Hz group (2.563±0.147 ml, $P<0.01$) and the 5 Hz group (2.905±0.087 ml, $P<0.01$). Analysis of changes in bladder leak point pressure (BLPP) revealed a significant increase only in the 35 Hz group. The BLPP in the 35 Hz group (74.966±5.320 cmH_2O) was significantly greater than that in the control group (60.150±5.719 cmH_2O, $P=0.0151$) and the 5 Hz group (59.416±7.946 cmH_2O, $P=0.0107$). Moreover, there was no significant difference in bladder compliance (BC) between the 5 Hz group (0.0568±0.0036 ml/cmH_2O) and the control group (0.0498±0.007 ml/cmH_2O, $P>0.05$). The BC in the 35 Hz group was 0.027±0 ml/cmH_2O, which was significantly lower than that in the 5 Hz group (0.0498±0.007 ml/cmH_2O, $P<0.01$) and the 14 Hz group (0.0388±0.001 ml/cmH_2O, $P<0.01$).

Conclusion: High-frequency sacral nerve modulation parameters (210 μs, 90% of motor threshold (MT) mA) demonstrate superior therapeutic efficacy for acute bladder function recovery in patients with neurogenic bladder disease due to spinal cord injury.

Keywords: Animal model; Neurogenic bladder; Parameter; Sacral neuromodulation; Urodynamic

Introduction

The Neurogenic Bladder (NB) is a common and challenging urological disease caused by damage to the central nervous system or peripheral nerves that controls urination, leading to dysfunction of the bladder and urethra. This results in neurogenic disturbances of the detrusor muscle and sphincter activity [1]. The lower urinary tract symptoms of NB include storage phase symptoms (urgency, frequency, incontinence), voiding phase symptoms (dysuria, bladder emptying disorders, urinary retention, pain), and postmicturition symptoms (terminal dribble), with voiding difficulties or urinary retention being among the most common symptoms [2-4]. Complications in the urinary system, such as damage to the upper urinary tract and renal failure, are the primary causes of death in patients [5,6]. Sacral Neuromodulation (SNM), a novel minimally invasive and reversible technique, has increasingly attracted the attention of clinicians for the treatment of various lower urinary tract symptoms caused by NB. However, there is still controversy and a lack of authoritative guidelines regarding the use of SNM parameters for treating different lower urinary tract symptoms, and the specific mechanism of SNM in

treating NB still requires further research [7]. An ideal animal model could help us to study the etiology, pathogenesis, and treatment methods of NB more deeply. This study used T10 Spinal Cord Injury (SCI) to establish an NB model in Sprague Dawley (SD) rats, further explored the impact of SNM on the recovery of bladder function in rats with NB, and studied the influence of different pulse frequencies of electrical stimulation on the recovery of bladder function in rats with NB, hoping to provide more valuable evidence for the determination of electrical stimulation parameters in SNM.

Materials and Methods

The Experimental Animal Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University approved the experimental protocol.

Animals

In all, 20 female Sprague-Dawley rats aged eight weeks and weighing 200–250 g were randomly assigned to one of four groups: the CTR (control) group (N = 5), 5 Hz group (N = 5), 14 Hz group (N = 5), and 35 Hz group (N=5). The animals were housed individually per cage, maintained on a 12:12 h alternating light–dark cycle, and given food and water ad libitum. In all groups, incomplete SCI was created, and needle electrodes were implanted bilaterally into the S2 sacral foramen in all animals, although only the SNM rats were stimulated postoperatively.

Animal Model of Neurogenic Bladder

Rats were fasted for 24 hours before surgery. For anesthesia during the experiments, the rats were intraperitoneally injected with 10% chloral hydrate (300 mg/kg). The entire surgical procedure was conducted under strict aseptic conditions, involving the removal of fur from the dorsal surgical area and three disinfections with iodine-soaked cotton balls. Using fingers to palpate the rat's spinal processes, the highest palpable point was identified as the T13 spinal segment, with the T10 vertebral process located three spinal segments above it. After marking the location with a puncture needle, correct positioning was confirmed under X-ray fluoroscopy (Figure 1A). A 3 cm incision was made centered at this point, with the skin and superficial fascia dissected and the subcutaneous tissue freed. Blunt dissection was used to separate the paraspinal muscles bilaterally to expose the T10 vertebral body. T10 laminectomy was performed to expose the rat spinal cord (Figure 1B). Using microsurgical forceps, the dura mater was gently lifted, and the T10 spinal segment was transected using microsurgical scissors. After removing any oozing blood with cotton swabs, the rat fascia, muscles, and skin were sequentially sutured (Figure 1C), followed by additional iodine disinfection of the rat skin.

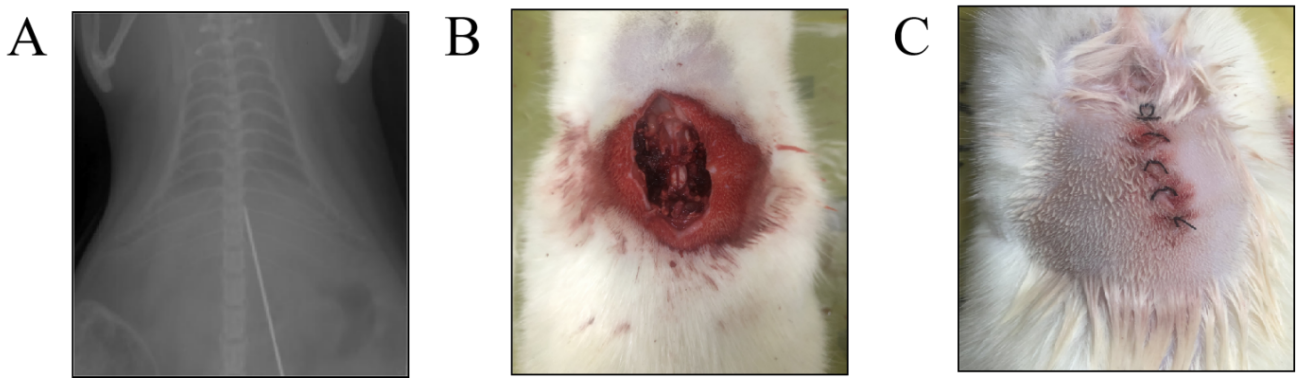

Figure 1: (A) X-ray localization of the T10 spinal segment in rats; (B) exposure of the spinal cord after laminectomy in rats; (C) suturing of the incision after spinal cord transection in rats.

SNM Treatment

Rats were fasted for 24 hours before surgery. For anesthesia during the experiments, the rats were intraperitoneally injected with 10% chloral hydrate (300 mg/kg). The entire surgical procedure was conducted under strict aseptic conditions. The fur from the sacral region of the rats was removed, and the area was disinfected three times using iodine-soaked cotton balls. Using fingers to palpate and locate the rat sacrum, the sacral promontory and wings were identified. Due to anatomical differences between rat and human sacral structures (humans have 4 pairs of sacral foramina, whereas rats have only 3 pairs), with the S2 nerve roots primarily controlling bladder function, electrodes were implanted into the S2 sacral foramina of rats in this study. Once the approximate sacral area was located, a puncture needle was inserted into the rat's S2 sacral foramen and secured to the rat's body surface. The correct placement of the needle into the S2 sacral foramen was confirmed using X-ray imaging equipment (Figure 2A-B), ensuring accurate positioning. A 2-3 cm incision was made in the S2 sacral foramen area, with the skin and fascia dissected, and the paraspinal muscles were bluntly separated from the center to both sides. Subsequently, a temporary cardiac pacing lead (due to the oversized human sacral neuromodulation stimulation electrode for use in this study) was inserted into the rat's S2 sacral foramen. The placement of the electrode was confirmed using X-ray imaging equipment (Figure 2C). After removing any oozing blood with cotton swabs, the rat's fascia, muscles, and skin were sequentially sutured. During suturing, the externalized end of the electrode lead was securely fixed and sutured. The skin of the rats was disinfected again with iodine. Postoperatively, all rats were given analgesics and antibiotics.

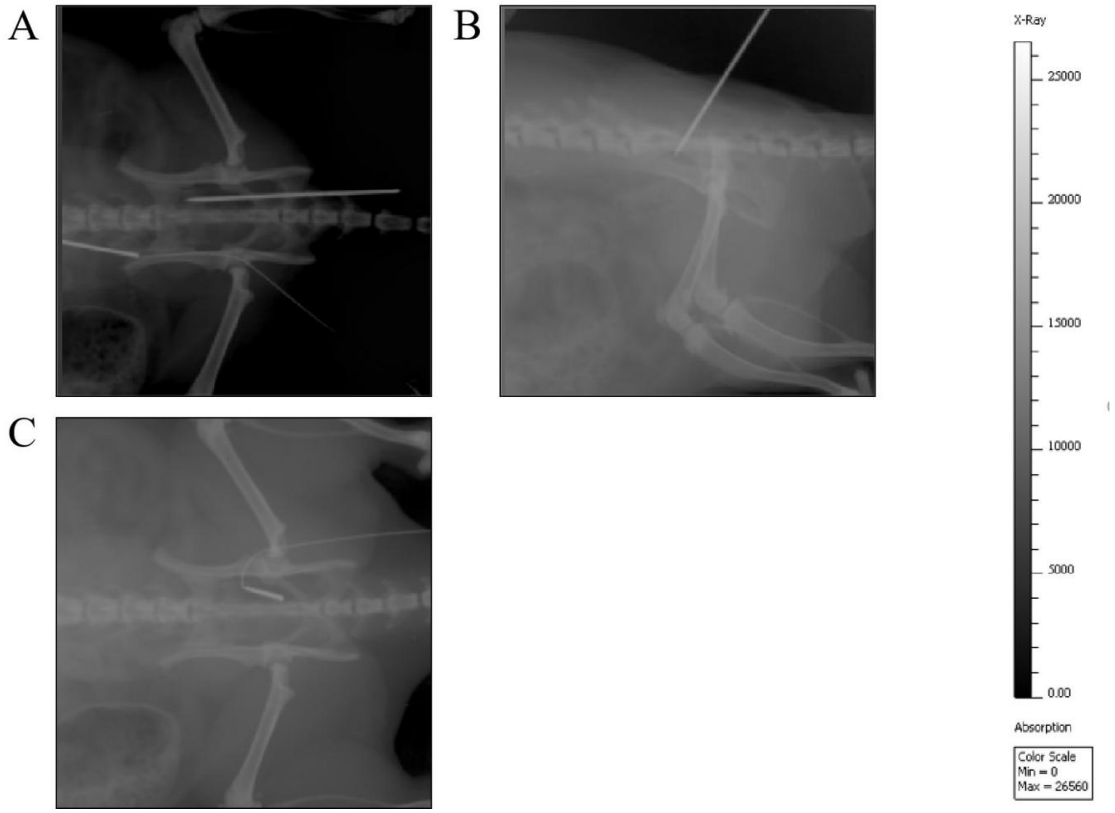

Figure 2: (A) Prone position of the rat, X-ray anteroposterior view of the S2 sacral foramen; (B) Left lateral position of the rat, X-ray view of the S2 sacral foramen; (C) Prone position of the rat, X-ray anteroposterior view after electrode implantation into the S2 sacral foramen.

Experimental Process

All groups of rats underwent urodynamic testing once after T10 spinal cord injury and electrode implantation into the sacral nerves prior to SNM therapy. Subsequently, each group received SNM therapy at different frequencies, which were administered daily for 1 hour over a period of 2 weeks. A second urodynamic evaluation was conducted to assess bladder function after the treatment period.

Statistical Analysis

The data in this study were statistically analyzed using GraphPad Prism (version 9.0.0). All the data are presented as the mean ± Standard Deviation (SD). For normally distributed data, a t test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was used for comparisons among multiple groups. For nonnormally distributed data, nonparametric tests were employed. A p value less than 0.05 was considered to indicate statistical significance. Significance in the figures is denoted as follows: * for $p < 0.05$, ** for $p < 0.01$, *** for $p < 0.001$, **** for $p < 0.0001$; "ns" indicates no significant difference.

Results

General description of each group of rats

Three days after establishing the NB rat model using the T10 spinal cord transection method and implanting SNM electrodes, no rats died. The Basso Mouse Scale (BMS) score for motor behavior was 0 for all four groups of rats, and their activity, diet, and water consumption were generally normal. The body weights of the rats in each group are shown in Table 1.

	CTR	5 Hz	14 Hz	35 Hz
Body weight	222.6±3.6 g	222.8±3.2 g	224.4±5.9 g	223.1±4.4 g

Table 1: Comparison of rat body weights among the four groups 3 days after model induction.

Comparison of Urinary Dynamics of Bladder Function Among the 4 Groups of SD Rats

After completing 2 weeks of sacral nerve modulation therapy, urinary dynamics were assessed using urodynamic testing to Measure Maximum Bladder Capacity (MCC), Bladder Leak Point Pressure (BLPP), and Bladder Compliance (BC) in each group of rats, as shown in Table 2.

Group	Number	MCC (ml)	BLPP (cmH_20)	BC (ml/cmH_20)
CTR	5	3.398±0.125	60.150±5.719	0.057±0.004
5 Hz	5	2.905±0.087	59.416±7.946	0.050±0.007
14 Hz	5	2.563±0.147	66.132±4.691	0.039±0.001
35 Hz	5	2.024±0.144	74.966±5.320	0.027±0.000

Table 2: Urodynamic parameters of the four groups of rats.

The urodynamic pressure–time curve revealed that SNM therapy at different frequencies significantly reduced the MCC of the rats compared to that of the control group. Among them, the 35 Hz group showed the most significant decrease in the MCC (2.024±0.144 ml vs. 3.398±0.125 ml, $P<0.01$) (Figure 3A). Compared to that in the control group, the increase in BLPP was statistically significant only in the 35 Hz group (74.966±5.320 cmH_2O vs. 60.150±5.719 cmH_2O, $P<0.01$) (Figure 3B). After further calculation, compared to that in the control group, there was a statistically significant decrease in BC in the 5 Hz group (0.050±0.007 ml/cmH_2O vs. 0.057±0.004 ml/cmH_2O, $P<0.05$), 14 Hz group (0.039±0.001 ml/cmH_2O vs. 0.057±0.004 ml/cmH_2O, $P<0.01$), and 35 Hz group (0.027±0.000 ml/cmH_2O vs. 0.057±0.004 ml/cmH_2O, $P<0.01$) (Figure 3C).

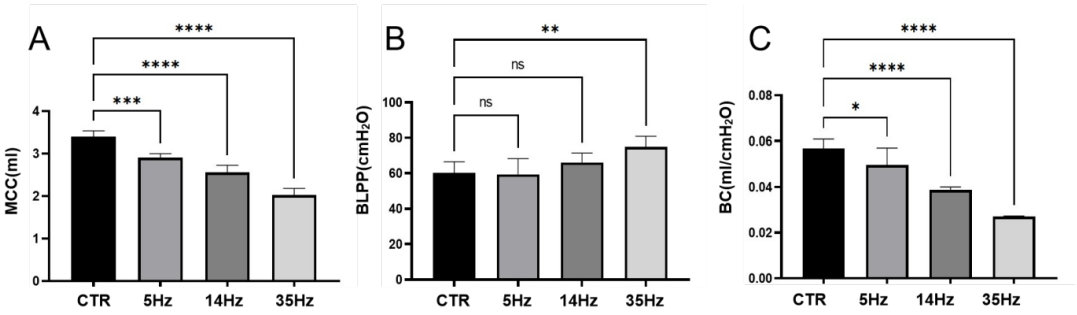

Figure 3: (A) There was a statistically significant difference in the MCC between the rat groups at different frequencies and the control group (P<0.01). (B) Only the rats in the 35 Hz group showed a statistically significant difference in the BLPP compared to the control group (P<0.01). (C) There was a statistically significant difference in the BC between the rat groups at different frequencies and the control group (P<0.01).

Discussion

Due to the complex and diverse etiology of NB, conducting clinical studies directly on patients with NB is extremely challenging. Currently, the understanding of the pathophysiological mechanisms of NB is limited [8, 9]. Therefore, establishing an effective and stable animal model is crucial to further our research into the pathogenesis and treatment of NB. A robust animal model serves as the foundation for our scientific investigations into the disease characteristics of NB.

We established a rat model of NB using T10 spinal cord injury. Within weeks following the transection of the spinal cord at the T10 segment, the bladder lost effective central nervous system control. The contraction of the detrusor muscle became weak, leading to ineffective bladder contraction and a significant increase in the MCC. BLPP decreased markedly, and BC increased [10]. Currently, effective treatments for NB are limited [11]. SNM is an unconventional treatment method, with some studies suggesting its effectiveness in improving lower urinary tract symptoms [12]. However, there is limited understanding regarding SNM parameter settings and therapeutic mechanisms [13,14]. Existing research primarily involves retrospective clinical case reviews, highlighting the need for prospective studies with larger and more diverse samples to further explore the underlying mechanisms involved [15,16].

This study confirmed that SNM therapy promotes early recovery of bladder function following SCI. The programming parameters of SNM significantly influence bladder functional recovery. This study demonstrated that high-frequency (35 Hz) electrical stimulation accelerates bladder voiding function recovery more effectively than low-frequency (5 Hz and 14 Hz) electrical stimulation post-SCI. These findings suggest that high-frequency SNM therapy could be beneficial for patients with NB, potentially improving therapeutic efficacy, protecting bladder function, reducing urological complications, enhancing patient quality of life, and extending survival.

Conclusions

This study demonstrated through urodynamic testing that SCI at T10 in rats leads to the formation of an NB model. The rats exhibited significantly increased MCC and BC, along with a marked decrease in BLPP. Higher-frequency parameters of SNM were shown to have superior therapeutic effects on bladder function recovery in the acute phase of NB.

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