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Effect of Sodium Nitroprussıde in Patients With Detrussor Overactivity

Detrüsör Aşırı Aktivitesi Olan Hastalarda Sodyum Nitroprussid'in Etkisi

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ABSTRACT

Introduction: Detrusor instability is a common cause of urgency and urge incontinence in neurologically normal patients. Nitric oxide, relaxes the smooth muscles of the detrusor, prostate, and urethra.
Aim: We aimed to explain the therapeutic effects of sodium nitroprusside on detrusor overactivity in patients with detrusor overactivity.
Methods: A total of 21 patients with detrussor overactivity have been enrolled in this research. The patients were divided into 3 groups according to their sodium nitroprusside dosage, as low-dose, medium-dose, and high-dose. Hydrostatic pressure in the bladder was measured and at the same time, intra-abdominal pressure was measured with a catheter inserted into the rectum. Cystometry results have been evaluated in terms of sensation (first sensation, first desire, strong desire), detrusor compliance, maximal detrusor pressure, maximal cystometric bladder capacity and instability index parameters.
Results: No statistical significance has been achieved between nitroprusside groups in terms of first sensation, first desire, and strong desire values ($p>0.05$). When the patients' maximal detrusor pressure, maximal cystometric bladder capacity and compliance values were interpreted, no significant difference was found between the isotonic and SNP groups and their doses. There was no significant difference between the groups in the duration of contractions. Additionally, no difference has been observed between the groups in the blood pressure values of the patients at the end of the study compared to the baseline.
Conclusion: This study indicated that SNP did not exhibit any positive or negative effects in individuals with detrussor overactivity. The reason for this could be stated as: first, the urothelium acts as a barrier to the passage of sodium nitroprusside and prevents it from reaching the detrusor and the latter may be due to the lack of effect of sodium nitroprusside on detrusor function.

Keywords: Detrussor Overactivity, Bladder, Sodium Nitroprusside.

ÖZET

Giriş: Detrüsör instabilitesi nörolojik açıdan normal hastalarda sıkışma ve sıkışma inkontinansının yaygın bir nedenidir. Nitrik oksit, detrüsör, prostat ve üretranın düz kaslarını gevşetmektedir.
Amaç: Detrüsör aşırı aktivitesi olan hastalarda sodyum nitroprussidin detrüsör aşırı aktivitesi üzerindeki terapötik etkilerini açıklamayı amaçladık.
Yöntem: Bu araştırmaya detrüsör aşırı aktivitesi olan toplam 21 hasta dahil edildi. Hastalar sodyum nitroprussid dozajına göre düşük doz, orta doz ve yüksek doz olmak üzere 3 gruba ayrıldı. Mesanedeki hidrostatik basınç ölçüldü ve aynı zamanda rektuma yerleştirilen kateter ile karın içi basınç da ölçüldü. Sistometri sonuçları duyu (ilk duyum, ilk istek, güçlü istek), detrusor kompliyansı, maksimum detrüsör basıncı, maksimum sistometrik mesane kapasitesi ve instabilite indeksi parametreleri açısından değerlendirildi.
Bulgular: Nitroprussid grupları arasında ilk duyum, ilk istek ve güçlü istek değerleri açısından istatistiksel olarak anlamlı bir fark bulunamadı ($p>0,05$). Hastaların maksimum detrüsör basıncı, maksimum sistometrik mesane kapasitesi ve kompliyans değerleri yorumlandığında izotonik ve SNP grupları ve dozları arasında anlamlı fark bulunamadı. Kasılma süreleri açısından gruplar arasında anlamlı fark yoktu. Ayrıca hastaların çalışma sonundaki kan basıncı değerlerinde başlangıca göre gruplar arasında bir fark gözlenmedi.
Sonuç: Bu çalışma SNP'nin detrüsör aşırı aktivitesi olan bireylerde herhangi bir olumlu ya da olumsuz etki göstermediğini göstermiştir. Bunun nedeni; öncelikle ürotelyumun sodyum nitroprussidin geçişine engel olarak etki ederek detrüsöre ulaşmasını engellemesi, ikincisi ise sodyum nitroprussidin detrüsör fonksiyonu üzerine etkisinin olmamasından kaynaklanabilir.

Anahtar Kelimeler: Detrüsör Aşırı Aktivitesi, Mesane, Sodyum Nitroprussid.

INTRODUCTION

Detrusor overactivity (instability), can be defined as the involuntary and abnormal activity of the bladder muscle other than the micturition process, is one of the problems that bother physicians in urology and

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gynecology practice due to the clinical manifestations (1). Detrusor instability is a common cause of urgency and urge incontinence in neurologically normal patients. Urinary incontinence (stress incontinence, urgency incontinence, incontinence after prostatectomy), enuresis point and other micturition disorders, when undiagnosed or overlooked, jeopardizes the results of medical and surgical treatment (2).

The etiology is unknown but it has been associated with congenital causes, aging, stress incontinence, and bladder outlet obstruction. Diagnosis relies on a urologic history and physical examination, a voiding diary, and a urodynamic evaluation. Detrusor overactivity is a diagnosis that can only be made after urodynamic evaluation (3). The clinician or the surgeon should avoid from directly including patients with urgency and urge incontinence symptoms in this group. Treatment is primarily pharmacologic and behavioral, with surgical options being reserved for selected patients (4).

It is stated that approximately 22% of female incontinence patients with symptoms suggestive of detrusor overacitivity have true stress incontinence. On the other hand, detrusor instability was found in 11 – 16% of women who only had symptoms suggestive of stress incontinence (5). Bladder instability at very young ages is physiological as the complete development of cortical inhibition of the voiding reflex varies from 2 to 3 years of age. The success of toilet training may depend on the maturation of the relevant neurological pathways and the voluntary control of this reflex (6).

Nitric Oxide (NO) has been identified as the main inhibitory transporter that causes smooth muscle relaxation during urinary excretion. NO – mediated smooth muscle relaxation is due to increased production of intracellular cyclic guanosine monophosphate (cGMP). It has been shown that NO level decreases with age (7). It is thought that when NO decreases, contractility occurs in the smooth muscles in the prostate stroma and capsule and in the muscles in the bladder tissue, and storage and excretion symptoms increase due to the subsequent obstruction (8).

The inability to completely inhibit detrusor contractions with anti-cholinergic agents suggested the presence of non-adrenergic non-cholinergic (NANC) receptors. Those that can be stimulated by ATP (adenosine triphosphate) of NANC receptors are called purinergic. ATP release is mediated by mechanical stress and electrical stimulation and plays an important role in initiating detrusor contraction and micturition. The cholinergic system ensures the continuation of contraction and micturition (7 – 9).

Another neurotransmitter that plays a role in the stimulation of NANC receptors is nitric oxide (NO), which has been defined as the main inhibitor that relaxes the urethral smooth muscles during urination. Mechanical signals that occur as the bladder begins to fill lead to the activation of CB2 (Cannabinoid receptors) receptors and transient receptor potential channels (TRP channels) in sensory neurons. This leads to the release of nitric oxide, which eventually relaxes the smooth muscles of the detrusor, prostate, and urethra (8, 10, 11).

Sodium Nitroprusside (SNP) is a potent releaser of NO. SNP exerts its action at the vascular system by augmented vascular capacitance and coronary vasodilatation. SNP is a rapid-acting intravenous vasodilator that has been widely used clinically in hypertensive crises for decades (11).

In this study we aimed to elucidate the treatment effects of sodium nitroprusside in detrusor overactivity in an open label, controlled, prospective study.

METHOD

A total of 21 patients with detrussor overactivity who have admitted to Kartal Research & Training Hospital Urology Outpatient Clinic have been enrolled in this research. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution and informed consent has been obtained from all participants.

International Continence Society (ICS) criteria were taken into account in the urodynamic evaluation (12). After the patient had voided before the procedure, a 7F two-way urodynamic catheter was placed into the bladder transurethrally under sterile conditions. Residual urine measurement was performed.

After the balloon rectal catheter was placed to measure the intraabdominal pressure, all the catheters were connected to the urodynamic device. Surface electrodes placed in the perianal region were used for electromyography (EMG) measurement in the anal sphincter working in combination with the external sphincter. While the catheter application was active, the measuring system was calibrated. The patients were also followed- up for blood pressure values.

The patients were divided into 3 groups according to their sodium nitroprusside dosage, as low-dose, medium-dose, and high-dose. During the cystometric study, the patients were in the supine position and the procedure was started by administering saline at a rate of 30 - 75 ml per minute through one lumen of the perfusion catheter at room temperature. Hydrostatic pressure in the bladder was measured and at the same time, intra-abdominal pressure was measured with a catheter inserted into the rectum. The device automatically recorded the difference between the 2 pressures, that is, the actual detrusor pressure, together with the other pressures on the monitor. During the procedure, the patient coughed frequently and the catheter in the bladder was moved, while the patient was listened to the sound of water to cause detrusor overactivity. Afterwards, the bladder was completely emptied and the cystometric examination was repeated with 5% dextrose solution prepared using sodium hydroxide. In the low-dose group, 120 milligrams in 500 c 5% dextrose, in the SNP medium-dose group 360 milligrams in 5% dextrose at 500 c, in the snp and high-dose group, it was repeated. In 500 c 5% dextrose, 1080 milligrams SNP was used.

Patients who had detrusor hyperreflexia, urethral stricture, bladder stones, bladder tumors, and patients who had undergone bladder and urethral surgery were not included in the study. Systemic and urological examinations of all patients were performed in detail.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data, mean and standard deviation for continuous data were given as descriptive values. Mann Whitney U – Test and Wilcoxon Test was utilized for comparisons. The results were considered statistically significant when the p value was less than 0.05

RESULTS

A total of 21 patients have been enrolled within the scope of this study. The mean age of patients (n=7, male/female = 4/3) in the low dosage group was 53±8 years, 60±12 years in the medium dosage group (n=7, male/female = 5/2), and 45±7 years in the high dosage group (n=7, male/female = 3/4). The etiology of all patients was idiopathic and the demographic findings were denoted in Table 1. There was no statistically significant difference between the groups in terms of mean age.

Table 1. Baseline Demographics of the Patients

	n	Female/male	Median Age (years)	Etiology
Low Dose SNP	7	3/4	53±8	idiopathic
Medium Dose SNP	7	2/5	60±12	İdiopathic
High Dose SNP	7	4/3	45±7	idiopathic
Total	21	9/12	51±5	

SNP: Sodium Nitroprusside

Cystometry results have been evaluated in terms of sensation (first sensation, first desire, strong desire), detrusor compliance, maximal detrusor pressure, maximal cystometric bladder capacity and instability index parameters. No statistical significance has been achieved between the nitroprusside groups in terms of first sensation, first desire, and strong desire values (p>0.05) (Table 2).

Table 2. Patients' sensation values

	isotonic			SNP		
Groups	First Sensation	First Desire	Strong Desire	First Sensation	First Desire	Strong Desire
Low Dose SNP	153.5±3.5	249.0±7.0	361.0±67.0	162.5±205	319.0±87.0	357.5±114.5
Medium Dose SNP	112.7±24.6	196.0±21.4	334.0±35.1	115.7±9.9.	187.0±23.7	224.7±28.6
High Dose SNP	95.0±13.6	159.2±12.7	279.9±36.8	111.8±23.7	184.8±29.1	294.0±37.0

SNP: Sodium Nitroprusside

When the patients' maximal detrusor pressure, maximal cystometric bladder capacity and compliance values were interpreted, no significant difference was found between the isotonic and SNP groups and their doses.

The number, duration and amplitude values of uninhibited contractions detected in the cystometric evaluation of the patients were examined. There was no significant difference between groups in the duration of contractions. Likewise, the number, amplitude and activity index scores were similar between the groups (Table 3).

Table 3. Evaluation of number, duration, amplitude and overactivity of uninhibited contractions

	isotonic				SNP			
Groups	n	Time (minutes)	Amplitude (cmH_20)	Overactivity index	n	Time (minutes)	Amplitude (cmH_20)	Overactivity index
Low Dose SNP	5.3±0.9	7.8±3.3	372.3±126.7	2.2±1.5	5.7±1.8	3.8±1.7	240.7±25.8	1.6±0.8
Medium Dose SNP	13.3±4.9	15.6±1.5	985.3±435.6	4.2±2.0	6.7±3.4	6.2±3.1	605.0±311.6	2.8±1.4
High Dose SNP	2.4±0.6	11.6±7.9	156.6±68.2	0.5±0.2	1.8±0.7	2.6±1.9	143.8±58.8	0.4±0.2

SNP: Sodium Nitroprusside

Additionally, no difference has been observed between the groups in the blood pressure values of the patients at the end of the study compared to the baseline.

DISCUSSION

Smooth and striated muscles of the bladder, urethra and external urethral sphincter coordinate the storage and periodical release of urine. The hemodynamics principle acts quite logical according to the pressure level of the bladder thus reflecting it to the kidneys even stopping the glomerular filtration and damaging renal cells due to increased capillary pressure. A healthy urine flow requires simultaneous contraction of the smooth muscle and a rapid increase in intravesical pressure empty the bladder. Smooth muscles of the urethra and bladder display characteristic patterns of spontaneous contractile activity in the filling phase of micturition cycle (13). Urinary symptoms of frequency and urgency are common with problem of bladder over activity. In absence of any pathological factors, bladder over activity may be with or without urge incontinence. Voiding dysfunction results either from failure to store urine, or from failure to empty (14).

Although urodynamics is the only investigation to explore detrusor underactivity (DU) or detrusor overactivity (DO), this method has some limitations, such as being invasive and time consuming (14).

Since detrusor overactivity mimics stress incontinence very well, corrective surgery in stress incontinence cases without revealing whether there is instability with cystometric examination is doomed to fail. In fact, the micturition complaints of the patients increase even more after the operation (13). Detrusor overactivity is also a factor in enuresis nocturna cases. Therefore, in the treatment of enuresis, bladder education, which is one of the general treatment principles of detrusor instability, can be used in cases with overactive bladder. In addition, it is among the literature information that urgency incontinence, which is quite common after protatectomy in urology clinics, is a result of detrusor overactivity due to infravesical obstruction (12). However, most of the cases with this type of complaint can mimic real incontinence and do not show any residual adenoma or external sphygmolar lesion in the clinical evaluation. As a matter of fact comprehensive treatment apprach is necessary for treatment success (13, 14).

Detrusor contraction and relaxation is mediated via different neurotransmitters hence nitric oxide (NO) is one of them (15). Three different isoforms of nitric oxide synthase (NOS) have been identified as: endothelial NOS (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS). In previous literature it was elaborated that NOS isoforms demonstrated variable effects on detrussor functions. Selective inhibition of iNOS was related to a decrease in bladder capacity (15), where an increase in nNOS and eNOS expression was detected in DO associated with BOO (16) and a decrease in eNOS expression has

been observed in BOO (17). Conversely, the inhibition of all 3 NOS isoforms has been reported to increase nonvoiding con¬tractions and to decrease the bladder capacity (18), there by worsening the bladder function. Other studies have shown that anticholinergics that can decrease the frequency of urination could increase nNOS expression and decrease iNOS expression in the bladder wall. The results suggested that nNOS is related to detrusor contractility, however these cannot be applied to actual clini¬cal practice as the role of NO in bladder dysfunction has been mainly investigated only in a few animal studies (19).

Bladder filling causes a minimal increase in intravesical pressure, followed by inhibition of parasympathetic activity, secondary to a stimulus in sympathetic activity, NO synthesis and bladder relaxation, This process is conducted via desensitization of calcium-sensitive contractile elements in the detrusor muscle via protein kinase G (20).

NOS enzyme was demonstrated in the lower urinary tract and nitric oxide was observed as a neurotransmitter in non-adrenergic non-cholinergic (NANC) receptors. Therefore, nitric oxide can play a relaxing role in the lower urinary tract, as in many smooth muscles. Andersonn et al. (21) reported that NOS-deficiency could lead to hypertrophy of bladder smooth muscle and decreased detrusor relaxation. Ozawa et al. (22) published that bladder instability might occur due to irritation and could be suppressed by NO. Hennenberg et al. (2014) elaborated that mechanical signals that occur as the bladder begins to fill lead to the activation of CB2 (Cannabinoid receptors) receptors and transient receptor potential channels (TRP channels) in sensory neurons. This leads to the release of nitric oxide, which eventually relaxes the smooth muscles of the detrusor, prostate, and urethra (23).

It is interesting to note that most of these studies have been to investigate the function of NO on smooth muscle. On the other han done should bear in mind that, it is possible that striated muscle may also take part along with urethral smooth muscle in NO – dependent neurogenic relaxation in different species (24).

Both animal and human studies suggest that nitric oxide mediates urethral sphincter relaxation. Nitric-oxide-synthase staining neurons have been identified in very high density in the urethral sphincters of a variety of animals and in human beings. Relaxation of the urethral sphincter is abolished by inhibitors of nitric oxide synthase and enhanced by nitric oxide donors (25 – 27).

In this research we have utilized sodium nitroprusside, an available nitric oxide donor to deliver nitric oxide to the detrussor muscle. The irregular detrussor contractions mostly originate from the exit region of bladder thus indicating the increased afferent activity could could be a result of nitric oxide insufficiency (28, 29).

CONCLUSIONS

The outcomes of our study indicated that SNP did not exhibit any positive or negative effects in individuals with detrussor overactivity. The reason for this could be stated as: first, the urothelium acts as a barrier to the passage of sodium nitroprusside and prevents it from reaching the detrusor and the latter may be due to the lack of effect of sodium nitroprusside on detrusor function. As a matter of the fact that no changes were detected in the arterial blood pressure of the patients suggesting that sodium nitroprusside did not enter the systemic circulation.

DESCRIPTIONS

No financial support.

No conflict of interest.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. Informed consent was obtained from all participants.

Note: This study was produced from a thesis.

REFERENCES

1. Ruffion A, Castro-Diaz D, Patel H, et al. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. Neuroepidemiology. 2013;41(3-4):146-55. doi: 10.1159/000353274.

2. Panicker JN. Neurogenic Bladder: Epidemiology, Diagnosis, and Management. Semin Neurol. 2020 Oct;40(5):569-579. doi: 10.1055/s-0040-1713876.

3. Panicker JN. Neurogenic Bladder: Epidemiology, Diagnosis, and Management. Semin Neurol. 2020 Oct;40(5):569-579. doi: 10.1055/s-0040-1713876.

4. Blomquist JL, Muñoz A, Carroll M, Handa VL. Association of delivery mode with pelvic floor disorders after childbirth. JAMA. 2018 Dec 18;320(23):2438-2447. doi: 10.1001/jama.2018.18315.

5. Clark CB, Ragam R, Das AK, Shenot PJ. Management of neurogenic detrusor overactivity. Can J Urol. 2021 Aug;28(S2):33-37.

6. Tapia CI, Khalaf K, Berenson K, Globe D, Chancellor M, Carr LK. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurologic condition: a systematic review. Health Qual Life Outcomes. 2013 Jan 31;11:13. doi: 10.1186/1477-7525-11-13.

7. Andersson KE, Garcia Pascual A, Persson K, Forman A, Tøttrup A. Electrically-induced, nerve-mediated relaxation of rabbit urethra involves nitric oxide. J Urol. 1992;147:253 9.

8. Andersson KE, Persson K. Nitric oxide synthase and the lower urinary tract:possible implications for physiology and pathophysiology. Scand J Urol Nephrol. 1995;175:43-53.

9. Kedia GT, Uckert S, Jonas U, Kuczyk MA, Burchardt M. The nitric oxide pathway in the human prostate: clinical implications in men with lower urinary tract symptoms. World J Urol 2008;26:603-9.

10. Bloch W, Klotz T, Loch C, Schmidt G, Engelmann U, Addicks K. Distribution of nitric oxide synthase implies a regulation of circulation, smooth muscle tone, and secretory function in the human prostate by nitric oxide. Prostate 1997;15:33:1-8.

11. Peyronnet B, Mironska E, Chapple C, et al. A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment. Eur Urol. 2019 Jun;75(6):988-1000. doi: 10.1016/j.eururo.2019.02.038.

12. Drake MJ, Doumouchtsis SK, Hashim H, Gammie A. Fundamentals of urodynamic practice, based on International Continence Society good urodynamic practices recommendations. Neurourol Urodyn. 2018 Aug;37(S6):S50-S60. doi: 10.1002/nau.23773.

13. Gajewski JB, Gammie A, Speich J, et al. Are there different patterns of detrusor overactivity which are clinically relevant? ICI-RS 2018. Neurourol Urodyn. 2019 Dec;38 Suppl 5:S40-S45. doi: 10.1002/nau.23964.

14. Ptashnyk T, Hatzinger M, Zeller FL, Kirschner-Hermanns R. Overactive bladder syndrome - focus onto detrusor overactivity. Scand J Urol. 2021 Feb;55(1):56-60. doi: 10.1080/21681805.2020.1839130.

15. Sellers D, Chess-Williams R, Michel MC. Modulation of lower urinary tract smooth muscle contraction and relaxation by the urothelium. Naunyn Schmiedebergs Arch Pharmacol 2018;391:675-94.

16. Kim HS, Kim JC, Choo MS. Effects of nitric oxide synthases on detrusor overactivity after removal of bladder outlet obstruction in rats. Urol Int 2008;81:107-12.

17. Yuan X, Wu S, Lin T, He D, Li X, Liu S, et al. Role of nitric oxide synthase in bladder pathologic remodeling and dysfunction resulting from partial outlet obstruction. Urology 2011;77:1008.e1-8.

18. Pereira ML, D'ancona CA, Rojas-Moscoso JA, Ramos AC Filho, Monica FZ, Antunes E. Effects of nitric oxide inhibitors in mice with bladder outlet obstruction. Int Braz J Urol 2017;43:356-66.

19. Kim SO, Choi D, Song SH, Ahn KY, Kwon D, Park K. Effect of detrusor overactivity on the expression of aquaporins and nitric oxide synthase in rat urinary bladder following bladder outlet obstruction. Can Urol Assoc J 2013;7:E268-74

20. Canda A.E, Cross C.R, Chapple C.R. Pharmacology of the Lower Urinary Tract and Management of Overactive Bladder. J Turkish-German Gynecol Assoc, 2006:7;146-57.

21. Anderson KE, Persson K. Nitricoxide synthase and the lower urinary tract: Possible implications for physiology and pathophysiology. Scand J Urol Nephrol 1995;175: 45-51

22. Ozawa H, Chancellor MB, Jung SY. Effect of intra vesical nitricoxide therapy on cyclophosphamide induced cytitis. J Urol 1999;162:2211-16.

23. Hennenberg M, Stief CG, Gratzke C. Pharmacology of the lower urinary tract. Indian J Urol 2014;30:181–188.

24. Robinson D, Cardozo L. Managing overactive bladder. Climacteric. 2019 Jun;22(3):250-256. doi: 10.1080/13697137.2018.1552254.

25. Wang HS, Cahill D, Panagides J, Nelson CP, Wu HT, Estrada C. Pattern recognition algorithm to identify detrusor overactivity on urodynamics. Neurourol Urodyn. 2021 Jan;40(1):428-434. doi: 10.1002/nau.24578.

26. Mancini V, Tarcan T, Serati M, Wyndaele M, Carrieri G, Abrams P. Is coexistent overactive-underactive bladder (with or without detrusor overactivity and underactivity) a real clinical syndrome? ICI-RS 2019. Neurourol Urodyn. 2020 Jul;39 Suppl 3:S50-S59. doi: 10.1002/nau.24311.

27. Chen LC, Kuo HC. Pathophysiology of refractory overactive bladder. Low Urin Tract Symptoms. 2019 Sep;11(4):177-181. doi: 10.1111/luts.12262.

28. Karakus S, Musicki B, Navati MS, Friedman JM, Davies KP, Burnett AL. NO-Releasing Nanoparticles Ameliorate Detrusor Overactivity in Transgenic Sickle Cell Mice via Restored NO/ROCK Signaling. J Pharmacol Exp Ther. 2020 May;373(2):214-219. doi: 10.1124/jpet.119.264697.

29. Loloi J, Babar M, Davies KP, Suadicani SO. Nanotechnology as a tool to advance research and treatment of non-oncologic urogenital diseases. Ther Adv Urol. 2022 Jul 26;14:17562872221109023. doi: 10.1177/17562872221109023.