Clinical efficacy of intravesical electrical stimulation on detrusor underactivity
8 Years of experience from a single center

Han Deng, MS[a,b,c], Limin Liao, MD, PhD[a,b,c,*], Juan Wu, MD[a,b,c], Guoqing Chen, MD[a,b,c], Xing Li, MD[a,b,c], Xiaohua Wang, MD[a,b,c], Li Wan, BS[a,b,c]

Abstract
The aim of this study was to retrospectively evaluate the effectiveness of intravesical electrical stimulation (IVES) on detrusor underactivity (DU).

From 2009 to 2016, a total of 105 patients with symptoms of DU who were treated with IVES were included in this retrospective study. The medical records, physical examination findings, urine culture results, and video-urodynamic studies were reviewed. Changes in post-void residual urine (PVR) and voiding efficiency (VE) were included for evaluation of efficacy. Patients achieving a >50% reduction in the PVR were regarded as responders. A >80% reduction in the PVR was considered obvious improvement. A questionnaire was administered to patients with bladder sensation.

Of the 105 patients, the information of residual urine volume and voiding volume was obtained in 89 patients, and detailed pre- and post-IVES bladder sensation information was available on 96 patients. Of the 89 patients, 47.2% (42/89) were responders and achieved a >50% reduction in the PVR. Obvious improvement in the PVR, defined as a >80% reduction, occurred in 27% (24/89) of the patients. VE developed in 76.4% (68/89) of the patients, and 30.3% (27/89) of the patients increased >50%. Significant improvements in the PVR and VE were observed during IVES treatment (P<.05). Based on the questionnaire, bladder sensation developed and was sustained in 44.8% (43/96) of the patients.

IVES provides a promising method for improving the PVR and VE in a majority of patients with DU. Thus, IVES is worth to further study and carry out.

Abbreviations: AIS = American Impairment Scale, ASIA = American Spinal Injury Association, CIC = clean intermittent catheterization, DU = detrusor underactivity, IVES = intravesical electrical stimulation, PVR = post-void residual urine, SCI = spinal cord injury, UTI = urinary tract infection, VE = voiding efficiency.

Keywords: detrusor underactivity, intravesical electrical stimulation, post-void residual urine, voiding efficiency

1. Introduction
The International Continence Society defines detrusor underactivity (DU) as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span.[1]

Aging contributes to this process, but the mechanism of DU has not been clearly clarified. Patients with DU may experience recurrent urinary tract infections (UTIs), vesicoureteral reflux, hydronephrosis, renal insufficiency, and renal failure, which may impair the quality of life and social interactions.[2]

Current treatment options for DU are limited. Clean intermittent catheterization (CIC) is regarded as an ideal treatment method, but long-term intermittent catheterization may be the cause of urethral injury and UTIs.[3] Pharmacologic treatments, such as parasympathomimetics, alpha-adrenergic blockers, botulinum toxin A, and prostaglandin E2, remain controversial due to efficacy and safety.[4] Latissimus dorsi detrusor myoplasty, transurethral bladder neck incision, and the Mitrofanoff procedure are surgical treatments for DU, but are associated with trauma and numerous complications, such as hemorrhage, vesicovaginal fistulas, stress urinary incontinence, urethral strictures, and retrograde ejaculation.[1,5] Prevention of upper urinary tract damage, avoidance of overdistension, and reduction of post-void residual urine (PVR) are considered proper management for patients with DU.[4] Intravesical electrical stimulation (IVES) represents a conservative treatment for DU that enhances bladder sensation, promotes bladder emptying, and reduces the PVR.[6–9]

IVES was initiated by Saxtorph to treat urinary retention by inserting an active electrocatheter into the bladder with a neutral electrode placed in the skin.[8] In 1959, Katona and Berenyi[10]
Table 1
Diagnoses in all 105 patients of DU.

| Diagnoses                              | No. patients | %   |
|----------------------------------------|--------------|-----|
| Incomplete spinal cord injury (SCI)    | 23           | 21.9|
| Complete SCI                           | 9            | 8.6 |
| Conus medullaris and cauda equina syndrome | 36          | 34.3|
| Lumbar disc surgery                    | 15           | 14.3|
| Hemorrhoids surgery                    | 4            | 3.8 |
| Myelomeningocele                       | 3            | 2.9 |
| Hysterectomy                           | 3            | 2.9 |
| Spinal canal stenosis                  | 3            | 2.9 |
| The appendix resection                 | 2            | 1.9 |
| Spine bifida                           | 2            | 1.9 |
| Lumbar spinal tumor                    | 2            | 1.9 |
| Cesarean section                       | 1            | 0.9 |
| Cervical cancer                        | 1            | 0.9 |
| Colorectal cancer                      | 1            | 0.9 |

DU = detrusor underactivity, SCI = spinal cord injury.

described a technique of intraluminal electrotherapy for various disorders of the gastrointestinal tract. Subsequently, in 1975, Katona used this technique extensively for neurogenic bladder dysfunction.[10] Intraluminal electrotherapy has been popularized for the treatment of voiding dysfunction. The effects of IVES remain controversial, several studies have shown similar success, but other studies did not achieve dramatic effectiveness.[11–14]

The aim of the present retrospective study was to evaluate the effectiveness of IVES on DU.

2. Methods

2.1. Device introduction

The Bladder-Pelvic Stimulator II (General Stim Inc, Hangzhou, Zhejiang, China) consists of 3 subsystems: a stimulator; a user interface device; and an electrode. Four independent output channels were supported. The stimulator can form monophasic and biphasic pulse waves. The stimulation parameters are as follows: 1 to 40 mA pulse amplitude; 0.1 to 200 Hz pulse frequency; 100 to 1000 μs pulse width; 1 to 100 s pulse train duration; 1 to 100 s pulse train interval; 1 to 100 s pulse train rising edge; and 1 to 100 s pulse train falling edge. The stimulation parameters can be adjusted individually to a level giving the most probable success. The stimulator can be immediately stopped should any adverse events occur, such as pain, unbearable itching, serious flustered, and any other insufferable discomfort during stimulation. Multiple types of surface electrodes can be selected in the electrode interface, but were not included in this retrospective study.

2.2. Patients

A retrospective review of DU patients with IVES at a single institution was conducted when the experimental protocol was approved by the Institutional Review Board at the China Rehabilitation Research Center (No. 2016-044-1). All patients and parents were informed about the retrospective review.

From 2009 to 2016, a total of 105 patients with symptoms of DU who were treated with IVES were included in this retrospective study. There were 37 female and 68 male patients. Mean patient age before IVES was 41.4 years (range, 10–65 years). The following data and data sources were collected from all patients: medical records; physical examination; urine culture; and video-urodynamic study. The normal urine culture finds were presented in all patients. The diagnoses for all 105 patients are shown in Table 1. CIC was used for all patients as conservative treatments, but the response was unsatisfactory with afibrile infection and febrile infection. We selected patients with incomplete spinal cord injury (SCI; class C or D) and complete SCI (class A) according to the American Spinal Injury Association (ASIA) American Impairment Scale (AIS).[15]

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: presence of symptoms, including hesitancy, straining, dysuresia, slow stream, intermittency, spraying, prolonged bladder emptying, and/or incomplete bladder emptying; presence of stable voiding dysfunction (PVR ≥ 50 ml); patients who completely filled in their voiding diaries from 3 days before IVES to the end of this technique; and no other treatments given before IVES.

The exclusion criteria were as follows: acute urinary retention, with UTIs, bladder tumors or stones, or SCI in the spinal shock period; mechanical bladder outlet obstruction (benign prostatic hypertrophy, bladder neck contraction, urethral stenosis, or prostatic cancer) as determined by a videourodynamic study, including pressure-flow study and ultrasonography of the prostate; overactive bladder, as determined by a urodynamic study; severe cardiac or cerebrovascular disease, and/or renal dysfunction; pregnancy; or bladder mucous membrane damage.

2.4. IVES technique and parameters setting

IVES was performed by inserting a sterile active electrocatheter (an electrode in the catheter) via the urethra into the bladder surrounded by a half-normal saline (Fig. 1). The neutral electrode was attached to the abdominal skin above the pubic bone with preserved sensitivity. The 2 electrodes were connected to the stimulator. The user interface was developed by clinicians. In this study, IVES was administered with a biphasic pulse wave. The pulse amplitude ranged from 1 to 30 mA, the pulse frequency was 10 to 25 Hz, and the pulse width was 200 to 800 μs. The parameters were individualized to enhance bladder sensation, promote bladder emptying, and reduce PVR. The daily session lasted 30 minutes. The series consisted of 5 days a week until normal was achieved or no further improvement could be observed. Care was taken to avoid inducing a serious discomfort and patients were instructed to stop the stimulation by depressing the stop-button at any time should any serious discomfort occur.

2.5. Evaluation

A voiding diary was used to record PVR and voiding volume mL-1 per void 3 days before starting the IVES. During the IVES procedure, each voiding diary was compared with pre-IVES 3 days before the end of IVES. The PVR was measured using ultrasonography. Patients were asked to lie flat on the treatment table with the abdominal skin above the pubic bone being exposed, and gel was applied on the skin. Subsequently, the ultrasound probe was placed over this area, and a recording was made. Voiding efficiency (VE) was calculated as follows: volume voided/(volume voided + PVR) × 100%. Patients achieving a >50% reduction in the PVR were regarded as responders. A >80% reduction in the PVR was considered to be an obvious improvement. A questionnaire was administered to patients with
bladder sensation at the end point. Questionnaire, voiding dairy recommended by international consultation on incontinence.

2.6. Statistical analysis

Data are expressed as the mean ± standard deviation. Paired Student t test was used for analyzing the data between post- and pre-IVES using SPSS19.0 software. A P value <.05 was considered significant.

3. Result

IVES was performed in 105 patients, 89 of whom had PVR and voiding volume information available and were included for evaluation. Detailed pre- and post-IVES bladder sensation information was available on 96 patients. Patients accepted a mean of 27.11 ± 25.35 treatment sessions (range, 5–181).

The pre-IVES data of the PVR and VE were 335.3 ± 152.8 mL and 23.39% ± 29.42%, respectively. The post-IVES data of the PVR and VE were 190.7 ± 156.4 mL and 55.28% ± 35.13%. Significant improvements in the PVR and VE were observed during IVES treatment (P < .05). The changes in the PVR and VE are shown in Figure 2. Of the 89 patients, 47.2% (42/89) were responders and achieved a >50% reduction in the PVR. Obvious improvement in the PVR, defined as a >80% reduction, occurred in 27% (24/89) of the patients. VE developed in 76.4% (68/89) of the patients, and 30.3% (27/89) of the patients had a >50% increase. Based on the questionnaire, bladder sensation developed was in 44.8% (43/96) of the patients. Overactive bladder was not observed in any patients. At the end of IVES treatment, no patients altered their initial ASIA/AIS class.

CIC is necessary for continence and to maintain a low bladder pressure. Three days before IVES, the average daily number of CIC was 3.3 in all patients (range, 1–6). Patients performed a mean of 2 CIC numbers per day (range, 0–6) 3 days before the end of IVES. The improvement of 105 patients in pattern of CIC was shown in Table 2. Of the 105 patients 63.8% (67/105)

![Image](image1.png)

**Figure 1.** The insert mode of the active electrode. Patients were treated by inserting a sterile active electocatheter via the urethra into the bladder.

![Image](image2.png)

**Figure 2.** A, Mean PVR and (B) mean VE of 89 patients between pre- and post-IVES. Values are expressed as the mean ± SD. A, P < .0001, (B) P < .0001. IVES = intravesical electrical stimulation, PVR = post-void residual urine, VE = voiding efficiency.

| Table 2 |
|---|
| Change in pattern of CIC. |
| | Utterly relied on CIC | Partly relied on CIC | Without CIC |
| Pre-IVES | 15 | 50 | 2 |
| Post-IVES | 0 | 26 | 12 |
| Total | 15 | 76 | 14 |

CIC = clean intermittent catheterization, IVES = intravesical electrical stimulation.
utterly relied on CIC in time before IVES, but 74.6% (50/67) of them could partly void by bladder sensation after IVES, and 3% (2/67) void without CIC.

Fifty-nine percent patients with incomplete SCI and 76% patients with conus medullaris and cauda equina syndrome showed no further notable improvement in the PVR after 4 weeks of IVES.

No immediate or long-term adverse events were observed associated with stimulation. Most patients tolerated the IVES without discomfort, although 1 patient failed to comply to the end. Compared to pre-IVES, patients went to bed earlier and slept more hours. Complications of IVES included a UTI in 1 patient, who was treated with antibiotics and resumed IVES after 1 week, and pruritus in 2 patients due to defective contact between the neutral plates better and/or lowering the stimulation intensity. In addition to those complications, mild urine leakage occurred in 1 patient that resolved after reducing the stimulation intensity. None of the patients had further upper tract defects.

4. Discussion
Our results showed that some patients with DU improved, with 47.2% (42/89) achieving a >50% reduction in the PVR, and 27% (24/89) with a >80% reduction in the PVR. Furthermore, VE developed in 76.4% (68/89) of the patients, and 30.3% (27/89) had a >50% reduction. These dramatic results were acquired without serious side effects or complications. Our results suggest that IVES is a promising method to treat DU in patients.

Normally, micturition is initiated by depolarization of intramural mechanoreceptors, which through complex central nervous system reflexes elicit detrusor contractions. The mechanism of action of IVES has been investigated with respect to anatomic and physiologic aspects. IVES has been shown to involve the direct artificial activation of A6 afferents from low-threshold bladder mechanoreceptors, which comprise the sensory system responsible for both initiating and maintaining the micturition reflex. Prolonged or repeated IVES may induce long-lasting enhancement of excitatory synaptic transmission in the micturition central reflex pathway. As a result, IVES lowers the micturition threshold and enhances the reflex amplitude. Jiang and Lindstrom found that a single brief IVES session induces a prolonged decrease in the micturition threshold volume of anesthetized rats, and suggested that this prolonged modulation of the micturition reflex might be an early manifestation of the neuronal changes that underlie the beneficial effect of IVES in patients with voiding disorders.

Intact pelvic nerve afferents are necessary to provide adequate afferent feedback to generate effective bladder contractions to empty the bladder. Most DU patients in our study were stratified for analysis based on changes in the PVR and VE (Table 3). We observed that patients with incomplete SCI, conus medullaris and cauda equina syndrome, post-lumbar disc surgery, and post-hemorrhoidal surgery demonstrated significant improvements in the PVR and VE after IVES. Improvement in the PVR and VE was less in patients with complete SCI compared to the other subgroups. This finding suggests that the principle mechanism underlying IVES involves direct field stimulation of the A6 afferents from low-threshold bladder mechanoreceptors, which comprise the sensory system responsible for initiating and maintaining the micturition reflex. We speculate that a full or partially complete central pathway reflex may be the premise condition. The other subgroups were too small to judge a significant difference. Patients who are post-hemorrhoidal surgery had the best response with respect to the PVR and VE, followed by conus medullaris and cauda equina syndrome. These results suggest that patients without central nerve damage may achieve increased success, which is consistent with the mechanism underlying IVES.

The effects on bladder sensation were lower compared to previous studies, likely because candidates had a mild condition. The gain in sensation enabled patients to perform CIC effectively and to use the toilet when they felt a desire to void instead of timed voiding. CIC was used by 63.8% (67/105) of the patients before IVES, but by the end of IVES treatment, 74.6% (50/67) of the patients no longer depended on CIC after IVES, who could partly void by bladder sensation. Many patients had modified the CIC regimen because they were now catheterizing based on sensation rather than timed voiding.

Our study indicated that 3 to 4 weeks of daily IVES sessions are sufficient to demonstrate dramatic success or failure. Van Balken et al reported that the first 10 to 15 stimulation sessions were considered a trial, to be continued only when a positive response
was documented. In fact, 59% patients with incomplete SCI and 76% patients with conus medullaris and cauda equina syndrome showed no further notable improvement in the PVR after 4 weeks of IVES. Previous data obtained from cats and rats showed that much lower frequencies (<20Hz) are of more benefit for IVES treatment. An additional reason for our success may have been lower frequency selection (10–25Hz).

The success rate of IVES at different centers may reflect differences in inclusion/exclusion criteria for IVES, the IVES treatment protocol, the skills of operators, and/or stimulation parameters. Currently, there is no universal standard of patient selection with DU. It must be emphasized that the management of IVES treatment is operator dependent. Adjustments of parameters and the position of the electrode must be made continuously during each session and may substantially affect the clinical outcome. Negative results can be traced back to a study by Nicholas and Eckstein who failed to observe any effect of IVES in patients with neurogenic dysfunction; the use of extremely low IVES current intensities (≤1 mA) may have been the main reason for failure. Approximately 10-fold higher intensities are required for effective stimulation of afferents in the much smaller bladders of rats and cats. Thus, we speculate that low stimulation intensities might result in negative results. In the present study, stimulation intensities were chosen individually at a level just below that causing an unpleasant sensation.

Another reason for failure can be the definitions of IVES success. Patients who were defined as responders by Lombardi et al were those with a minimum of 50% reduction in the number of daily catheterizations and the PVR. Our patients achieving a >50% reduction in the PVR were regarded as responders and attaining a >80% reduction in the PVR was regarded as obvious improvement. In addition, this efficacy needed to be durable.

In this retrospective study, a shorter interval of time elapsed from damage to IVES treatment (≤1 years) was a predictive parameter, which can increase the likelihood of success. Our study revealed that 30 patients experiencing a shorter elapsed time obtained a >55% reduction in the PVR and a notable improvement in bladder sensation. Another predictive parameter emerged from this study for increasing the effectiveness of IVES was the first sensation of bladder filling diagnosed by urodynamics before IVES. In most patients experiencing the first sensation of bladder filling before IVES, the PVR was reduced to <100 mL. This suggests that inducing and/or improving bladder sensation is the fundamental mechanism underlying IVES.

Lacking a control group was a limitation of the present study, this was a retrospective study. In our study, we did not perform urodynamic at the end-point and carry out follow-up. So further study with a control group will be necessary to observe the role of IVES treatment for patients with DU. The mechanism underlying IVES warrants further research, which might be used to refine patient selection, optimize stimulation schemes, and prolong clinical efficacy.

5. Conclusion
IVES provides a promising method for improving the PVR and VE in a majority of patients with DU. Thus, IVES is worth to further study and carry out.

Acknowledgment
The authors want to thank GenralStim Inc (Hangzhou, Zhejiang, China) for providing products and technical support.

References
[1] Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Am J Obstet Gynecol 2002;187:116–26.
[2] Hoebelke P, Van Laecke E, Van Camp C, et al. One thousand video-urodynamic studies in children with non-neurogenic bladder sphincter dysfunction. BJU Int 2001;87:575–80.
[3] Webb RJ, Lawson AL, Neal DE. Clean intermittent self-catheterisation in 172 adults. Br J Urol 1990;65:20–3.
[4] Miyazato M, Yoshimura N, Chancellor MB. The other bladder syndrome: underactive bladder. Rev Urol 2013;15:11–22.
[5] Moreno-Palacios J, Maldonado-Alcaraz E, Montoya-Martínez G, et al. Outcomes and complications of sphincterotomy with bladder neck incision in neurologically healthy male patients with voiding dysfunction. Arch Esp Urol 2012;65:244–50.
[6] Kaplan WE, Richards I. Intravesical transurethral electrotherapy for neurogenic bladder. J Urol 1986;136:243–6.
[7] Wyndaele JJ, Madersbacher H, Kovindha A. Conservative treatment of the neuropathic bladder in spinal cord injured patients. Spinal Cord 2001;39:294–300.
[8] Madersbacher H. Intravesical electrostimulation for the rehabilitation of the neuropathic bladder. Paraplegia 1990;28:349–52.
[9] Wyndaele JJ, Conservative treatment of patients with neurogenic bladder. Euro Urol Suppl 2008;7:557–65.
[10] Kataon F, Berenyi M. Intravesical transurethral electrotherapy of bladder paralysis. Orv Hetil 1975;116:554–6.
[11] Hagerly JA, Richards I, Kaplan WE. Intravesical electrotherapy for neurogenic bladder dysfunction: a 22-year experience. J Urol 2007;178:1680–3.
[12] Glad G, Mattsson S, Lindstrom S. Intravesical electrostimulation in the treatment of micturition dysfunction in children. Neurourol Urodyn 2003;22:233–42.
[13] Madersbacher H, Pauer W, Reiner E, et al. Rehabilitation of micturition in patients with incomplete spinal cord lesions by transurethral electrostimulation of the bladder. Eur Urol 1982;8:111–6.
[14] Kaplan WE. Intravesical electrostimulation of the bladder: pro. Urology 2000;56:2–4.
[15] Maynard FM, Bracken MB, Creasy G, et al. International standards for neurological and functional classification of spinal cord injury. Spinal Cord 1997;35:266–74.
[16] Van Balken MR, Vergunst H, Beemleins B.LH. The use of electrical devices for the treatment of bladder dysfunction: a review of methods. J Urol 2004;172:846–51.
[17] Jiang CH. Modulation of the micturation reflex pathway by intravesical electrical stimulation: an experimental study in the rat. Neurourol Urodyn 1999;18:525–30.
[18] Jiang CH, Lindstrom S. Intravesical electrical stimulation induces a prolonged decrease in micturition threshold volume in the rat. J Urol 1996;155:1477–81.
[19] Jiang CH, Lindstrom S. Prolonged enhancement of the micturition reflex in the cat by repetitive stimulation of bladder afferents. J Physiol 1999;517:599–605.
[20] Chot EK, Hong CH, Kim MJ, et al. Effects of intravesical electrical stimulation therapy on urodynamic patterns for children with spina bifida. A 10-year experience. J Pediatr Urol 2013;9:798–803.
[21] Ehner A, Jiang C, Lindstrom S. Intravesical electrical stimulation—an experimental analysis of the mechanism of action. J Urol 1992;148:920–4.
[22] Nicholas JL, Eckstein HB. Endovesical электроtherapy in treatment of urinary incontinence in spina-bifida patients. Lancet 1975;2:1276–7.
[23] Lombardi G, Celso M, Mencarini M, et al. Clinical efficacy of intravesical electrostimulation on incomplete spinal cord patients suffering from chronic neurogenic non-obstructive retention. A 15-year single centre retrospective study. Spinal Cord 2013;51:232–7.