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Effects of different pulse widths on acute tibial nerve stimulation for overactive bladder in cats

Dongsheng Shang[1,2], Haoyu Sun[2], Han Deng[2], Gongyue Liu[2], Limin Liao[1,2] and Xing Li[1,2*]

Abstract

Purpose This study aimed to assess the effectiveness of different pulse widths in suppressing bladder overactivity using tibial nerve stimulation (TNS) in cats.

Methods Hook electrodes were implanted on the left tibial nerve. Cystometry was conducted by infusing either acetic acid (AA) or normal saline (NS). TNS was applied at intensities of 2–4 times the threshold (T) with pulse widths ranging from 60 to 624 μsec. Cystometrograms were used to evaluate the impact of different pulse widths on the micturition reflex.

Results Bladder capacity (BC) was significantly reduced to 49.71% ± 6.76% of the NS control level (8.58 ± 1.70 mL) due to AA-induced bladder overactivity ($P < 0.001$). During AA infusion, TNS at pulse widths of 60, 210, 420, and 624 μsec significantly increased BC to 70.65% ± 9.06%, 73.22% ± 6.28%, 73.79% ± 8.56%, and 76.25% ± 7.95% of the NS control level, respectively ($P < 0.001$). No significant differences were observed among the four pulse widths ($P > 0.05$). The threshold intensity (T) was higher at 60 μsec than at 624 μsec ($P < 0.01$), while T at 210 μsec, 420 μsec, and 624 μsec showed no significant differences ($P > 0.05$).

Conclusions All four pulse widths demonstrated inhibitory effects on bladder overactivity. However, no significant differences were observed among the four pulse widths.

Keywords Pulse widths, Tibial nerve stimulation, Overactive bladder, Cystometry, Cats

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as urinary urgency, with or without increased frequency and nocturia, and with or without urgency urinary incontinence, in the absence of urinary tract infection or other evident pathology [1]. A questionnaire-based survey in mainland China reported an OAB prevalence of 2.1%, while the prevalence in some European countries is approximately 17% [2, 3]. OAB negatively affects patients' physical and mental well-being and imposes a significant economic burden on families and the public healthcare system. The standard clinical treatment includes antimuscarinics and beta-3 agonists. However, many patients cannot tolerate these medications due to their side effects.

Tibial nerve stimulation (TNS) is a minimally invasive neuromodulation method for the treatment of overactive bladder (OAB), introduced by Stoller in the late 1990s [4]. It has been approved by the United States Food and Drug Administration (FDA) as a third-line treatment for OAB [5]. The efficacy and safety of TNS have been well established [6–8]. A report exploring long-term

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percutaneous durability showed that: sustained improvement from 12 weeks at 6 and 12 months, with 94% and 96% of responders, respectively [9]. TNS uses low-voltage electrical currents, and its clinical therapeutic effects are influenced by stimulation parameters, such as frequency, intensity, pulse width, and waveform. While the optimal frequency and intensity of TNS have been confirmed in the previous studies [10–12], the ideal pulse width remains uncertain.

Currently, a pulse width of 210 μsec is commonly used in clinical practice. Studies suggest that shorter pulse widths are more neuroselective than longer ones and may offer a broader therapeutic window [13, 14]. Some experts believe that adjusting the pulse width can improve treatment outcomes for patients experiencing diminished clinical efficacy, discomfort from painful stimuli, or issues with stimulation localization, thereby restoring satisfactory results [15]. Identifying the optimal pulse width is crucial for enhancing clinical neuromodulation. This study aimed to evaluate the inhibitory effects of TNS at various pulse widths and to determine the optimal pulse width to provide a strong basis for clinical application.

Materials and methods

The animals were housed under standard conditions at an ambient temperature of 20–26 °C and a humidity of 30–70%. They were provided with pellet food and unlimited access to water. All experimental protocols were approved by the Institutional Animal Care and Use Committee of Capital Medical University (AEEI-2024-213) and adherence to ARRIVE guidelines for animal research.

Sample size

The total sample size and effect size were estimated. The effect size was 1.32, indicating significance. G*Power software calculated a minimum of 4 cats per group for a one-way ANOVA with 80% power and $\alpha = 0.05$. All data met the normality ($P = 0.746$) and homogeneity of variance ($P = 0.667$).

Surgical procedure

Six cats (two females and four males, aged 6–12 months, weighing 2.5–3.5 kg) were used in the experiments. Isoflurane (2%–5% in oxygen) was administered for anesthesia during surgery, and intravenous α-chloralose (65 mg/kg, supplemented as needed) was used during data collection. Fluids and anesthesia were delivered via the left cephalic vein. Blood oxygen levels and heart rate were monitored throughout the experiment, and a heating pad was used to maintain stable body temperature. The bladder was accessed through a mid-abdominal incision. The ureters were isolated, with the right ureter externally drained and the left ureter ligated. A two-lumen catheter was inserted into the bladder through a small incision in the proximal urethra and secured with a ligature. One lumen was connected to a pump for normal saline infusion at 1–2 mL/min, while the other lumen was linked to a pressure transducer (MP150; BIOPAC Systems, Camino Goleta, CA, USA) to measure bladder pressure. Hook electrodes were placed on the tibial nerve, which was exposed in the left leg above the ankle (Fig. 1). Electrical pulses were delivered using an external stimulus generator (AD Instruments; Shanghai, China). After the surgical procedure, the incisions were closed.

Stimulation protocol

Acute trials began approximately 30 min after surgery. The bladder was drained before each experiment. Bladder capacity (BC), defined as the bladder volume required to trigger a large-amplitude (> 30 cmH_2O) and long-duration (> 20 s) bladder contraction, was measured at the start of each experiment using multiple cystometrograms (CMGs) with normal saline (NS). Two-to-three baseline CMGs were recorded as controls after bladder emptying. Bladder overactivity was induced by infusing the bladder with 0.25% acetic acid (AA), which irritated the bladder and activated nociceptive C-fiber afferent neurons. After BC stabilized, consecutive CMGs were performed with TNS. Uniphasic rectangular pulses at a frequency of 5 Hz were applied to the tibial nerve. The minimum intensity required to induce visible toe movement was recorded as the threshold (T). CMGs were conducted under the following conditions: 1) NS control CMG; 2) AA CMG without TNS; 3) CMG during 60 μsec TNS; 4) CMG during 210 μsec TNS; 5) CMG during 420 μsec TNS; 6) CMG during 624 μsec TNS; 7) AA CMG once again to investigate any effects of post-stimulation. After each CMG, the bladder was emptied, and a 3–4-min rest period was provided to allow bladder recovery.

Data analysis

Statistical analyses were performed using Prism version 10.1.2 (GraphPad Software, La Jolla, CA, USA). Urodynamic parameters, including BC, maximum amplitude of micturition contraction, duration of micturition contraction, and the area under the curve of micturition contraction, were normalized to the first NS control CMG measurement. Two-to-three control CMGs were averaged for each animal under identical conditions (NS or AA). Normalized data from all animals were expressed as mean ± SE. Urodynamic parameters for the AA and TNS groups (60 μsec, 210 μsec, 420 μsec, and 624 μsec) during NS instillation were compared with the first control CMG measurements. All data are presented as mean ± standard error (SE). One-way ANOVA was used

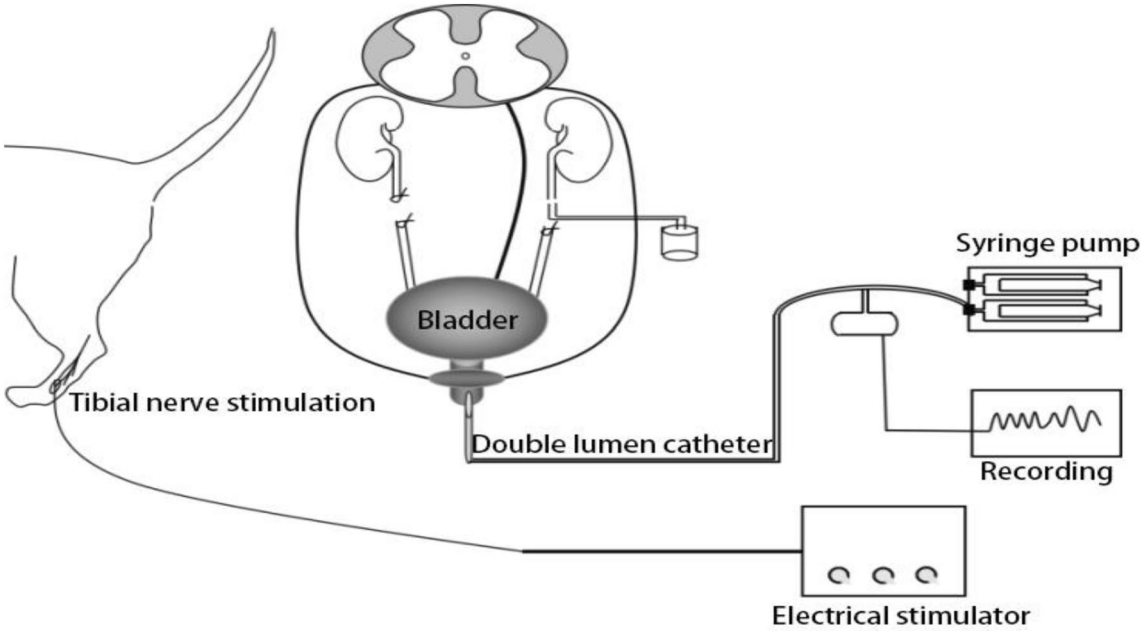

Fig. 1 Experimental setup. CMG was performed by introducing a 2-lm catheter into the bladder through a small incision in the proximal urethra, and bladder activity was induced in cats through continuous instillation of 0.9% NS or 0.25% AA through syringe pump. After achieving continuous and stable micturition cycles, TNS was performed

to analyze differences across various CMG conditions and threshold values for different pulse widths, followed by a Bonferroni multiple-comparison post hoc test.

Results

Inhibitory effects of different pulse widths on bladder overactivity caused by AA infusion

Infusion of 0.25% acetic acid (AA) into the bladder induced bladder overactivity, significantly reducing bladder capacity (BC) to 49.71% ± 1.59% of the normal saline (NS) control level (8.58 ± 1.70 mL) ($P < 0.001$) (Figs. 2 and 3). During AA infusion, TNS at different pulse widths significantly increased BC compared to the AA group ($P < 0.001$). Specifically:

At 60 μsec, BC increased to 70.65% ± 2.01% of the NS control level ($P < 0.001$, (Cohen's d) = 1.25, 95% CI [65.49%, 75.81%]).

At 210 μsec, BC increased to 73.22% ± 1.62% of the NS control level ($P < 0.001$, (Cohen's d) = 1.15, 95% CI [69.07%, 77.38%]).

At 420 μsec, BC increased to 73.79% ± 2.02% of the NS control level ($P < 0.001$, (Cohen's d) = 1.09, 95% CI [68.69%, 78.99%]).

At 624 μsec, BC increased to 76.25% ± 1.95% of the NS control level ($P < 0.001$, (Cohen's d) = 1.02, 95% CI [71.25%, 81.26%]).

However, no significant differences were observed among the four pulse widths ($P > 0.05$).

Bladder micturition contraction

In the AA group, TNS groups, and NS control group (80.39 ± 20.91 cmH_2O), the maximum amplitude of bladder micturition contraction did not change significantly ($P > 0.05$) (Fig. 4). AA significantly reduced the duration of bladder micturition contraction compared to the NS control level (3.18 ± 0.77 min) ($P < 0.001$) (Figs. 5 and 6). TNS at 210 μsec, 420 μsec, and 624 μsec significantly increased the duration of bladder micturition contraction compared to the AA group ($P = 0.02$). However, the area under the curve of bladder micturition contraction showed no significant differences among the NS control, AA, and TNS groups ($P > 0.05$).

Intensity thresholds for different pulse widths

The actual intensity thresholds (T) ranged from 0.05 to 0.4 mA. At pulse widths of 60 μsec, 210 μsec, 420 μsec, and 624 μsec, the mean T values were 0.27 ± 0.13 mA, 0.20 ± 0.10 mA, 0.16 ± 0.06 mA, and 0.11 ± 0.09 mA, respectively. As shown in Fig. 7, the 60 μsec pulse width had a significantly higher T value than the 624 μsec pulse width ($P = 0.007$). No significant differences in T values were observed among the 210 μsec, 420 μsec, and 624 μsec pulse widths ($P > 0.05$).

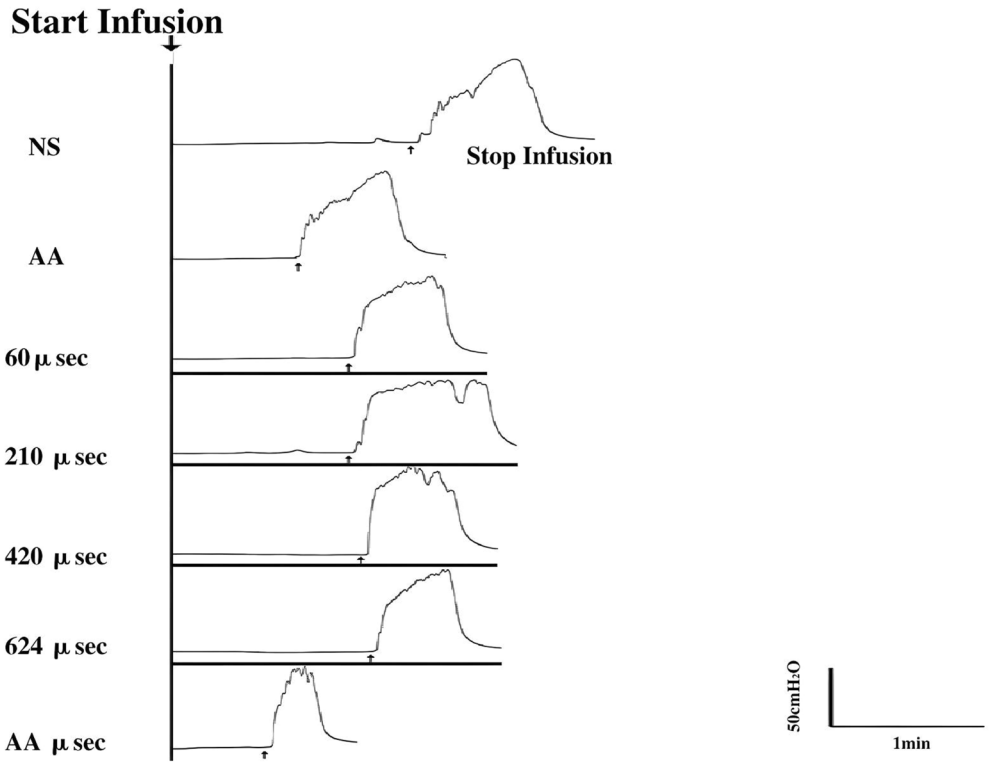

Fig. 2 Repeated CMGs during the infusion of 0.9% NS or 0.25% AA. The arrows indicate the start and end of bladder infusion. The black bars indicate the duration of TNS. The distance from the arrow to the vertical axis represents the bladder infusion time. The height of the curve represents the bladder contraction pressure. The pulse width range of TNS is 60–624 μsec. NS: normal saline; AA: acetic acid; CMGs: Cystometrograms; TNS: tibial nerve stimulation

Discussion

Under physiological conditions, bladder distension due to NS infusion predominantly activates non-nociceptive Aδ fiber afferent neurons, triggering the supraspinal micturition reflex. In pathological conditions, bladder stimulation with AA infusion activates nociceptive C-fiber afferent neurons [16]. In this study, AA infusion caused bladder overactivity and significantly reduced BC compared to the NS control (Figs. 2 and 3). TNS at pulse widths of 60 μsec, 210 μsec, 420 μsec, and 624 μsec significantly improved BC during AA-induced bladder overactivity. These results suggest that TNS effectively inhibits bladder overactivity. However, the effects of TNS were not significantly dependent on pulse width within the 60–624 μsec range, as no notable differences were observed among the pulse widths tested.

Vandoninck and Bemelmans reported that TNS regulates the excitatory and inhibitory activity of the bladder by balancing the afferent and efferent signals to and from the bladder [17, 18]. In this study, AA infusion increased bladder sensory afferent activity and decreased BC [19]. However, reduced bladder perfusion caused by AA infusion may have shortened the duration of bladder micturition contraction (Figs. 5). TNS inhibited these sensory afferents, leading to increased BC, prolonged micturition contraction duration [20, 21]. However, TNS appeared to have minimal influence on the efferent pathway. Choudhary et al. suggested that TNS does not inhibit bladder contraction [22]. Similarly, Lyon et al. reported that TNS suppressed bladder reflex activity but did not affect bladder contractions triggered by the pontine micturition center (PMC). The inhibitory effects of TNS may occur in the ascending afferent limb or the brain, rather than the descending limb of the micturition reflex pathway [23]. This finding aligns with our observation that TNS at all pulse widths did not affect bladder contraction compared to AA-induced levels (Figs. 4, 5, 6).

The neural circuitry that controls micturition is known to be complex, involving many levels of pathways in the brain, spinal cord, and peripheral nervous system. Inhibition by TNS may occur at multiple sites in the central nervous system. Previous experimental studies have shown that TNS inhibition during saline CMGs may occur at the spinal cord level, perhaps via the periaqueductal gray (PAG)-PMC circuit or by inhibiting the ascending or descending limbs of the upper spinal cord

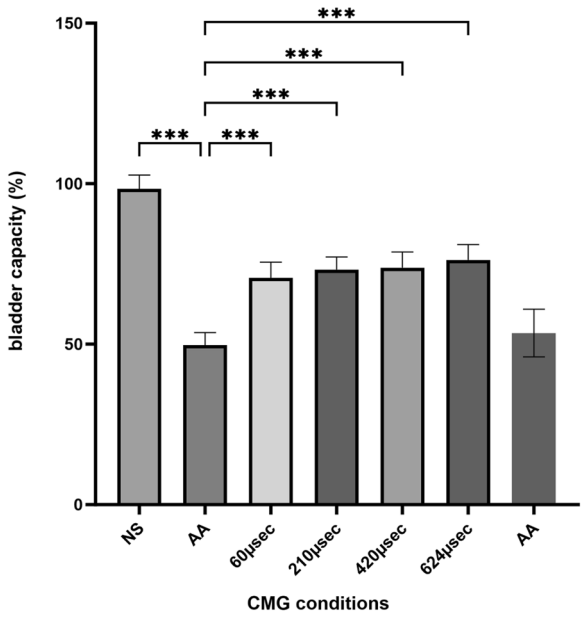

Fig. 3 Infusion of 0.25% AA into the bladder induced bladder overactivity, significantly reducing BC to 49.71% ± 1.59% of the NS control level (8.58 ± 1.70 mL) ($P < 0.001$). During AA infusion, TNS at pulse widths of 60 μsec, 210 μsec, 420 μsec, and 624 μsec significantly increased BC to 70.65% ± 2.01%, 73.22% ± 1.62%, 73.79% ± 2.02%, and 76.25% ± 1.95% of the NS control level, respectively ($P < 0.001$). However, no significant differences were observed among the four pulse widths ($P > 0.05$). Stimulation: frequency, 5 Hz; BC: bladder capacity; NS: normal saline; AA: acetic acid; CMGs: Cystometrograms; TNS: tibial nerve stimulation. ***$P < 0.001$. $n = 6$ cats

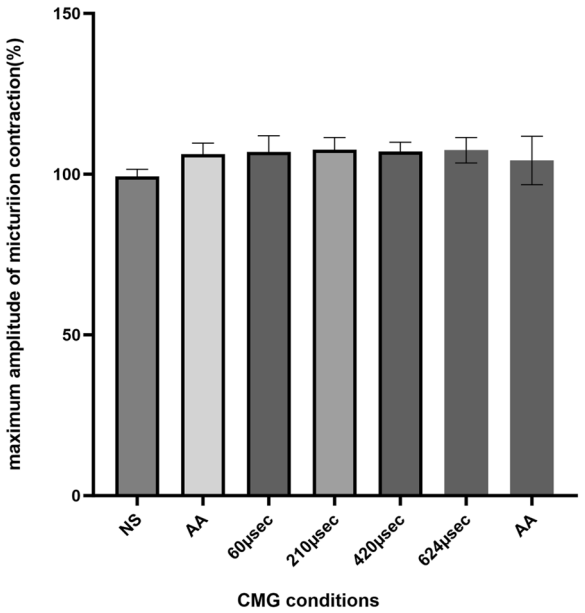

Fig. 4 The maximum amplitude of micturition contraction of the bladder did not change between the NS group, the AA group and the TNS at groups. Stimulation: frequency, 5 Hz; NS: normal saline; AA: acetic acid; CMGs: Cystometrograms; TNS: tibial nerve stimulation. $n = 6$ cats

reflex [16]. However, during AA CMGs, TNS inhibition may involve the activation of neuronal circuits in the brainstem [24]. Our experiments did not investigate the supraspinal effects of TNS, so future studies are needed to further explore the extent of brain involvement.

Our study also compared T visual values across different pulse widths and confirmed that T visual values decreased as pulse width increased (Fig. 7), consistent with the findings of Suxin [25]. Grill et al. explained that nerve fibers of varying diameters have different electrical recruitment properties [26]. Longer pulse widths recruit smaller-diameter, harder-to-stimulate nerve fibers, increasing the number of activated nerves [26–28]. However, there were no significant differences in T visual values among pulse widths of 210 μsec, 420 μsec, and 624 μsec, likely due to the consistent distribution of recruited nerve fibers within the pulse width range of 300 μsec to 1 ms.

Previously, Reub et al. conducted a single-center clinical trial evaluating the effects of short (60 μsec), standard (210 μsec), and long (420 μsec) pulse widths on treatment efficacy, quality of life, and device parameters

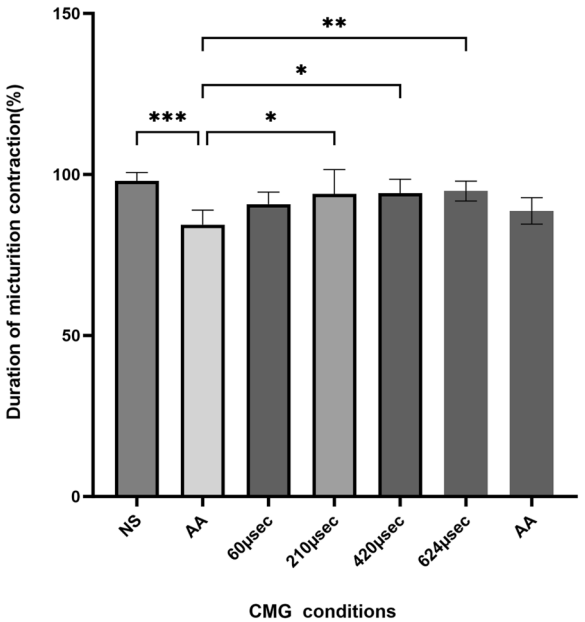

Fig. 5 Effects of TNS with different pulse widths on the duration of bladder micturition contraction. AA infusion significantly reduced the duration of bladder micturition contraction, compared to NS control level ($P < 0.001$). TNS at 210 μsec, 420 μsec, and 624 μsec significantly increased the duration of bladder micturition contraction compared to AA level ($P < 0.05$). Stimulation: frequency, 5 Hz; AA: acetic acid; CMG: cystometrogram. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. $n = 6$ cats

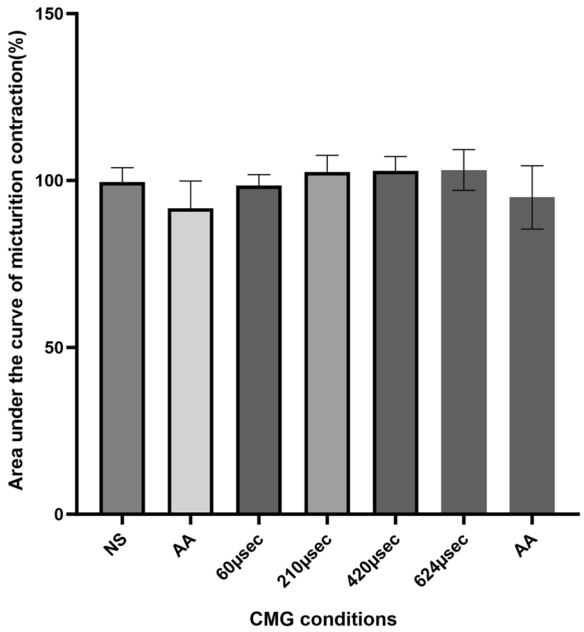

Fig. 6 The area under the curve of micturition contraction did not change between the NS group, the AA group and the TNS groups. Stimulation: frequency, 5 Hz; NS: normal saline; AA: acetic acid; CMGs: Cystometrograms; TNS: tibial nerve stimulation. $n=6$ cats

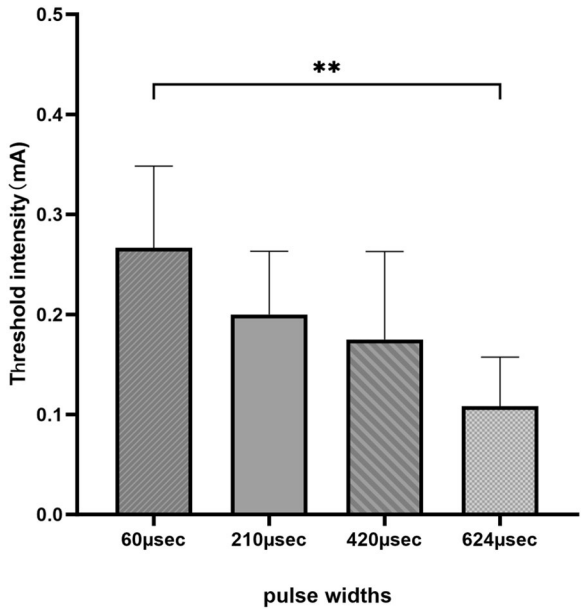

Fig. 7 T intensity of TNS with different pulse widths. T visual for pulse width of 60 μsec was greater than T visual for pulse width of 624 μsec ($P<0.01$). No significant differences were found among the T visual for pulse widths of 210 μsec, 420 μsec and 624 μsec. $^{**}P<0.01$. $n=6$ cats

in patients [29]. All pulse widths were effective, but shorter pulse widths reduced the stimulator's energy output, prolonging device lifespan. And another of their earlier retrospective studies found that shorter pulse widths eliminated activation of certain nerve fibers, reducing undesired sensations and improving patient comfort [15]. In our study, T visual values were higher for the 60 μsec pulse width compared to the other pulse widths, which may be intolerable for patients and unsuitable for clinical use. Although no significant differences were observed among the T visual values for pulse widths of 210 μsec, 420 μsec, and 624 μsec, longer pulse widths may increase patient discomfort and unnecessary energy consumption. Therefore, a pulse width of 210 μsec may be optimal for TNS, balancing efficacy, patient comfort, and energy efficiency.

Current impedance is considered to be a non-negligible factor during electrical stimulation, as it is a non-linear function of current density and time. Electrical impedance can alter the extent to which current reaches the nerve and thus may affect the selective activation of the nerve. During the experiment, we chose constant current stimulation to ensure that the magnitude of the current delivered to the nerve by the electrode did not change with stimulation time. However, we did not directly measure the impedance during stimulation. This relationship needs to be further clarified in future studies.

This experimental study investigated the effects of different pulse widths on TNS in cats with OAB. The results showed the short-term effects of TNS. However, OAB is a chronic disease, so the long-term effects of TNS still need to be further explored. Moreover, our study utilized cats as experimental subjects, which is notable, because there are differences in neuromodulatory responses between cats and humans. Specifically, the anatomical structure of the tibial nerve in humans is more intricate than that in cats, characterized by greater variability in branching and distribution. In humans, TNS involves both spinal cord reflexes and higher order control from the cerebral cortex. In contrast, the modulation mechanism in cats primarily depends on spinal reflex pathways.

Our research findings possess certain clinical significance. Short pulse widths demonstrate comparable efficacy to long pulse widths. By adjusting pulse width, it is possible to reduce the energy consumption of the stimulator without compromising its therapeutic efficacy. This can also help minimize the discomfort associated with stimulation. These improvements can significantly enhance the patient's treatment experience and overall quality of life. Additionally, this flexibility in pulse width adjustment may enhance the versatility of medical devices across different patients and lesion types,

potentially reducing treatment failure or complications due to improper pulse width settings.

This study has certain limitations. The four pulse widths used are commonly applied in clinical practice. However, due to the limited modulation range of the stimulator parameters, we could not investigate pulse widths greater than 624 μsec or shorter than 60 μsec, which deserve further exploration. In addition, this study was conducted in anesthetized animals, whereas patients are awake during real-life treatments, which may have influenced the results [30]. Additionally, there is a possible interaction between stimulus intensity and pulse width. Some pulse widths may work better at lower intensities, while others require higher intensities. We did not analyze this interaction, which needs to be further explored in the future. The clinical translation of results from animal experiments presents several challenges. First, due to the physiological differences between animals and humans, the experimental results of this study may not be directly applicable to humans. Second, subjective symptoms such as urgency of urination cannot be accurately replicated in animal models. Finally, our sample size was small, and further studies with larger sample sizes are needed to validate the findings.

Conclusion

This study demonstrated that all four tested pulse widths in TNS effectively inhibited bladder overactivity induced by 0.25% AA, but there was no significant difference among these four pulse widths.

Acknowledgements
Not applicable.

Author contributions
X.L conceived and designed the study. D.S performed the experiments and collected data. D.S, H.S, H.D, X.L analyzed the data and interpreted results. D.S drafted and reviewed the manuscript. G.L assisted in the experimental process. L.L participated in the supervision of the experiment.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics of approval statement and consent to participate
All experimental protocols were approved by the Institutional Animal Care and Use Committee of Capital Medical University (AEEI-2024-213).

Consent for publication
All authors were informed and gave their consent for publication.

Competing interests
The authors declare no competing interests.

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