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Ultra-High Frequency Spinal Nerve Neuromodulation for Improving Bladder Continence: Implications for Overactive Bladder Management

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ABSTRACT

Objective: Ultrahigh frequencies (UHF) have been shown to selectively suppress the sensory pathway with a rapid onset and prolonged effect compared with low frequencies. Few studies have explored the feasibility of UHF electrical stimulation in treating overactive bladder. This study aimed to investigate whether bladder overactivity could be inhibited by UHF stimulation at the L6 nerve root.

Materials and Methods: Female Sprague-Dawley rats ($n = 12$) were divided into two groups: sham and UHF groups. Bladder overactivity was induced by continuous intravesical infusion of 0.5% acetic acid (AA). UHF L6 nerve root stimulation (500 kHz, 20 mA for 5 minutes) was applied to the rats in the UHF group. To investigate the effects of the treatment, intravesical pressure was recorded by cystometrography during continuous transvesical infusion, with volume threshold (VT) and intercontraction interval (ICI) used to conduct the investigation.

Results: Bladder overactivity was successfully developed in all rats with a significant decrease of median VT and ICI to 83.7% and 86.4%, respectively. UHF stimulation of the L6 nerve root was able to counteract the AA effect by significantly increasing median VT and ICI to 220% and 36.1%, respectively; these effects persisted for ≥two hours. There was a significant difference in the effects of UHF electrical stimulation between the sham and UHF groups ($p < 0.05$).

Conclusion: This preliminary study provides evidence for UHF stimulation of the L6 spinal nerve root, analogous to the sacral nerve root in humans, as a potential alternative neuromodulation technique to suppress bladder overactivity.

Keywords: Electrical stimulation, neuromodulation, overactive bladder, spinal nerve, ultrahigh frequency stimulation

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INTRODUCTION

Overactive bladder (OAB) is a condition that causes a serious reduction in quality of life that is mainly characterized by urgency and usually accompanied by frequency and nocturia. This condition can be accompanied with or without incontinence and should be in the absence of a urinary tract infection or other obvious pathology.[1] OAB affects one in five individuals aged ≥40 years in Asia.[2] This condition was reported to cause significant sleep disruptions, decreased self-esteem, reduced sexual well-being, and a sense of overall deteriorating health.[3] In addition, people with OAB can potentially spend twice as much on health care as can those without OAB, placing a significant burden on families and healthcare systems.[4]

The pathophysiology of OAB is multifactorial, involving neurogenic, myogenic, autonomous bladder, and afferent signaling theories. One pathophysiological theory suggests that alterations in the sensitivity of bladder afferent fibers, namely, Aδ fibers and C fibers, can lead to bladder overactivity.[5] Thus, the primary objective of OAB therapy is to prevent inappropriate bladder contraction and maintain normal control of micturition. Although lifestyle modification and behavioral therapy alone may not suffice to achieve significant results,[6] the efficacy of pharmacotherapy is limited by its side effects and low adherence.[3] Consequently, researchers are now exploring alternative treatments, such as neuromodulation of the sacral nerve targeting afferent pathways and/or bladder smooth muscles, intending to effectively suppress OAB.[7] In rats, neurons from the sensory pelvic nerve innervate the bladder[8] and are believed to transverse L6 and S1 spinal nerves, akin to S2–S3 in humans.[9] Stimulation in the L6–S1 spinal nerve was reported to increase bladder capacity and reduce micturition frequency in anesthetized rat.[9,10]

Ultrahigh frequency (UHF) stimulation serves as a modulatory neurotechnology by ameliorating pain-related neuropeptides and regulating neuroinflammatory gene expression.[11] It also is known for its wide use in humans to treat chronic pain by inhibiting C-fiber afferent responses, and blocks pain conduction signals.[12] Because some cases of OAB are pathophysiologically associated with increased sensitivity of C-fibers, UHF may have potential benefits in treating OAB. UHF is more advantageous given it requires a shorter neuromodulation time than that of the conventional low-frequency electrical stimulation technique (15 min–20 h/d) for OAB treatment.[13]

To the best of our knowledge, few studies have explored the feasibility of UHF electrical stimulation in treating OAB. We believe this is the first pilot research study using short-term animal experiments to evaluate the therapeutic effects of low-voltage UHF electrical stimulation in the L6 nerve root by quantifying urodynamic changes using cystometrograph of rat's bladder overactivity. The results of this pilot study may be important for understanding the effectiveness of UHF neuromodulation in the treatment of OAB.

MATERIALS AND METHODS

Animal Preparation

All experimental protocols involving animal use in this study were reviewed and approved by the animal care committee of Taipei Medical University. Female Sprague Dawley rats (n = 12) aged between nine and 12 weeks were used and adapted to the environment seven days before the start of the test, with ad libitum water and food. The body temperature was maintained at 36 to 38 °C with a recirculating water blanket. The animals were divided into two groups (n = 6 per group) according to the location and parameters of electrical stimulation: a sham group, in which the L6 nerve root was hooked with the electrode but no electrical stimulation was applied, and a UHF group, in which the L6 nerve root received UFH electrical stimulation. Before any surgery, all rats were anesthetized with urethane (1.2 g/kg subcutaneous, supplemented as required). Urethane is regarded as the most suitable anesthetic agent for lower urinary tract experiments because it maintains the micturition reflex with minimal alterations in bladder function.[14] To minimize the potential influence of anesthesia on the recorded data, anesthesia was administered uniformly to both the UHF and sham groups, and baseline cystometrography (CMG) was measured for all groups to ensure that there were no significant differences in the baseline CMG.

L6 Nerve Root Exposure Surgery

The L6 spinal nerve root exposure was performed according to the method explained by Chung et al.[15] The animal was placed prone, with its limbs secured using surgical tape, and the skin on the surgical field was shaved. The S1 processes were removed and the L6 nerve trunks localized caudal and medial to the sacroiliac junction. The L6 nerve root can be exposed by removing the S1 process bone using a bone drill (ULTIMATE XL-GT, NSK, Japan). The L6 nerve root is located caudally and medially to the sacroiliac joint. The paraspinal muscles from the fifth lumbar spinal nerve (L5) to the second sacral spinal nerve (S2) were separated from the vertebral spinous processes, and the left L6 transverse process was removed. To expose the L6 nerve root, the S1 process bone was removed using a bone drill (ULTIMATE XL-GT, NSK, Japan). Next, a sheet of fascia connecting the sacrum to the ilium was removed, revealing the L6 nerve root, which is located caudally and medially to the sacroiliac joint.[15]

Bladder Surgery

In all experiments, after one to two hours of anesthesia, the urinary bladder was exposed through a midline abdominal incision, and a polyethylene (PE) tube 50 (0.58 mm internal diameter and 0.96 mm outside diameter) was inserted into the bladder lumen for bladder pressure measurement. The bladder end of the PE tube was heated to form a collar and passed through a small incision at the apex of the bladder dome. The tube was sutured to the bladder roof using 6-0 surgical sutures, with the smallest possible suture margin to minimize bladder injury and to reduce bladder capacity owing to the closure. Two stainless steel wires (0.002" bare, 0.0045" insulated) were inserted into the external urethral sphincter muscle through an abdominal approach. The abdominal wall was closed using nylon sutures. The PE tube was then connected through a three-way stopcock to an infusion pump (KDS 100 LEGACY, USA) for filling with physiological saline and to a pressure transducer (P23XL-1, Becton Dickinson, NJ) for monitoring bladder pressure. The bladder pressure was amplified 100 times, filtered using a 500-Hz low-pass filter, and sampled at 1 kHz using a biological signal acquisition system (Biopac MP 36, BIOPAC Systems, Inc, Goleta, CA).

After L6 nerve root exposure surgery and bladder surgery were performed, the rats were rested overnight with continuous parenteral hydration through femoral intravenous drip of physiological saline 1 mL/h. They were kept warm at 36 to 38 °C using a recirculating water blanket, and the urethra was left open to facilitate fluid elimination during micturition.

Cystometrography Measurements

The next day, still under urethane anesthesia, rats underwent urodynamic examination and electrical stimulation. After manually emptying the bladder, the first CMG recording was performed at a 0.2 mL/min infusion rate with physiological saline at room temperature to obtain CMG saline baseline data. Initial CMG was measured for both groups to ensure that there were no significant differences in baseline CMG. After a 30-minute rest, the second CMG recording was obtained with 0.5% acetic acid (AA) infusion at the same flow rate for 60 minutes to induce bladder overactivity (AA baseline). Next, the bladder was again rested for 30 minutes before another CMG recording after AA infusion (CMG AA baseline); then, the rats underwent sham or UHF electrical stimulation. Directly after electrical stimulation, we performed another three urodynamic recordings with 0.5% AA infusion for 15 minutes (AA first, AA second, AA third), and a 45-minute recovery period was observed between each of the AA infusions to prevent bladder fatigue. The experimental flowchart is presented in Figure 1.

UHF Electrical Stimulation Protocol

A hook electrode was positioned beneath (hooking) the L6 nerve to maintain contact with it. The electrode was connected to a UHF external electrical stimulator and controller (Cube) (GIMER Medical, Taiwan). The UHF stimulation was then applied at an intensity of 20 mA, a frequency of 500 kHz, a pulse width of 25 milliseconds, and a duration of 5 minutes. The external stimulator could adjust the output value on the basis of the current impedance around the nerve. According to our previous experimental records, the average impedance around the L6 nerve is 700 to 800 Ω, which translates to an output of approximately 12 to 14 mA (500 kHz). The hook electrode used in this experiment was custom-made by fixing two acupuncture needles at the tip of chopsticks through insulated single-core wires. The hook electrode was held steadily by a three-dimensional CCD Stent (Stoelting Company, IL) to create microadjustment when maintaining contact with the nerve. The UHF electrical stimulation is illustrated in Figure 2. At the end of all experiments, rats were euthanized by an overdose of urethane (4 g/kg body weight, intravenous).

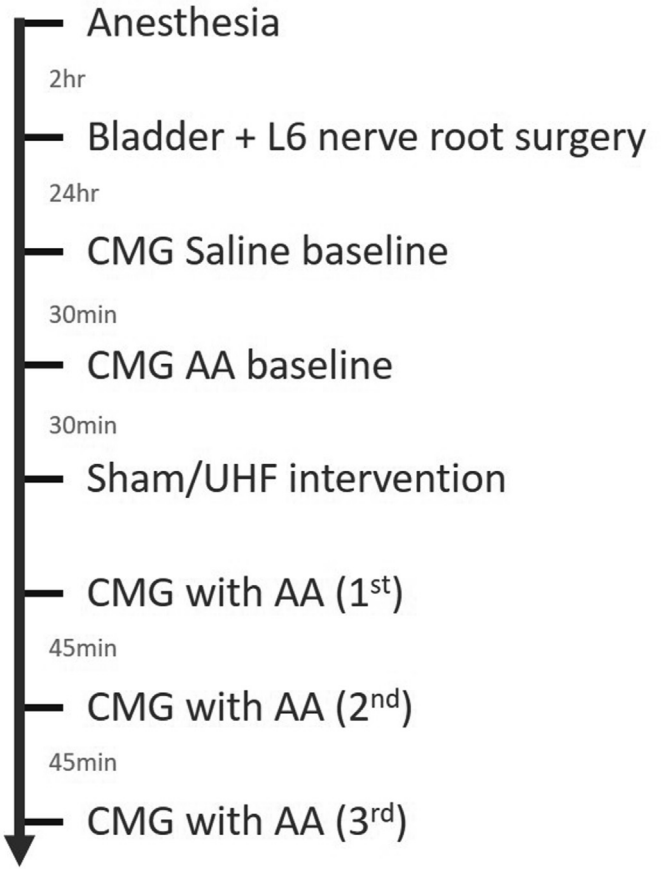

Figure 1. Schematic of study design for evaluating the effects of UHF electrical stimulation L6 nerve root. Time schedule of experimental procedures involving rat preparations, UHF stimulation of L6 nerve roots, and subsequent CMG assessments with AA.

Data Analysis

OAB is associated with storage dysfunction. Therefore, to assess the effects of UHF electrical stimulation on storage function, two cystometric parameters were measured in all rats. The main outcome parameters were the micturition volume threshold (VT), defined as infused volume of saline sufficient to induce the first voiding contraction >15-cm H2O, and the intercontraction interval (ICI) defined as the interval (the time interval [point d′-point c′]) between two successive bladder contractions. CMG parameters are presented as median (interquartile range [IQR]). The Wilcoxon matched-pairs signed-rank test was used to analyze the effects of AA infusion and UHF stimulation on bladder activity using GraphPad Prism version 9.0.0. The unpaired Mann-Whitney test was used to compare the data of the sham group and the UHF group (GraphPad Prism version 9.0.0, GraphPad Software, Boston, MA), and for all statistical measurements, $p < 0.05$ was deemed statistically significant.

RESULTS

Effects of AA Treatment on CMG Measurements

The instillation of 0.5% AA into the bladder caused a notable decrease in VT and ICI when compared with the control conditions. As depicted in Figure 3a, the median VT for the control was 0.92 mL (IQR: 0.67–1.14 mL), whereas for AA, the median VT was 0.15 mL (IQR: 0.11–0.22 mL). The difference in VT between the control and AA was statistically significant ($p = 0.0005$, Wilcoxon matched-pairs signed-rank test). Figure 3b showed that for ICI, the control had a median ICI of 2.87 minutes (IQR: 1.81–5.28 minutes), compared with the AA, which had a median ICI of 0.39 minutes (IQR: 0.29–0.54 minutes). The difference in ICI between the control and AA also was statistically significant ($p = 0.0005$, Wilcoxon matched-pairs signed-rank test).

Effects of UHF Electrical Stimulation Pretreatment of L6 Nerve Root

Within the treatment group, UHF electrical stimulation caused a significant increase in both the median VT and median ICI. The VT increased by 220%, from a median of 0.10 mL (IQR: 0.08–0.12 mL) to 0.32 mL (IQR: 0.25–0.35 mL) (Fig. 4c) ($p = 0.0313$, Wilcoxon matched-pairs signed-rank test), and the ICI increased by 36.1%, from a median of 0.36 minutes (IQR: 0.30–0.42 minutes) to 0.49 minutes (IQR: 0.45–0.53 minutes) (Fig. 4d) ($p = 0.0625$, Wilcoxon matched-pairs signed-rank test), respectively, compared with the control AA. However, it is worth noting that this increase did not reach the levels observed in the normal control group. The sham group showed inconsistent results, with the median VT increasing by 18.75%, from 0.16 mL (IQR: 0.13–0.25 mL) to 0.19 mL (IQR: 0.12–0.27 mL), although this change was not statistically significant ($p = 0.8750$, Wilcoxon matched-pairs signed-rank test) (Fig. 4a). Meanwhile, the median ICI decreased by 36%, from 0.50 minutes (IQR: 0.30–0.67 minutes) to 0.32 minutes (IQR: 0.25–0.51 minutes) ($p = 0.1875$, Wilcoxon

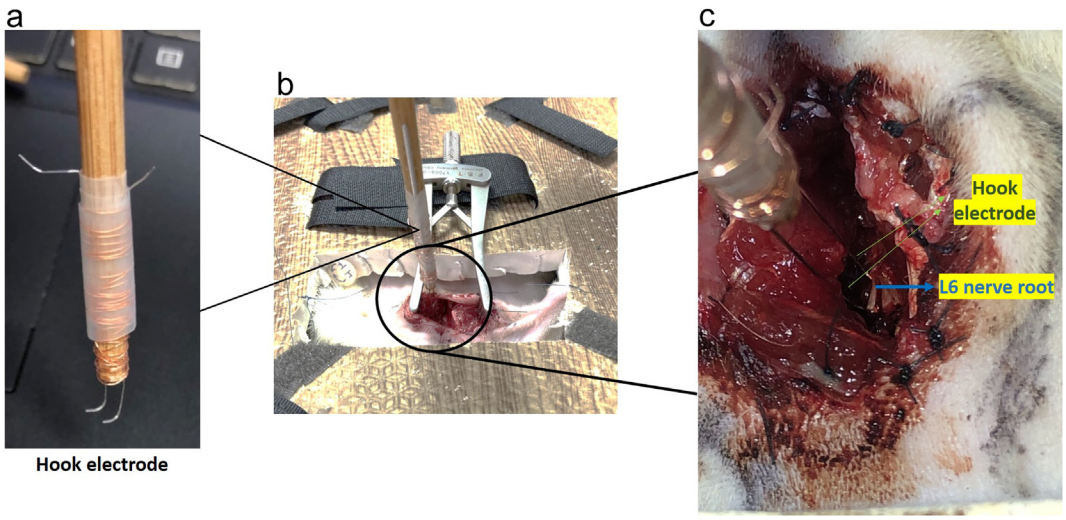

Figure 2. UHF electrical stimulation position. Panel a shows the custom-made hook electrode. Panel b shows the L6 nerve root exposed and a hook electrode placed beneath the L6 nerve to maintain contact during the stimulation or sham period. Panel c shows a close-up view of Figure 2b. [Color figure can be viewed at www.neuromodulationjournal.org]

matched-pairs signed-rank test) (Fig. 4b). The results for VT and ICI were averaged across the three segments of AA infusion (AA first, AA second, AA third), with a 45-minute recovery interval observed between each of the AA infusions. After normalizing the treatment data for each individual rat to their respective AA data, a direct comparison of the impact of UHF on the L6 nerve root in the sham and UHF groups was feasible (Fig. 5). The results consistently indicated a significant difference in VT and ICI between the sham and UHF groups. Specifically, for sham compared with UHF group, there was an observed increase of 290% in median VT, 100 (IQR: 78.1–141.3) vs 333 (IQR: 307.5–333) ($p = 0.0022$, Mann-Whitney test) and 87% in median ICI, 69.9 (IQR: 50.61–105.1) vs 129.2 (IQR: 113.8–168.2) ($p = 0.0087$, Mann-Whitney test) (Fig. 5).

DISCUSSION

The results of this study were consistent with many studies showing that infusion of AA in rats generated a model of OAB characterized by reduced bladder capacity and/or contraction interval.[5,13,16,17] OAB condition caused by AA also is sensitive to oxybutynin and more

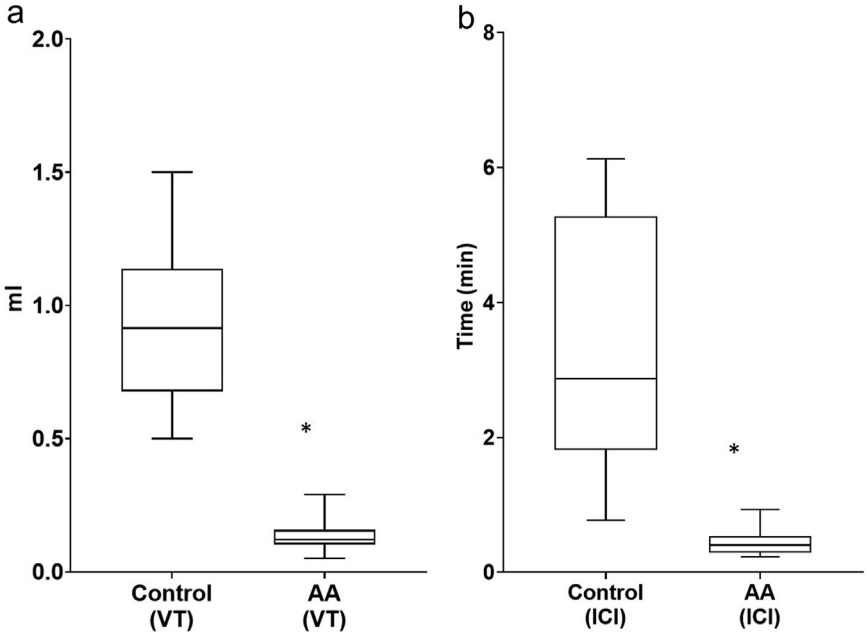

Figure 3. Effects of continuous infusion AA on bladder activity. The AA infusion successfully increased the bladder capacity. The VT and ICI were considerably reduced by AA infusion in all CMG measurements. The cystometric parameters were calculated in rats ($n = 12$). The central line in each box represents the median value of the variable for each group. The upper and lower edges of the box represent the 75th (Q3) and 25th (Q1) percentiles, respectively, indicating the IQR. The whiskers extend to the minimum and maximum values within 1.5 times the IQR from the first and third quartiles. *These values were significantly different from the control data.

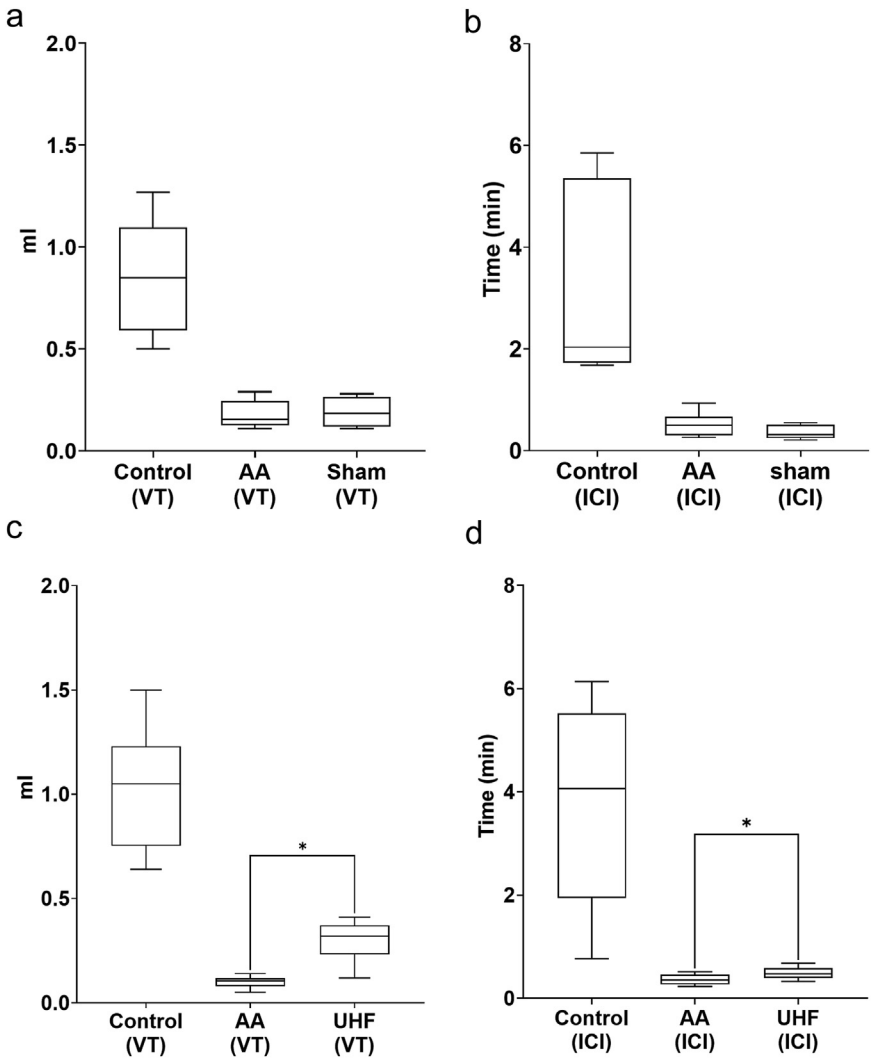

Figure 4. Effects of UHF electrical stimulation pretreatment of L6 nerve root on bladder activity. Sham treatment (a) and (b) exhibited inconsistent results on the VT and ICI across all CMG measurements. In contrast, (c) and (d) indicate that UHF causes a noteworthy increase in VT and ICI in all CMG measurements. Cystometric parameters were computed for each group ($n = 6$), and the central line in each box represents the median value of the variable for each group. The upper and lower edges of the box represent the 75th (Q3) and 25th (Q1) percentiles, respectively, indicating the IQR. The whiskers extend to the minimum and maximum values within 1.5 times the IQR from the first and third quartiles. *These values were found to be significantly distinct when compared with the AA data.

closely resembles OAB because it does not produce histologic changes in the bladder urothelium.[16] The intervention's mechanism of action involving the stimulation of nociceptive C-fibers and subsequent increases in afferent activity merely reflects phenotypes associated with a decrease in VT, and increases in ICI indicates of bladder hyperactivity.[18] In addition, given this OAB model does not reflect the long-term changes that may accompany human chronic OAB pathophysiology and the urodynamic study was performed in anesthetized rats, caution is advised when interpreting cytometric results obtained using this acute rodent model.

This research showed that the application of UHF electrical current to stimulate the L6 nerve root effectively suppressed bladder contraction. This finding was evidenced by a noteworthy increase in VT and ICI in the UHF group when compared with the sham treatment. Although the increase in ICI may seem modest compared with the control ICI, it is important to recognize that even slight changes can have significant implications in the treatment of OAB because small improvements can greatly enhance patient quality of life. Furthermore, in Figure 4b, the decrease in ICI observed in the sham group compared with AA is likely to reflect natural variation or the influence of external factors unrelated to treatment. The consistency and reproducibility of the ICI increase in the UHF group over several trials suggest that the observed effect was probably more than just chance variation. Therefore, the findings of this study should be viewed as an initial indication of UHF's potential rather than a conclusive clinical outcome. Further research with larger sample sizes and more rigorous controls is needed to more accurately determine the true clinical significance of UHF stimulation on urodynamic function.

Stimulation of the L6 nerve root is important given the principal pathway for afferent and efferent input related to bladder fullness sensation and bladder contraction is through the parasympathetic fibers present in the pelvic nerves.[17,19] Pelvic visceral afferent fibers, which originate at the lumbosacral level of the spinal cord (L6–S1), comprise small myelinated Aδ-fibers and unmyelinated C-fibers, and govern the processes of bladder filling and emptying.[19] In a study by Choudhary et al, the authors found that OAB is associated with higher afferent activity in bladder nerve.[5] Therefore, inhibiting the afferent input from the L6 nerve root was effective in

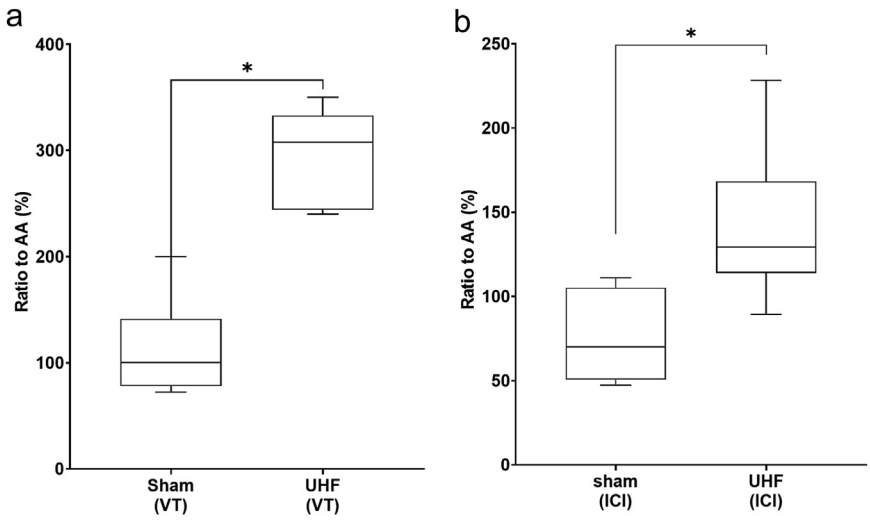

Figure 5. The comparison effects of electrical stimulation in the sham and UHF groups. The medians of VT and ICI were significantly higher in the UHF group treatment than in the sham group. Data were normalized to each corresponding AA and presented in percentages (%). The central line in each box represents the median value of the variable for each group. The upper and lower edges of the box represent the 75th (Q3) and 25th (Q1) percentiles, respectively, indicating the IQR. The whiskers extend to the minimum and maximum values within 1.5 times the IQR from the first and third quartiles. *These values were significantly different from the sham data.

preventing bladder contraction because the L6–S1 spinal cord constitutes the spinal micturition center in the rat.[20] Furthermore, in rats, a predominant route for pelvic nerve afferent fibers from the urinary bladder to enter the spinal cord is through the L6 dorsal root, with a smaller portion entering through S1.[21] This observation is supported by the study of Brouillard et al, who found that stimulation of the S1 nerve root could inhibit micturition for the whole stimulation period in only 50% of stimulated animals.[22] In contrast, in our present study, all rats stimulated in the L6 nerve root experienced the suppressing effect from the UHF stimulation.

Current sacral nerve stimulation (SNS) techniques generally deliver continuous low-frequency stimulation, typically approximately 10 to 15 Hz, which requires continuous application to be effective.[23] Constant stimulation may not be suitable for every OAB case.[22] Consequently, there is a need for alternative SNS strategies that act quickly, have few side effects, and are long lasting. In the present study, the effect of UHF stimulation was evaluated after 5 minutes' application and not the effect during the acute stimulation period. The effect was observed until 135 minutes after stimulation, showing that the effect of a short period of UHF stimulation on increasing VT and ICI can persist up to two hours after the stimulation. In contrast, with low-frequency stimulation, the carry-over effect of stimulation on the subsequent filling phase was only observed if the stimulation was performed in the latter half of the filling phase.[24]

Lower urinary tract function in animals can be assessed using a variety of behavioral experiments including metabolic cage, urodynamics in anesthetized animals, urodynamics in restrained animals, and urodynamics in freely moving animals.[25] For urodynamics in anesthetized animals, the outcome measure could be baseline pressure, threshold pressure, intravesical pressure, voided volume, voiding time, voiding frequency, flow rate, bladder compliance, and external urinary sphincter. Because our study only focused on VT and ICI, which is a limitation of this study, a further study that evaluates all those parameters would help increase understanding of the urinary effect of UHF stimulation on the L6 nerve root in the OAB model.[25]

The mechanisms behind the efficacy of high-frequency neuromodulation in regulating bladder function remain incompletely understood. However, SNS has been suggested to affect the sensory function of the bladder, thereby interfering with spinal reflexes and the micturition center in the brain.[26] Research by Crook et al suggests that high-frequency neuromodulation works by creating a nonphysiological pattern of afferent activity from the bladder; this pattern then disrupts the central micturition control system in addition to spinal cord coordination to inhibit voiding.[23] In pain management, UHF has been shown to directly modulate neural signaling through enhancement of descending inhibitory tone and reduced excitation of nociceptive C-fibers. UHF application also has been shown to selectively suppress the conduction of signals through nociceptive C-fibers, without affecting normal sensory transmission through A-β fibers.[27] This targeted inhibition of C-fiber activation may effectively block the propagation of nociceptive input from the periphery to the central nervous system.

This research only focused on short-term effects and has not yet assessed long-term outcomes, which is a limitation of the study. In addition, the study did not evaluate the mechanical effects of UHF on the nerve owing to the small size of the L6 nerve root for such an evaluation. However, electron microscopic studies showing minor damage to nociceptive C-fibers and A-Δ fibers with UHF stimulation suggest that UHF stimulation does not cause obvious tissue damage.[28] There also are theories that UHF alternating current treatment directly to the nerve produces fast onset and selectively disrupts nerve conduction and sensation. It is therefore deemed efficient, fast, and safe, with few adverse effects, and its benefits are long lasting without causing neurologic damage.[29] After all, further research is needed to assess the long-term effects of UHF on OAB and any potential side effects.

It is important to consider that although animal models are valuable tools for advancing our understanding of bladder dysfunction and exploring potential treatments, for animal welfare and practical and ethical reasons, the experiment should limit the use of animals to minimal numbers and restrict the researcher to performing experiments in both sexes or multiple strains. Another issue is although hormonal differences between sexes may affect lower urinary tract function, fundamental parameters such as vesical pressure, detrusor distension, sphincter electromyogram, and neural wiring are generally similar across many species and both sexes.

Despite its benefits and efficacy, the current understanding of UHF remains incomplete. Nevertheless, UHF has valuable potential as an alternative method of treating refractory OAB. Further research is necessary to fully understand the mechanisms of action of UHF. This will help improve procedural parameters and identify ideal indications, thereby maximizing the clinical utility and value of UHF.

CONCLUSIONS

The results of this study provide evidence to support the development of UHF stimulation as a method of inhibiting bladder overactivity. The application of UHF electrical stimulation to the L6 nerve root caused a notable augmentation of both VT and ICI values. Remarkably, these effects persisted for approximately two hours after a 5-minute stimulation period. These findings suggest that UHF stimulation may offer rapid onset and long-lasting effects, potentially beneficial for subjects with refractory OAB that does not respond to low-frequency stimulation.

Acknowledgements

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Authorship Statements

Chih-Wei Peng designed and conducted the study, collected and analyzed data, and revised the manuscript. Bor-Shing Lin, Nurida Khasanah, and Chun-Ying Cai conducted the study, collected and analyzed data, and prepared the manuscript draft with important intellectual input from Chih-Wei Peng, Kuo-Hsiang Lu, and Wei-Tso Lin. Chun-Ying Cai, Chun-Wei Wu, Kuo-Hsiang Lu, and Wei-Tso Lin also participated in the study's execution, data collection, and data analysis. All authors approved the final manuscript.

Conflict of Interest

The authors reported no conflict of interest.

How to Cite This Article

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2024.09.476.

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