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Original Research

Can inter-sphincteric and pelvic floor botulinum toxin type A injections enhance clinical outcomes in pediatric patients with non-neurogenic dysfunctional voiding?

Pooya Hekmati [*,1], Negar Mohammadi Ganjaroudi [1], Arash Hassanpour Dargah, Mahdiyar Jaberi, Mohammad Amin Siri, Alvand Naserghandi, Soroush Mozafari, Abdol-Mohammad Kajbafzadeh [**]

* Correspondence to: Pooya Hekmati, Pediatric Urology and Regenerative Medicine Research Center, Pediatric Center of Excellence, Children's Medical Center, No. 62, Dr. Qarib's St, Keshavarz Blvd, Tehran 14194 33151, Iran, Tel./fax: +982166565400

** Correspondence to: Abdol-Mohammad Kajbafzadeh, Department of Pediatric Urology, Pediatric Center of Excellence, Children's Medical Center, Tehran University of Medical sciences, Tehran, Iran, Tel./fax: +982166565400
pooya.hekmati@gmail.com (P. Hekmati)
kajbafzd@sina.tums.ac.ir (A.-M. Kajbafzadeh)

Keywords
Urethra; Botulinum toxins; Type A; Urinary incontinence; Urinary tract infections; Urination disorders

Abbreviations
AFR, Average Flow Rate.; BNI, Bladder Neck Incision.; BTX-A, Botulinum Toxin Type A.; BWT, Bladder Wall Thickness.; CIC, Clean Intermittent Catheterization.; DV, Dysfunctional Voiding.; DVSS, Dysfunctional Voiding Scoring System.; EUS, External Urethral Sphincter.; EMG, Electromyography.; HUN, Hydroureteronephrosis.; LUTD, Lower Urinary Tract Dysfunction.; MFR, Maximal Flow Rate.; NNDV, Non-neurogenic dysfunctional voiding.; PedsQL, Pediatric Quality of Life Inventory.; PUV, Posterior Urethral Valve.; PVR, Post-void Residue.; UTIs, Urinary Tract Infections.; VCUG, Voiding Cystourethrography

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Summary

Purpose
To evaluate the effectiveness of external urethral sphincter (EUS) and perineal body BTX-A injections on uroflowmetric factors as well as severity of dysfunctional voiding.

Methods
In a prospective cohort study, patients diagnosed with refractory non-neurogenic voiding dysfunction were included in this study. All cases were evaluated pre-operatively by ultrasonography, uroflowmetric study and electromyography (EMG). Voiding cystourethrography or direct radionuclide cystography and other diagnostic modalities were performed if indicated. Using a rigid pediatric endoscope, the urethra and bladder evaluated for underlying concurrent anomalies. BTX-A injection of the perineal body and EUS, was performed transperineally or/and endoscopically. The uroflowmetric parameters and dysfunctional voiding scoring system (DVSS) were evaluated as therapeutic outcomes. Post-operative voiding satisfaction was assessed using a 7-point Likert-type scale with higher response values reflecting greater symptom improvement.

Results
The study demonstrated significant improvements in DVSS and uroflowmetric parameters in the included cases after a mean follow-up period of 16.14 ± 6.14 months. Among the 82 included cases, 12 patients experienced transient post-injection urinary incontinence, which resolved on average within 0.32 ± 0.91 weeks post-injection. Post-operative voiding satisfaction demonstrated a median score of 7 with an inter-quartile range of 1.25. Several limitations can be addressed including single center cohort study and absence of control group.

Conclusion
This study demonstrates the therapeutic potential of BTX-A injection in refractory non-neurogenic dysfunctional voiding pediatric cases. In addition, the BTX-A injection depicted promising improvements of post-operative voiding satisfaction.

Pediatric Urology and Regenerative Medicine Research Center, Gene, Cell and Tissue Research Institute, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[1] Both authors have contributed equally as co-first authors.

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Introduction

The therapeutic application of Botulinum toxin type A (BTX-A) has been increasingly evaluated for its efficacy in addressing urological issues, particularly over the past two decades [1—4]. Several clinical studies have assessed the effectiveness of BTX-A injections in lower urinary tract dysfunction (LUTD) management [5,6]. The inhibitory characteristics of BTX-A on releasing acetylcholine in the pre-synaptic junction contributed to BTX-A injection effectiveness in LUTDs [7,8]. Reported voiding improvements in adult patients with LUTDs receiving BTX-A injection led to the conduction of several studies evaluating the efficacy of the aforementioned treatment option in pediatric patients with refractory neurogenic and non-neurogenic dysfunctional voiding (DV) [1,7]. While there is substantial literature highlighting the therapeutic efficacy of BTX-A in improving functional voiding parameters primarily in pediatric neurogenic DV [1,5], there is limited research evaluating the effectiveness and sustainability of BTX-A injections in pediatric cases with refractory non-neurogenic dysfunctional voiding (NNDV) [7,9—12]. Among conducted studies on pediatric cases with refractory NNDV, there is a notable limit of evaluation on quality of life alongside clinical outcomes following BTX-A injections [7,10,12—14]. Hence, the aim of our study is to evaluate the severity of dysfunctional voiding and overall post-operative voiding satisfaction as a reflection of quality of life and intermediate therapeutic outcomes following perineal body and external urethral sphincter (EUS) BTX-A injection in pediatric patients with refractory NNDV.

Materials and methods

Study design and patient selection

A prospective cohort study with a minimum of 6 months follow-up was conducted on refractory NNDV candidates for BTX-A intervention at our tertiary care pediatric Center. The study's inclusion criteria were children aged 4—18 years, presence of interrupted or fractional voiding pattern on uroflowmetry study in combination with active pelvic floor electromyography (EMG) during the voiding phase, presence of measured ultrasonographic post-void residue (PVR) exceeding 10 % of the expected bladder capacity and refractory to pelvic floor physiotherapy with biofeedback and medical treatments, i.e., α-blocker and anticholinergic therapies (according to our center's NNDV management strategy). Refractory cases of NNDV are defined as patients who, despite adherence to standard urotherapy and second-line management strategies, continue to exhibit persistent clinical and paraclinical features of DV. In other words, during the follow-up sessions, these cases demonstrate the following findings: (a) lack of decreasing trend in ultrasound-measured PVR (b) recurrent episodes of urinary tract infection (UTI) (c) absence of improvement in uroflowmetric voiding patterns (d) failure to show an increasing trend in maximal flow rate (MFR) and average flow rate (AFR); and (e) presence of pharmacological side effects. The study's exclusion criteria were patients with a history or evidence of neurogenic bladder or other concurrent congenital anomalies of the genitourinary tract that were not corrected before the study and are responsible for DV or unable to continue the minimum of 6-month follow-ups. Detailed history taking (e.g., seizures) and physical examination were performed with an emphasis on identifying any neurological or developmental abnormalities. The normal neurological examination considered as having normal muscle tone, gait, symmetric deep tendon reflexes, intact perineal sensation, presence of anocutaneous reflex, age-appropriate gross motor milestones, and lack of lumbosacral region's cutaneous stigmata of spinal dysraphism (e.g., hemangiomas, lipomas, hypertrichosis). The presence of functional constipation was assessed preoperatively in all enrolled cases based on the ROME IV diagnostic criteria [15]. All children underwent kidney-ureter-bladder ultrasonography, uroflowmetry, and EMG evaluation prior to the procedure. In addition, voiding diary (i.e. frequency of diurnal wetting, night wetting, severity bed wetting, diurnal voiding, night voiding), dysfunctional voiding scoring system (DVSS), Bristol stool classification, and number of UTIs were evaluated during history taking session. In voiding diary evaluations, night wetting was defined as the frequency of repeated nocturnal wetting episodes, assessed using a 4-point scale: 0 (almost never), 1 (less than half the time), 2 (about half the time), and 3 (almost every time). Severity of bed wetting reflected the extent of each nocturnal episode and was graded as follows: 0 (none), 1 (underwear wetting), and 2 (bed wetting involving bed linen). This distinction allowed for a more nuanced characterization of each child's voiding patterns. The validated DVSS questionnaire, originally developed by Farhat et al. was utilized in this study [16]. Voiding cystourethrography (VCUG) or direct radionuclide cystourethrography was performed only when clinically indicated, with the latter involving the direct instillation of the radiopharmaceutical agent ^{99m}TC-Sodium Pertechnetate into the bladder via a catheter under sterile conditions. The indications that were considered for VUR investigations are: (a) Recurrent UTI (b) First UTI episode with a history of hydroureteronephrosis or having siblings with diagnosed VUR (c) Abnormal ultrasound finding suggestive of upper or lower urinary tract involvement (d) Recent history of recurrent afebrile UTI with a prior unexplained febrile illness, with evidence of renal cortical scars on ^{99m}TC-dimercaptosuccinic acid scan (e) Referred cases of refractory NNDV whom have not undergone contrast enhanced cystourethrography prior to referral. In our center's stepwise management of NNDV protocol, standard urotherapy is considered as the first-line option. After three months of adherence to standard urotherapy, in cases with persistent clinical and paraclinical signs and symptoms, second-line options (specific urotherapy either as standalone interventions or in combination with pharmacotherapy) are selected after discussing the options with the patient and their legal guardians. If the patient did not respond to the second-line treatment option. BTX-A injection as a minimally invasive management strategy is considered in refractory cases (Fig. 1). The current study was approved by the Institutional Ethics Committee Review Board and was conducted in accordance with the Helsinki Declaration.

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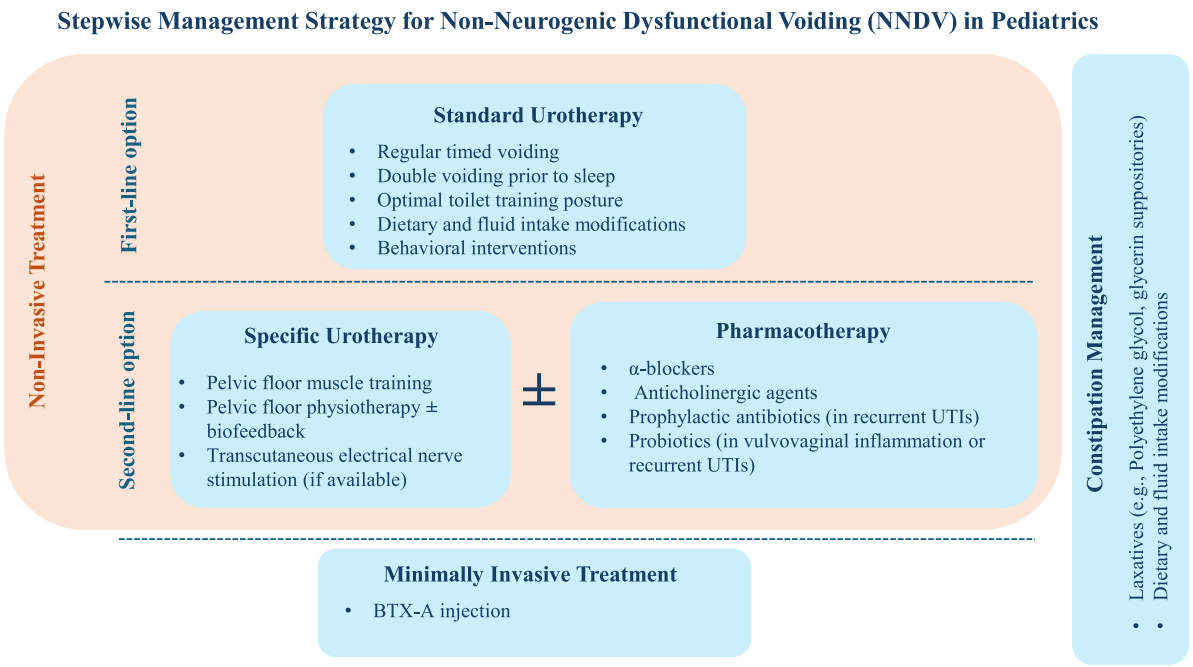

Fig. 1 The graph provides an overview of the stepwise management of non-neurogenic dysfunctional voiding (NNDV) at our tertiary care pediatric center. Standard urotherapy is the first-line treatment option, encompassing regular timed voiding, double voiding prior to sleep, optimal toilet training posture, and dietary and fluid intake modifications. At this stage, constipation management is considered a crucial aspect of dietary and fluid intake modifications. At each step, the following parameters are re-evaluated 4–6 weeks after initiating management: voiding diary, presence of urinary tract infection (UTI), urinary symptoms (frequency, urgency, diurnal wetting, nocturnal wetting), post-void residual (PVR) measured via ultrasonography (US), voiding pattern assessed through uroflowmetry study and pelvic floor activity evaluated via electromyography (EMG) during the voiding phase. If an improvement trend was observed in each category, adherence to the step was recommended. Non-responsiveness was attributed to cases where maximal flow rate (MFR) and average flow rate (AFR) failed to increase, uroflowmetry patterns did not approximate a near bell-shaped curve, UTI episodes occurred during therapy, PVR did not decrease, or urinary symptoms remained persistent without resolution or noticeable improvement. If patients fail to respond to standard urotherapy after three months, specific urotherapy as second-line management is introduced following discussions with patients and their legal guardians. Specific urotherapy for DV includes pelvic floor physiotherapy with biofeedback and pelvic floor muscle training, either as standalone interventions or in combination with pharmacotherapy. Selection of second-line treatment options is based on child's demonstrated cognitive capacity and family's supportive environment. In terms of pharmacological management, α-blockers (e.g., Terazosin) are utilized for cases with high PVR contributing to incomplete bladder emptying. For patients on α-blockers who experience urinary incontinence (i.e., episodes of wetting), anticholinergic agents (e.g., Oxybutynin, Tolterodine) are incorporated into treatment. In addition to the aforementioned pharmacological options, antibiotics were administered for prophylaxis in cases of recurrent UTIs, and probiotics were particularly recommended for female patients experiencing vulvovaginal inflammation, persistent discharge, or recurrent UTIs despite antibiotic use. BTX-A injection is considered a minimally invasive management strategy for refractory cases experiencing persistent clinical and paraclinical features of voiding dysfunction despite appropriate first-and second-line treatments. In high-risk NNDV cases (trabeculated urinary bladder, significant hydroureteronephrosis, poor renal reserve, history of recurrent UTI hospitalizations) with high PVR, clean intermittent catheterization is discussed with child and legal guardians prior to BTX-A intervention.

Surgical management

Prior to BTX-A injection, all candidates were evaluated for: (a) Presence of UTI using urine analysis and culture (b) Presence of constipation (c) Activity of pelvic floor EMG during voiding phase contributing to lower MFR and interrupted or fractional voiding pattern. All patients under general anesthesia were evaluated for the presence of underlying obstructive or other concurrent genitourinary anomalies using rigid endoscopy. Considering sterile conditions, the BTX-A injection method is assisted by a 31 G needle in the peri-urethral, perineal body, and peri-anal area (Fig. 2), whereas in male patients to target the EUS, the injection is assisted by a 23 G needle through a working channel of 6–19 Fr. rigid cystoscopy based on patients' age (Fig. 2A and B). Regardless of gender, the peri-anal BTX-A injection site is merely selected in patients who had functional constipation based on physical examination, history taking, and ultrasonography. The BTX-A injection sites are delineated as follows: in the peri-urethral area (in female) and endoscopic view of EUS (in male), injections are to be administered at the 3 and 9 O'clock positions. Similarly, in the peri-anal area, the injections are located at 3 and 9 O'clock positions. All injections, except endoscopic-

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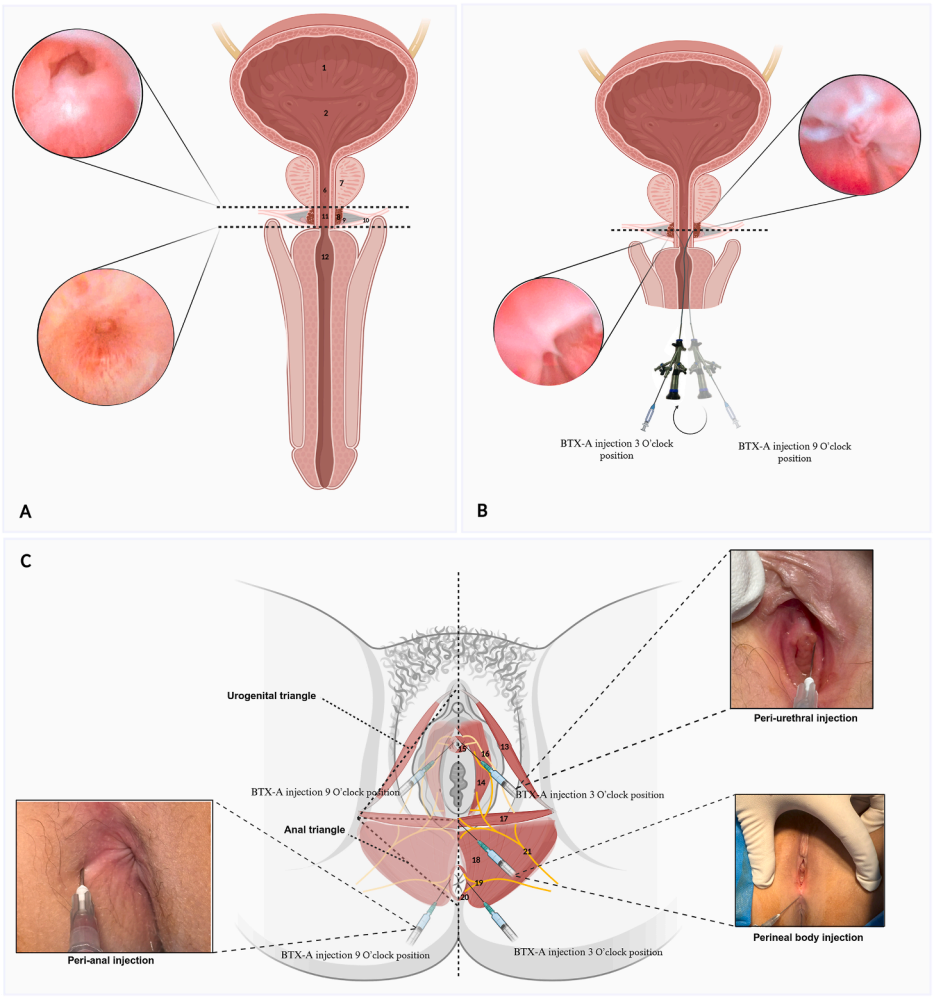

Fig. 2 (A) The cystoscopy view of the verumontanum and membranous urethra prior to BTX-A injection (B) The endoscopic injection of male BTX-A external urethral sphincter (EUS) at 3 and 9 O'clock positions, which is assisted by a 23 G needle through a working channel of 6—19 Fr. rigid cystoscopy based on patients' age. (C) The schematic view of female peri-urethral, perineal body, and peri-anal Botulinum toxin type A (BTX-A) injections. This method is assisted by a 31 G needle in the peri-urethral area, to target the sphincter urethrae muscle at 3 and 9 O'clock positions. In addition, the perineal body injection site where the boundaries of the urogenital and anal triangles of the perineum are intersected. The numbered anatomical locations are as follows: (1) Bladder, (2) Trigonal space, (3) Sphincter urethrae, (4) Transverse perineal ligament. (5) Subcutaneous fat of the perineum, (6) Verumontanum in the prostatic urethra, (7) Prostate, (8) External urethral sphincter muscle, (9) Bulbourethral (Cowper's) gland, (10) Perineal membrane, (11) Membranous urethra, (12) Bulbar urethra, (13) Ischiocavernosus muscle, (14) Bulbospongiosus muscle, (15) Peri-urethral area, (16) Deep perineal nerve, (17) Superficial transverse perineal muscle, (18) Levator ani muscle, (19) Inferior rectal nerve, (20) External anal sphincter, (21) Pudendal nerve.
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assisted EUS injections, were initially performed using US guidance alongside anatomical landmarks, and subsequent injections were performed using anatomical landmarks alone. The perineal body injection site is positioned at the midline, intersecting the boundaries of the urogenital and anal triangles of the perineum. The administration of BTX-A occurred at 5—10 IU/Kg (e.g. in a patient who weighed 20 kg, the injection dose of BTX-A is 100—200 IU). In order to reduce dose-related adverse effects, in this study we adhere to the lower limit injection dose range and preserve the upper limit dose range in selected cases refusing to perform clean intermittent catheterization (CIC) despite being in high-risk group of NNDV (i.e. trabeculated bladder, significant HUN, poor renal reserve, or recurrent UTI hospitalizations). After establishing the measured BTX-A dose, the injection volume at each site was allocated proportionally based on the number of injections, ensuring appropriate distribution.

Post-operative evaluation and follow-up

All patients' follow-ups were scheduled on a regular basis for one month and then every three months till one-year post-operation. During each follow-up session, the voiding diary, DVSS, Bristol stool type, number of UTIs,

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uroflowmetry and EMG study were evaluated. Kidney-ureter-bladder ultrasonography was performed with a focus on assessing hydroureteronephrosis (HUN), PVR measurements and bladder wall thickness (BWT). Overall voiding satisfaction was assessed using a 7-point Likert-type scale, where 1 represents no improvement and 7 indicates full symptom relief. To evaluate the voiding satisfaction scale as a proxy for treatment-related quality-of-life assessment, the Pediatric Quality of Life Inventory (PedsQL) questionnaire was administered to a subset of patients from the enrolled cohort. This validated questionnaire, originally developed by Varni et al. [17], was used to support convergent validation of the voiding satisfaction scale within the context of our study. Additionally, postoperative complications, including urinary retention, urinary incontinence, and fecal incontinence were documented. The US was conducted by an experienced pediatric radiologist, who also performed pre-operative evaluations. BWT was defined as the distance from the outer mucosal border to the outer adventitial border on the anterior bladder wall in a semi-distended bladder [18]. HUN was classified based on the APD classification system: normal ($<$5 mm), mild HUN (5.1−10 mm), moderate HUN (10.1−15 mm), and Severe HUN ($>$15 mm). The uroflowmetry and EMG studies were performed after informing the legal guardians of cases and describing the procedure thoroughly. All uroflowmetry and EMG studies were performed according to an established and previously published standard method using the CONUS Andromeda Uroflowmeter device (Model, ANDROMEDA medizinische Systeme GmbH, Germany) [19,20]. All uroflowmetric parameters, including MFR, AFR, voided volume, and flow curve pattern, were obtained by one of the authors who was blinded to the patient's identity and whether uroflowmetry and EMG study results were pre- and post-operative. This author was received training by co-corresponding authors for uroflowmetry and EMG studies interpretation adhering to ICCS terminology for pediatric LUTD [21]. Prior to assessing the study findings, we evaluated the inter-observer variability among the co-corresponding authors and the trained author. Following BTX-A injections, standard urotherapy is rescheduled for all enrolled cases. During the six-month follow-up after BTX-A injections, cases in which voiding diaries and urinary symptoms show improvement but remain unresolved, or cases where MFR and AFR increase without uroflow curve progression toward a near bell-shaped pattern, undergo discussions with the patient and their legal guardians regarding commencing specific urotherapy as complementary options.

Statistical analysis

Frequencies and percentages were used to describe categorical variables, while the median (interquartile range [IQR]) was used to describe continuous variables due to non-normal distribution. Continuous variables with a normal distribution are expressed as mean $\pm$ SD. The comparison of categorical variables between pre-and post-operative findings was performed by the chi-square, likelihood ratio test, or McNemar tests. For continuous variables, the paired t-test and Wilcoxon rank-sum test were used to compare pre-and post-operative values. To evaluate the convergent validity of the voiding satisfaction scale as a proxy for treatment-related quality of life, PedsQL was used as a reference measure. Spearman's rank correlation test demonstrated a moderate positive correlation ($\rho = 0.51$) between the two instruments. To assess the inter-observer variability in interpreting uroflowmetry and EMG study findings, Fleiss' Kappa tests were performed for both pre- and post-operative outcomes, revealing substantial agreement and robust inter-observer reliability with Kappa values of 0.867 and 0.906 for pre- and post-operative outcomes, respectively. The post-operative variables considered for the statistical analysis of outcomes following BTX-A injection were obtained from the last follow-up findings for each case. The duration of the last follow-up varied for each individual, with a minimum of 6 months. To evaluate the potential influence of follow-up duration on outcome consistency, the linear regression analysis between follow-up duration and post-operative outcomes, including MFR, AFR, voided volume, BWT, PVR, and DVSS index were performed.

In this study, we evaluated the significance of the differences between the pre-and post-operative numerical variables, including the US-measured PVR, BWT, and DVISS, by determining the differences in these variables across all included cases. We also assessed the differences between pre-and post-operative values using independent t-tests between subgroups with and without a history of previously performed posterior urethral valve (PUV) ablation and bladder neck incision (BNI). To evaluate the significance of the post-operative effect on ultrasound-evidenced HUN, we categorized cases into two subgroups: absence or presence of HUN. Additionally, to assess the effect of BTX-A injection on HUN grading, we categorized the cases into seven groups: no HUN, mild unilateral HUN, mild bilateral HUN, moderate unilateral HUN, moderate bilateral HUN, severe unilateral HUN, and severe bilateral HUN.

In cases that candidates for secondary pharmacotherapy or pelvic floor physiotherapy with biofeedback started at 6-month follow-up the differences between pre-and post-operative values were evaluated using Kruskal−Wallis test among Pharmacotherapy, Physiotherapy, and non-pharmacotherapy/non-physiotherapy subgroups.

Furthermore, uroflowmetric voiding patterns were categorized into the non-bell shape and bell shape voiding patterns for pre-and post-operative statistical analysis. To determine whether patient age is associated with post-operative voiding patterns, while adjusting for follow-up duration, we performed a binary logistic regression analysis. A p-value of <0.05 was considered statistically significant. All statistical analyses and graphical designs were performed using R Statistical software (v4.4.2; R Core Team 2021).

Results

Among the 82 cases included in our study, the mean age was 8.18 $\pm$ 3.19 years. Of these, 51 (62.2 %) patients were female and 31 (37.8 %) were male. The mean follow-up period was 16.14 $\pm$ 6.14 months, with a minimum duration of 6 months and a maximum follow-up of 39.3 months. There

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were no reports of post-operative complications of urinary retention or other respiratory-related side effects; however, 12 (14.63 %) cases experienced urinary incontinence with an average duration of 0.32 ± 0.91 weeks, which self-resolved without any intervention. There were no reports of fecal incontinence in patients receiving peri-anal BTX-A injections.

Among 82 cases in our cohort, 13 cases never had a single febrile UTI, and 26 cases never had UTI admissions, prior to BTX-A injection. During the follow-up period, only one case experienced an episode of febrile UTI six months after receiving BTX-A injection. Comparing the voiding diary outcomes in terms of the number of diurnal wetting episodes, night wetting episodes, and severity of bed wetting, there were significant improvements in post-operative evaluations, evidenced by a likelihood ratio value of 21.96, 35.77, and 49.31, respectively (P value < 0.05). Pre-operative US indicated 40 (48.8 %) cases as no HUN, 23 (28 %) cases with mild HUN, and 19 (23.17 %) cases with moderate HUN. Patients with severe HUN were not presented in this cohort pre-operatively. Post-operative US findings revealed 66 (80.5 %) cases with no HUN, 15 (18.3 %) cases with mild HUN, and 1 (1.2 %) case with moderate HUN. Notably, all cases with pre-operative mild HUN were completely resolved. Among 19 patients with moderate HUN pre-operatively, those with unilateral HUN (3 cases) showed complete resolution following surgery, while 15 cases with bilateral moderate HUN regressed to bilateral mild HUN. Only one case with pre-operative bilateral moderate HUN, regressed to unilateral moderate HUN. Ultrasound assessments demonstrated a significant improvement in post-operative HUN severity across the seven pre-defined HUN grading groups, with a likelihood ratio value of 0.707 (P value < 0.001). Moreover, the McNemar test confirmed a significant resolution effect of HUN in the post-injection follow-ups ($\chi^2 = 24.03$, P value < 0.001).

Among the 82 patients, there was a significant reduction in post-operative ultrasound PVR measurements (30.83 ± 22.4) compared to pre-operative PVR measurements (4.93 ± 6.85), with a P value < 0.001. As demonstrated in Table 1, other paraclinical measurements, including BWT (Fig. 3a), and clinical outcomes as measured by the DVSS index (Fig. 3b), showed statistically significant improvements in the post-operative follow-up compared to pre-operative measurements (P value < 0.001). Additionally, comparison of voiding satisfaction scores revealed a significant enhancement in patient-reported satisfaction following treatment (6.12 ± 1.29) compared to pre-operative levels (1.06 ± 0.24) with a P value < 0.001. However, there was a non-significant reduction of post-operative Bristol stool scale scores in cases that received the peri-anal BTX-A injection in comparison to their pre-operative scores, with a likelihood ratio value of 0.312 (P value = 0.145). Although, there is variability in the last follow-up duration of each individual and the post-operative outcomes are attributed to the last follow-up time-point, the regression analysis indicated that the follow-up duration did not significantly affect the post-operative outcomes of MFR (F value = 0.299, P value = 0.586), AFR (F value = 1.286, P value = 0.26), voided volume (F value = 0.414, P value = 0.522), PVR (F value = 0.683, P value = 0.411), BWT (F value = 0.922, P value = 0.34), and DVSS index (F value = 0.283, P value = 0.596), respectively.

Among 82 enrolled cases in our study, 25 patients (30.48 %) had a history of previous PUV ablation and BNI surgery, with a mean age of 9.32 ± 3.57 years that despite successful post-operative follow-up outcomes (e.g., documented period of normal voiding on uroflowmetry, normal posterior-to-anterior urethral ratio), exhibit symptoms consistent with DV. Of the 25 cases with history of PUV ablation and BNI surgery, pre-operative ultrasound demonstrated mild HUN in 6 patients and moderate HUN in 9 patients. As demonstrated in Table 2, there was no significant difference in post-operative PVR reduction between patients who had undergone previous PUV ablation and BNI surgeries (27.75 ± 18.39) and other included cases (25.09 ± 20.54), with a P value of 0.558. Additionally, Improvements in other ultrasound and uroflowmetric

Table 1 Summary of patients' baseline and post-operative paraclinical and clinical outcomes.

	Pre-operative	Post-operative	P value
Uroflowmetric measurements			
MRF (ml/s)	9.98 ± 5.39	16.41 ± 6.79	**< 0.001**
AFR (ml/s)	4.28 ± 2.66	9.03 ± 3.87	**< 0.001**
Voided volume (ml)	82.99 ± 58.67	186.89 ± 76.2	**< 0.001**
EMG activity (μV)	122.83 ± 105.06	36.16 ± 51.01	**< 0.001**
Ultrasonographic measurements			
Right side renal pelvis APD (mm)	8.09 ± 6.7	4.23 ± 2.42	**< 0.001**
Left side renal pelvis APD (mm)	7.81 ± 6.07	4.55 ± 3.11	**< 0.001**
BWT (mm)	5.04 ± 1.92	3.78 ± 1.32	**< 0.001**
Urine volume residue (ml)	32.09 ± 26.84	9.15 ± 12.7	**< 0.001**
PVR (%)	30.83 ± 22.4	4.93 ± 6.85	**< 0.001**
Dysfunctional voiding questionnaire			
DVSS	16.27 ± 5.39	4.83 ± 4.33	**< 0.001**

It is worth noting that all statistically significant values are indicated in bold.
MRF, Maximal flow rate; AFR, Average flow rate; EMG, Electromyography; APD, Anteroposterior diameter; BWT, Bladder wall thickness; PVR, Post-void residue; DVSS, Dysfunctional voiding scoring system.

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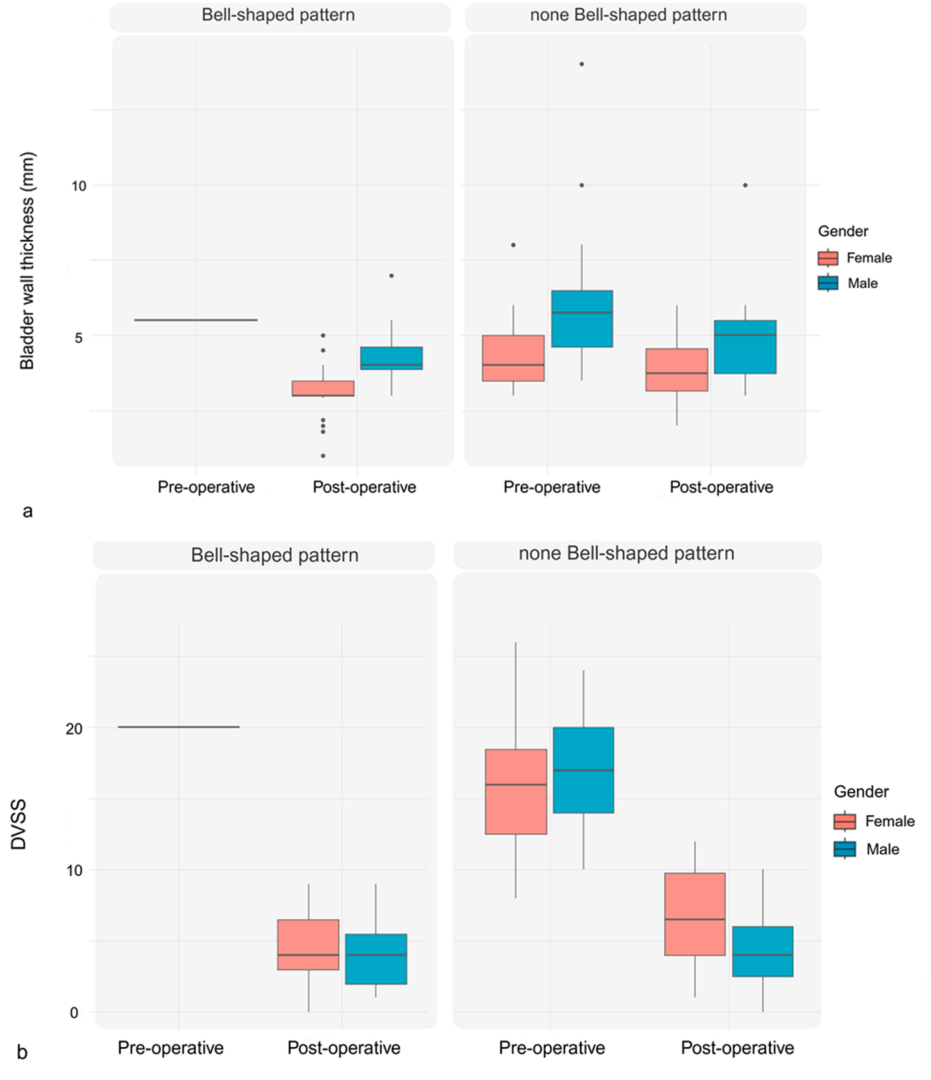

Fig. 3 The pre-and post-operative outcomes of (a) ultrasound-measured bladder wall thickness (BWT) and (b) the Dysfunctional Voiding System (DVSS) questionnaire boxplots. These outcomes are illustrated separately by gender and type of post-operative uroflowmetric voiding patterns in enrolled cases. (a) The BWT was measured in millimeters. (b) The DVSS can range from a minimum of 0 to a maximum of 30. BWT, Bladder Wall Thickness; DVSS, Dysfunctional Voiding Scoring System.

measurement parameters, except BWT and DVSS index, were not significantly different between subgroups with or without history of PUV ablation and BNI (Table 2). However, comparative analysis revealed that post-operative reductions in BWT and DVSS index differed significantly between the overall groups with and without history of PUV ablation and BNI. To examine whether this finding persists specifically among male patients, an additional analysis was performed comparing male patients with and without a history of PUV ablation and BNI. In this comparison, no statistically significant difference in post-operative BWT or DVSS index was observed between the male subgroups (Table 2).

Among 82 patients with staccato or interrupted voiding patterns, 59 cases (72 %) achieved near bell-shaped voiding patterns. While 23 patients with non-near bell-shaped flow patterns, despite increased MFR and AFR, started on pharmacotherapy or pelvic floor physiotherapy with biofeedback. The analysis indicated no significant difference in post-operative PVR reduction among pharmacotherapy (14.49 [24.94]), physiotherapy (20.37 [11.97]), and non-pharmacotherapy/non-physiotherapy subgroups (24.04 [23]), with a P value of 0.282 (Table 3). Of 23 cases with non-near bell-shaped voiding patterns, 15 (65.21 %) patients had follow-up duration less than 18 months. In addition, there was a non-significant difference in follow-up duration between cases with non-near bell-shaped (17.96 ± 5.87) and near bell-shaped voiding patterns (15.43 ± 6.15) with a P value of 0.095. The binary logistic regression analysis demonstrated statistically significant combined effect of age and follow-up duration on post-operative voiding patterns ($X^2(2) = 6.103$, P value $= 0.047$). Age emerged as marginally non-significant predictor (P value $= 0.071$) and follow-up duration did not independently predict voiding patterns (P value $= 0.297$).

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Table 2 Baseline and post-operative difference in paraclinical and clinical outcomes in different study subgroups with and without history of previous posterior urethral valve (PUV) ablation and bladder neck incision.

	PUV (n = 25)	Non-PUV (n = 57)	P value
Uroflowmetric measurements			
Diff MRF (ml/s)	6.28 ± 3.89	6.48 ± 4.81	0.852
Diff AFR (ml/s)	4.43 ± 2.79	4.88 ± 2.98	0.521
Ultrasonographic measurements			
Diff BWT (mm)	1.62 ± 1.36	1.09 ± 0.73	**0.024**
Diff PVR (%)	27.75 ± 18.39	25.09 ± 20.54	0.578
Dysfunctional voiding questionnaire			
Diff DVSS	13.2 ± 3.59	10.66 ± 4.36	0.013
	PUV male cases (n = 25)	**Non-PUV male cases (n = 6)**	**P Value**
Uroflowmetric measurements			
Diff MRF (ml/s)	13.48 ± 2.86	14.95 ± 5.58	0.54
Diff AFR (ml/s)	8.41 ± 3.54	8.06 ± 2.64	0.825
Ultrasonographic measurements			
Diff BWT (mm)	4.44 ± 1.48	5.25 ± 1.36	0.236
Diff PVR (%)	6.34 ± 7.99	12.34 ± 11.5	0.14
Dysfunctional voiding questionnaire			
Diff DVSS	4.12 ± 2.71	5.33 ± 2.65	0.332

It is worth noting that all statistically significant values are indicated in bold.
Diff, the difference between pre-and post-operative measurements; MRF, Maximal flow rate; AFR, Average flow rate; BWT, Bladder wall thickness; PVR, Post-void residue; DVSS, Dysfunctional voiding scoring system.

Table 3 Baseline and post-operative difference in paraclinical and clinical outcomes in post-BTX-A injection therapeutic subgroups.

	Ph.Tx (n = 14)	Physio.Tx (n = 9)	Non-Ph.Tx/non-Physio.Tx (n = 59)	P value
Uroflowmetric measurements				
Diff MRF (ml/s)	5.2 [4.7]	3.2 [5.4]	6.5 [5.5]	0.1
Diff AFR (ml/s)	4.05 [5.15]	1.9 [3.7]	4.5 [3.9]	0.084
Ultrasonographic measurements				
Diff BWT (mm)	1.5 [1.55]	1.5 [1]	1 [1]	0.081
Diff PVR (%)	14.49 [24.94]	20.37 [11.97]	24.04 [23]	0.282
Dysfunctional voiding questionnaire				
Diff DVSS	9 [9]	14 [9]	12 [4]	0.053

It is worth noting that all statistically significant values are indicated in bold.
Diff, the difference between pre-and post-operative measurements; MRF, Maximal flow rate; AFR, Average flow rate; BWT, Bladder wall thickness; PVR, Post-void residue; DVSS, Dysfunctional voiding scoring system; Ph.Tx, Pharmacotherapy subgroup; Physio.Tx, Physiotherapy subgroup; Non- Ph.Tx/non- Physio.Tx, Non-Pharmacotherapy/non-Physiotherapy.

Discussion

DV is a voluntary and habitual contraction of the urethral sphincter during the voiding phase, leading to lack of coordination between the detrusor muscle and the EUS/pelvic floor during voiding [12,22]. This results in detrusor contraction with simultaneous EUS/pelvic floor contraction [12], which can be evaluated using uroflowmetric patterns companied by EMG [23]. This condition can affect the voiding patten (e.g., interrupted, staccato), which corresponds to future incomplete voiding, increased PVR, and consequently leads to episodes of UTI, deterioration of detrusor function, urinary incontinence, hydroureteronephrosis, and deterioration of the upper urinary tract system [1,14,24,25]. In addition to the effects of dysfunctional voiding on detrusor function and the urinary tract system, severe VUR can also adversely impact bladder and detrusor function. Through chronic inflammation and bladder overload following megacystitis, Severe VUR acts as a modifying factor influencing bladder compliance and intravesical pressure [26]. Hence, considering the underlying causes of secondary NNDV such as high grade VUR is crucial. Moreover, post-obstructive DV can be seen in cases with history of PUV ablation surgeries [27]. In addition, the patient may face ongoing psychological and emotional stress related to their earlier urologic history. This burden may contribute to post-obstructive DV, even after successful resolution of the primary anatomic anomaly, reflecting a clinically relevant subgroup of patients with potential differences in treatment response.

Currently, several medical treatment options and therapeutic algorithms have been addressed, which determine

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the steps in managing DV [28,29]. However, challenges remain in groups of pediatric cases with NNDV who either do not appropriately respond to conventional therapeutic options or do not have adequate treatment compliance [9,12,30]. The primary therapeutic options in pediatric NNDV cases are pelvic floor physiotherapy with biofeedback and pharmacological agents, such as α-blocker and anti-cholinergic therapies, following standard urotherapy [28]. Similar to several studies, we evaluated therapeutic outcomes of EUS BTX-A injection in pediatric patients with NNDV who are refractory to other conventional therapies or do not comply with the aforementioned treatment options [7,9,10,12].

Several methods of BTX-A application for neurogenic and non-neurogenic DV in pediatric patients have been described in the literature, including endoscopic-guided EUS injection, US-guided EUS injection, endoscopic-guided intra-detrusor injection, and electromotive drug-assisted BTX applications [5,7,9,10]. In this cohort study, in addition to gender-specific BTX-A injection techniques and peri-anal injection for confirmed constipation cases, we introduced a novel technique for BTX-A injection into the perineal area, specifically at the midline of the urogenital and anal triangles in the perineum.

The rationale behind this technique is that the BTX-A targets the perineal body area, a structural and functional convergence zone of urogenital and anal triangles, coordinating transverse perineal muscles with EUS. This approach may reduce pelvic floor overactivity, as observed in EMG studies during the voiding phase, supporting the findings depicted in Table 1. The perineal body serves as an anatomical landmark rather than an exact injection site, allowing the injected BTX-A to diffuse into adjacent or overlying structures. Several studies have indicated that BTX-A injections can spread locally, with diffusion ranging from 1 to 4 cm from the injection site [31,32]. Histological evaluations of injection sites in animal models have demonstrated BTX-A diffusion extending 30—45 mm from the injection site, depending on the dose and injection volume [33]. Additionally, loosely structured tissues such as connective tissue within the perineal area may facilitate wider area of diffusion [31—33]. Since DV is primarily a behavioral and functional disorder, BTX-A injection may provide a temporary neuromodulatory effect that disrupts the maladaptive voiding reflexes of pelvic floor musculature hyperactivity [34]. As literature suggests temporary persistence of BTX-A's effects [35], our findings support the hypothesis that it can facilitate a smoother transition toward normal voiding, especially when combined with standard urotherapy. To better assess therapeutic outcomes and the hypothesis, we considered a minimum follow-up duration of 6 months, aligning with existing literature that reports BTX-A's neuromodulatory effects persisting between 6 and 9 months [35].

In our cohort study, we observed that a single BTX-A injection provided sustained clinical improvement for many patients, in terms of voiding diaries, urinary symptoms, and UTI episodes. The pre-operative and post-operative ultrasound measurements indicate a reducing HUN effect in the post-operative outcomes. It is noteworthy that the significant reduction in post-operative PVR in our study, similar to previously conducted ones, indicates less probability of incomplete urination and a reduction in the occurrence of unfavorable outcomes such as UTI and urinary incontinence in the mentioned group of pediatric patients with DV [7,9,10,12].

Moreover, the post-operative clinical outcomes in our study demonstrate a significant improvement in the DVSS index compared to the pre-operative scoring index (Fig. 3b). This finding is comparable to the significant decrease in the post-operative Lower Urinary Tract Symptom Score (LUTSS) questionnaire index observed in the Austin et al. study [9]. Align with the DVSS index, 7-point Likert-type satisfaction scale used in this cohort study indicated significantly greater patient-reported voiding satisfaction post-operatively compared to pre-operative evaluations. This scale was utilized as a proxy for treatment-related quality-of-life assessment, supported by its convergent validity with PedsQL. Among the limited studies evaluating quality-of-life outcomes following BTX-A injection in pediatric patients, the intervention method was predominantly intra-vesical [36,37]. Although the BTX injection technique in our study differs from those employed in existing literature, similar to the findings reported by Al Edwan et al., our cohort demonstrated measurable enhancement in post-operative patient-reported voiding satisfaction [36]. However, current literature reflects heterogeneous application of quality-of-life instruments in studies involving pediatric BTX-A applications [36,37], and single study has specifically addressed pre-operative psychological aspects in children diagnosed with NNDV [9].

In addition, our study findings were similar to previous study regarding the improvement in voiding pattern and other uroflowmetric measurements during post-operative follow-ups [7,9,10,12]. While achieving the near bell-shaped voiding pattern was gradual in follow-ups, MFR and AFR had significant improvements compared to pre-operative measures (Table 1), which were maintained throughout the one-year follow-up. Although 23 cases did not achieve near bell-shaped voiding patterns, there were significant improvements in the post-operative MFR and AFR measurements, which indicate the need for continuing primary therapeutic options, including pelvic floor physiotherapy with biofeedback and medical treatments [14]. The study results indicate that several factors may have combined effect on near-bell shaped voiding patterns, including age and follow-up durations. In addition, individualized characteristics of each child and their family support may lead to further influence on the duration of achieving near bell-shaped voiding patterns and evaluating these two factors were far beyond this study scope. These findings suggest the necessity of continuing primary conventional therapies in NNDV pediatric patients who are candidates for BTX-A injection (i.e., non-responders to first- and second-line therapies and exhibited inappropriate pelvic floor activity during the voiding phase, leading to a fractional voiding pattern), as mentioned in previous studies [9,12,14].

The temporary reduction in pelvic floor hyperactivity creates an opportunity for patients to undergo muscle retraining through urotherapy and pelvic floor biofeedback, reinforcing long-term functional improvements. The rapid symptom improvement in our cases following BTX-A

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injection, especially reduction in constipation, urinary incontinence, and UTI episodes led to enhanced treatment compliance and engagement in standard urotherapy from both patients and caregivers, often eliminating the need for further BTX-A injections. However, in a subset of patients with persistent DV which is often influenced by psychological or behavioral factors may benefit from repeated injections of BTX-A to maintain clinical stability. Notably, in cases where pharmacotherapy or pelvic floor physiotherapy with biofeedback was initiated at 6-month follow-up, BTX-A injection aid in reducing the frequency of these non-invasive interventions, contributing to high overall treatment satisfaction among families.

This study faces three main limitations. Firstly, it was conducted as a single-center study, which may affect its scientific accuracy and generalizability. Secondly, our study was conducted without control groups, and we evaluated the patient's clinical outcomes who may have been concurrently receiving other treatment options in addition to EUS and perineal body BTX-A intervention. Thirdly, the variability in follow-up duration, with final outcomes measured at each individual's last visit. However, to the best of our knowledge this study is one of the computed pediatric studies that evaluate the therapeutic outcomes of EUS and perineal body BTX-A injections in a remarkable number of participants with refractory non-neurogenic DV.

Conclusion

The study demonstrated that EUS and perineal body BTX-A injections would have considerable improvement in the uroflowmetric and ultrasonographic measurements in pediatric patients who are categorized as the refractory NNDV. In addition, there was evidence that indicated the ability of this therapeutic option as an alternate method in the treatment course of refractory NNDV as well as improving the patient's quality of life and decreasing the DV scoring index in the treatment process, which can avoid experiencing recurrent febrile UTI episodes or urinary incontinence without a significant increase in the BTX-A injection complications. Moreover, BTX-A injection may offer therapeutic value both as a complementary intervention alongside specific urotherapy strategies and as a standalone treatment option in selected cases, warranting further investigation into its independent efficacy and role within integrated management frameworks.

Data availability statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the co-corresponding authors upon reasonable request.

Ethical approval

All procedures were performed in accordance with the Tehran University of Medical Sciences' Guidelines and approved by the university's Ethics Committee (IR.TUMS.CHMC.REC.1402.125). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent achieved from parents or legal guardians of all cases.

Author's contribution

AM Kajbafzadeh: Conceptualization, Project administration, Supervision, and Critical review.

P Hekmati: Conceptualization, Project administration, Supervision, and Critical review.

N Mohammadi Ganjaroudi: Data collection, Investigation, Methodology, Graphical design, Data analysis, Writing original draft, Review and editing.

A Hassanpour Dargah: Data collection, Investigation, Review and editing.

M Jaberi: Data collection, Investigation, Review and editing.

MA Siri: Data collection, Investigation, Review and editing.

A Naserghandi: Data collection, Investigation, Review and editing.

S Mozafari: Investigation, Review and editing, and data analysis.

Declaration of generative AI

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

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Competing interests

The authors have no competing interests to declare relevant to this article's content.

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