Can Sexual Intercourse Be an Alternative Therapy for Distal Ureteral Stones? A Prospective, Randomized, Controlled Study

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OBJECTIVE To investigate the effect of sexual intercourse on spontaneous passage of distal ureteral stones.

MATERIAL AND METHODS The patients were randomly divided into 3 groups with random number table envelope method. Patients in group 1 were asked to have sexual intercourse at least 3-4 times a week. Patients in group 2 were administered tamsulosin 0.4 mg/d. Patients in group 3 received standard medical therapy alone and acted as the controls. The expulsion rate was controlled after 2 and 4 weeks. Differences in the expulsion rate between groups were compared with the chi-square test for 3×2 tables. $P < .05$ was considered as statistically significant.

RESULTS The mean stone size was 4.7 ± 0.8 mm in group 1, 5 ± 1 mm group 2, and 4.9 ± 0.8 mm group 3 ($P = .4$). Two weeks later, 26 of 31 patients (83.9%) in the sexual intercourse group, and 10 of 21 patients (47.6%) in tamsulosin group passed their stones, whereas 8 of 23 patients (34.8%) in the control group passed their stones ($P = .001$). The mean stone expulsion time was 10 ± 5.8 days in group 1, 16.6 ± 8.5 days in group 2, and 18 ± 5.5 days in group 3 ($P = .0001$).

CONCLUSION Our results have indicated that patients who have distal ureteral stones ≤ 6 mm and a sexual partner may be advised to have sexual intercourse 3-4 times a week to increase the probability of spontaneous passage of the stones. UROLOGY 86: 19–24, 2015. © 2015 Elsevier Inc.

The agents used in the medical expulsive therapy (MET) of ureteral stones act either by inhibiting calcium channel pumps or by blocking α-1 receptors to decrease the smooth muscle tone.[1,2] Meta-analyses showed that patients on MET pass their stones with less colic attacks compared with the ones who did not have this therapy.[1,2] Tamsulosin is one of the most frequently used α-blockers.[3-5] MET is based on the high α-receptor density in the distal ureter. It was shown that α-1 adrenergic receptor blockage decreased contractions and peristaltic frequency in the distal ureter and inhibited basal tone.[6]

Pharmacologic studies performed 20 years ago showed nitrinergic fibers in human and porcine intravesical ureters.[7,8] A nitric oxide (NO) donor, 3-morpholinosydnonimine, caused relaxation in human ureter. In addition, both endogenously released and exogenously administered NO caused relaxation in porcine intravesical ureter.[8,9] The main neurotransmitter that plays a role in erection and during sexual intercourse is NO. However, the type of neural stimulus that is transmitted to ureter during sexual intercourse is not clearly known. The aim of this study was to investigate whether sexual intercourse had an effect on passage of distal ureteral stones.

MATERIAL AND METHODS

This study was performed between September 2013 and October 2014 after obtaining the approval of our hospital's local ethics committee. Literate male patients who admitted to our clinic with renal colic and inguinal pain or lumbar pain, as well as the patients who were referred to our clinic with those symptoms and diagnosed with distal ureteral stones, were included in the study. All patients gave their written informed consents. The patients were randomly divided into 3 groups with the random number table envelope method. The names of the groups were written on small papers with the same size, they were folded, put in an envelope, and drawn by the patients. All patients included in the study had radiopaque distal ureteral stones. The ones aged <18 years, who did not have an active sexual partner, who described erectile dysfunction, had diabetes mellitus, had a stone >6 mm, had a stone located in the mid-ureter or proximal ureter

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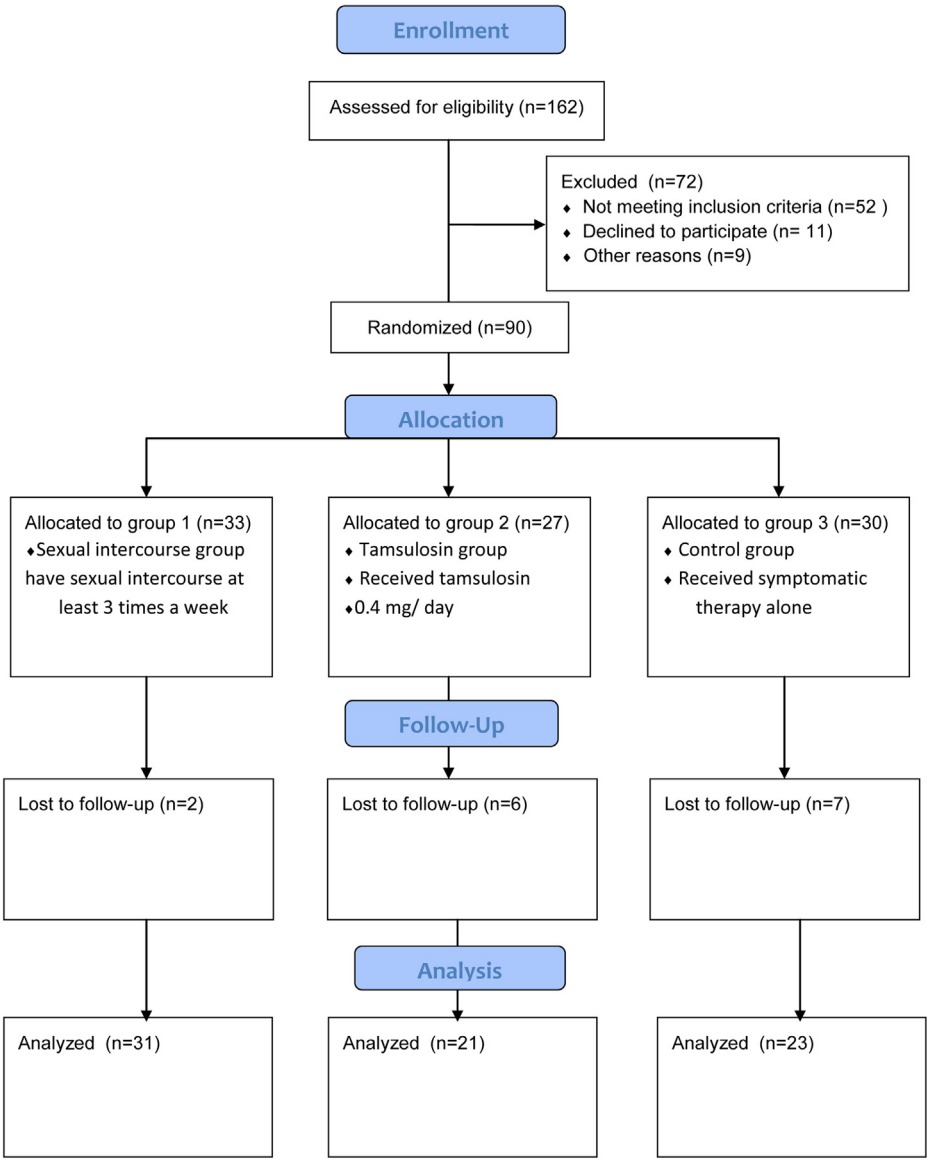

Figure 1. CONSORT flow diagram. (Color version available online.)

(above iliac vessels), had nonopaque or multiple stones, had urinary tract infection, had severe hydronephrosis, had a history of stone passage or previous endoscopic or open ureteral surgery, had high serum creatinine levels, and the ones who previously used α-1 adrenergic receptor or calcium canal blockers were excluded.

The age of the patient and the size and side of the stone were noted. The size of the stone was determined by measuring the longest diameter of the stone on plain urinary tract x-ray. All patients were prescribed hyoscine-*N*-butyl bromide (Buscopan, Boehringer Ingelheim) 10 mg twice daily orally and 75 mg diclofenac injections, when needed. In addition, all patients were advised to drink 2 L of water at minimum. The patients in the sexual intercourse group (group 1) were told to have sexual intercourse at least 3 times a week. Tamsulosin group (group 2) was given 0.4 mg/d tamsulosin. Group 3 received symptomatic therapy alone and acted as the control group. Sexual intercourse and masturbation were prohibited in groups 2 and 3 throughout the treatment period. On follow-up, all patients filled in questionnaires considering the number of the pain episodes, the need for analgesic injections, and the number of sexual intercourses.

All patients had plain urinary tract x-ray, urinary tract ultrasonography, noncontrast computerized tomography, and urinalysis before study, and their urea and creatinine levels were measured. Patients were followed-up with plain urinary tract x-ray, ultrasonography, and urinalysis every week until the passage of the stone or for a maximum period of 4 weeks. Passage of the stone was determined by declaration of the patient and loss of the radiopaque appearance of the stone on plain urinary tract x-ray. On follow-up, plain urinary tract r-ray images of the patients were seen and analyzed by an urologist (MFK) blinded to the group of the patients.

Before patient recruitment, the sample size required for each arm was calculated on the basis of previous studies that predicted stone expulsion rate as 90% and 65% with and without tamsulosin therapy, respectively, with a difference of 25%.[10-12] Because stone expulsion rate in the sexual intercourse group has not been studied before, we estimated the sample size similar

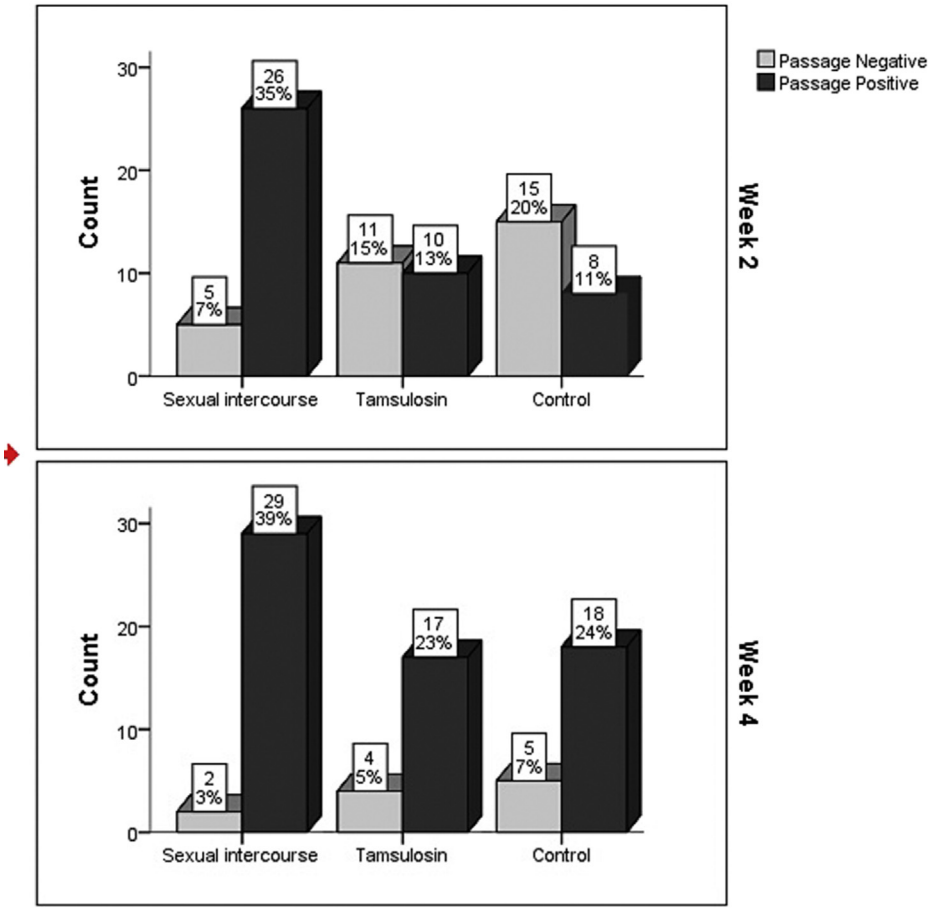

Figure 2. Expulsion rate after 2 and 4 weeks of groups. (Color version available online.)

to tamsulosin and control groups. Thirty-three patients in each arm were estimated to provide 80% power with a type II statistical error of 20% and a type I statistical error of 5%. In addition, we applied post hoc power analysis after the comparison of the sexual intercourse, tamsulosin, and control groups. The power was calculated as 80% between tamsulosin and sexual intercourse groups and as 97.3% between control and sexual intercourse groups. A post hoc power analysis was performed to assess the power of the hypotheses test to detect differences in "passage" rates between the 3 groups.

The data analyses were performed with PASW 18 (SPSS, IBM, Chicago, IL) software. Kolmogorov-Smirnov and P-P plot tests were used to verify the normality of the distribution of continuous variables. The results were reported as means ± standard deviations, or in situations in which the distributions were skewed, as the median (minimum-maximum). Categorical variables were given as percentages. All statistical tests were 2-tailed. Differences in the success rates among the groups were compared with the chi-square test for 3 × 2 tables. Continuous variables were analyzed with the Kruskal-Wallis test. $P < .05$ was considered as statistically significant.

RESULTS

A total of 90 male patients were randomly divided into 3 groups with the random number table envelope method. Fifteen patients were excluded because of loss to follow-up. Thirty-one patients in group 1, 21 patients in group 2, and 23 patients in group 3 completed the study (Fig. 1). The mean ages of the patients in groups 1, 2, and 3 were 34.9 ± 10.6, 39.3 ± 8.1, and 34 ± 10.4 years, respectively ($P = .07$). The mean stone size was 4.7 ± 0.8 mm in group 1, 5 ± 1 mm in group 2, and 4.9 ± 0.8 mm in group 3 ($P = .4$). The difference among the groups was not statistically significant. The sides of the stones were similar in all groups ($P = .31$).

Two weeks later, 26 of 31 patients (83.9%) in the sexual intercourse group, 10 of 21 patients (47.6%) in the tamsulosin group, and 8 of 23 (34.8%) patients in the control group passed their stones ($P = .001$). At the end of the fourth week, 29 of 31 patients (93.5%) in the sexual intercourse group, 17 of 21 patients (81%) in tamsulosin group, and 18 of 23 patients (78.3%) in the control group passed their stones ($P = .23$; Fig. 2).

The mean stone expulsion time was 10 ± 5.8 days in group 1, 16.6 ± 8.5 days in group 2, and 18 ± 5.5 days in group 3 ($P = .0001$). The analgesic needs in groups 1, 2, and 3 were found as 1.04 ± 0.5, 1.8 ± 1.1 and 2.3 ± 1.04 times, respectively ($P = .001$; Table 1). The patients that could not pass their stones at the end of 4 weeks (2 patients in group 1, 4 patients in group 2, and 5 patients in group 3) were treated successfully with ureterorenoscopic lithotripsy. None of the patients had treatment-related adverse effects in the follow-up period. Post hoc power

Table 1. Overall results

	Group 1	Group 2	Group 3	*P* Value
Expulsion rate (%) after 2 wk	83.9	47.6	34.8	.001*
Expulsion rate (%) after 4 wk	93.5	81	78.3	.23
Expulsion time (d), mean ± SD	10 ± 5.8	16.6 ± 8.5	18 ± 5.5	.0001*
Need for analgesic (times, injection), mean ± SD	1.04 ± 0.5	1.8 ± 1.1	2.3 ± 1.04	.001*

* Statistically significant.

analysis was performed and the power of our test in analyzing the difference in "passage" rates among the 3 groups was found as 98.0%.

COMMENT

Ureteral peristalsis is a myogenic process that regulates urine transport, and it is controlled by autonomic nervous system.[13] Distal ureter is rich in α-1 adrenergic receptors.[13] Alpha 1 adrenergic receptor blockage was shown to decrease peristaltic frequency and basal ureteral tone.[14] On the basis of those data, many studies have shown that distal ureteral stones can be successfully treated with different α-adrenergic receptor blockers.[2,4,5,10] Those findings made MET the first-line treatment in patients who do not need surgery.[15]

NO is a known nonadrenergic, noncholinergic inhibitory neurotransmitter of both central and peripheral neurons.[16,17] Nitrinergic fibers have been shown in human and porcine intravesical ureters about 20 years ago.[7,8] In addition, 3-morpholinosydnonimine, which is an NO donor, caused ureteral relaxation in the human ureter. Studies showed that both endogenously released and exogenously administered NO resulted in relaxation of porcine intravesical ureter.[8,9] However, no studies investigated the role and effect of nonadrenergic, noncholinergic system on passage of ureteral stones before. As known, ureter is supplied by renal plexus, superior hypogastric plexus, and inferior hypogastric plexus. Its sympathetic supply originates from T11-L1 and parasympathetic supply comes from S2-4. Hypogastric and pelvic plexuses have rich synaptic interconnections. Stimulation of pelvic plexus and cavernous nerves causes erection, whereas stimulation of sympathetic system results in detumescence. The main neurotransmitter that plays a role in erection and during sexual intercourse is NO. NO is released from the endothelium and directly from the nitrergic nerves. Stimulation of cavernous nerve activates nitrergic nerve fibers and causes release of NO from the nerve endings, resulting in penile smooth muscle relaxation.[18] However, the type of neural stimulus that is transmitted to the ureter during sexual intercourse is not clearly known. We hypothesized that the distal ureter could be stimulated by nonadrenergic, noncholinergic (nitrergic) nerve endings during sexual intercourse. If we suppose that the main neurotransmitter that increases in body and particularly in penile cavernous tissue is NO during erection, this hypothesis seems logical. Indeed, higher stone expulsion rate in the sexual intercourse group after 2 weeks when compared to tamsulosin and control groups supports our hypothesis.

The probability of spontaneous passage of distal ureteral stones <5 mm is 71%-98%, and observation is recommended in those patients initially. Spontaneous passage chance of distal ureteral stones sized >5 mm is 25%-51%.[19] In addition, 95% of the stones ≤4 mm in size may pass spontaneously within 40 days.[20] Conservative treatment has been recommended for 4 weeks in distal ureteral stones, as the complication risk increases at the end of this period.[21,22] This is why we included stones ≤6 mm that have a high probability of passage in our study and determined the follow-up period as 4 weeks. Although the spontaneous stone expulsion rate was higher in group 1 at the end of 4 weeks, the difference among the groups was not statistically significant. If we suppose that spontaneous expulsion probability is high for the stones of this size, our results seem feasible. The chance of spontaneous expulsion increases with increased fluid intake.[23] We recommended at least 2 L of fluid intake to all patients included in our study.

In this study, we investigated the effect of having at least 3 sexual intercourses a week on stone expulsion rate and found that median expulsion time was significantly shorter in sexual intercourse group when compared to other 2 groups ($P = .0001$). In our opinion, sexual intercourse increases the probability of spontaneous stone expulsion and shortens expulsion time in distal ureteral stones.

A number of studies on MET showed that tamsulosin decreased renal colic episodes and the need for diclofenac injections.[5,12,21,22] Similarly, our study showed that the need for injections was less in the sexual intercourse group when compared to the control group ($P = .001$). Those results support the hypothesis that frequency of ureteral peristalsis and basal tone of ureter decrease in those patients.

CONCLUSION

Today, MET is recommended as the first-line treatment in ureteral stones that do not necessitate surgery. In our opinion, if the patient has a sexual partner, having sexual intercourse at least 3 times a week may be beneficial to increase the probability of spontaneous stone expulsion in patients with distal ureteral stones ≤6 mm in size.

References

1. Seitz C, Liatsikos E, Porpiglia F, et al. Medical therapy to facilitate the passage of stones: what is the evidence? *Eur Urol.* 2009;56:455-471.

2. Liatsikos EN, Katsakiori PF, Assimakopoulos K, et al. Doxazosin for the management of distal-ureteral stones. *J Endourol*. 2007;21:538-541.
3. Hollingsworth JM, Rogers MA, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet*. 2006;368:1171-1179.
4. Lojanapiwat B, Kochakarn W, Suparatchatpan N, Lertwuttichaikul K. Effectiveness of low-dose and standard-dose tamsulosin in the treatment of distal ureteric stones: a randomized controlled study. *J Int Med Res*. 2008;36:529-536.
5. Al-Ansari A, Al-Naimi A, Alobaidy A, et al. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. *Urology*. 2010;75:4-7.
6. Obara K, Takeda M, Shimura H, et al. Alpha-1 adrenoreceptor subtypes in the human ureter. Characterization by RT-PCR and in situ hybridization. *J Urol*. 1996;155(suppl):472A; abstract:646.
7. Smet PJ, Edyvane KA, Jonavicius J, Marshall VR. Colocalization of nitric oxide synthase with vasoactive intestinal peptide, neuropeptide Y, and tyrosine hydroxylase in nerves supplying the human ureter. *J Urol*. 1994;152:1292-1296.
8. Hernandez M, Prieto D, Orensanz LM, et al. Nitric oxide is involved in the non-adrenergic, non-cholinergic inhibitory neurotransmission of the pig intravesical ureter. *Neurosci Lett*. 1995;186:33-36.
9. Stief CG, Taher A, Meyer M, et al. A possible role of nitric oxide (NO) in the relaxation of renal pelvis and ureter. *J Urol*. 1993;149:492A.
10. De Sio M, Autorino R, Di Lorenzo G, et al. Medical expulsive treatment of distal ureteral stones using tamsulosin: a single-center experience. *J Endourol*. 2006;20:12-16.
11. Porpiglia F, Ghignone G, Fioric C, et al. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol*. 2004;172:568-571.
12. Hermanns T, Sauermann P, Rufibach K, et al. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomized, double-blind, placebo-controlled trial. *Eur Urol*. 2009;56:407-412.
13. Weis RM. Physiology and pharmacology of the renal pelvis and ureter. In Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell's Urology*, Vol. 3, 9th ed. pp. 1891-1921. Philadelphia, Pennsylvania.
14. Richarson CD, Donatucci CF, Page SO, et al. Pharmacology of tamsulosin: saturation binding isotherms and competition analysis using cloned alpha 1-adrenergic receptors subtypes. *Prostate*. 1997;33:55-59.
15. Bensalah K, Pearle M, Lotan Y. Cost-effectiveness of medical expulsive therapy using alpha blockers for the treatment of distal ureteral Stones. *Eur Urol*. 2008;53:411-419.
16. Bredt DS, Hwang PM, Snyder SH. Localization of nitric oxide synthase indicating a neural role for nitric oxide. *Nature*. 1990;347:768-806.
17. Bredt DS, Snyder SH. Nitric oxide: a novel neuronal messenger. *Neuron*. 1992;8:8-11.
18. Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. In Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell's Urology*, Vol. 1, 9th ed. pp. 718-749. Philadelphia, Pennsylvania.
19. Segura JW, Preminger GM, Assimos DG, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. *J Urol*. 1997;158:1915-1921.
20. Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. *J Urol*. 1999;162:688-690; discussion 690-691.
21. Yilmaz E, Batislam E, Basar MM, et al. The comparison and efficacy of 3 different alpha-1 adrenergic blockers for distal ureteral stones. *J Urol*. 2005;173:2010-2012.
22. Agrawal M, Gupta M, Gupta A, et al. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral Stones. *Urology*. 2009;73:706-709.
23. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol*. 2003;170:2202-2205.

EDITORIAL COMMENT

The prevalence of urolithiasis in the United States has steadily increased over the past several years.[1] The morbidity caused by stone disease is similarly significant, as 30% of patients diagnosed with stone disease report loss of work associated with the diagnosis.[2] Furthermore, when medical expulsive therapy is unsuccessful, procedural intervention often presents a significant financial burden to both the patient and practice.[3] As such, and in light of health care reform with greater focus on financial responsibility, the potential therapeutic effect of lifestyle modifications such as diet and exercise remains an important consideration.[4] In the accompanying article, Doluoglu et al[5] hypothesize that sexual intercourse may facilitate the passage of distal ureteral stones via a nitric oxide—mediated pathway. Specifically, the authors propose that nitric oxide released in high concentrations in cavernous tissue during erection and intercourse may be released in the distal ureter as well, triggering relaxation of ureteral muscle. Indeed, previous studies have identified nitrergic fibers in the distal ureter and demonstrated a relaxant effect of NO on ureteral smooth muscle.[6,7]

The authors describe their observations and analysis from a prospective study of 90 men with distal ureteral stones. In the study, men randomized to sexual intercourse at least 3 times weekly demonstrated shorter time to stone passage and lesser need for analgesia than men receiving either conventional alpha-blocker therapy or symptomatic treatment alone. Although certainly interesting, many of the usual caveats apply. First, the level of compliance is difficult to confirm in such a study, particularly among control groups asked to abstain from sexual activity throughout. Similarly, it is notable that loss to follow-up was only 6% in the intercourse group compared to 23% in the alpha-blocker and control arms. Although one could consider that such a disparity in follow-up more likely favors a beneficial effect of intercourse, similar high compliance among all groups would provide a more complete picture. Finally, although the exposure tested in the analysis was sexual intercourse, the proposed mechanism would indicate that erection may be the more physiologically relevant factor.

Despite its limitations, this study has great value in again bringing to light the potential role of the nitric oxide pathway in treatment of stone disease. As thoughtful investigation tends to do, the study raises additional questions which may pave the way toward more effective therapies. Namely, is there a role for phosphodiesterase inhibitors in the medical treatment of stone disease? Preliminary investigations have shown promise in some settings,[8,9] but additional data are necessary to better define if, when, and how treatment of the nitric oxide pathway can be effectively incorporated into clinical practice.

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References

1. Scales CD Jr, Smith AC, Hanley JM, et al. Prevalence of kidney stones in the United States. *Eur Urol*. 2012;62:160.

2. Pearle MS, Calhoun EA, Curhan GC, et al. Urologic diseases in America project: urolithiasis. *J Urol*. 2005;173:848.
3. Tosoian JJ, Ludwig W, Sopko N, et al. The effect of repair costs on the profitability of a ureteroscopy program. *J Endourol*. 2015;29:406-409.
4. Hyams ES, Matlaga BR. Cost-effectiveness treatment strategies for stone disease for the practicing urologist. *Urol Clin North Am*. 2013; 40:129.
5. Doluoglu OG, Demirbas A, Kilinc MF, et al. Can sexual intercourse be an alternative therapy for distal ureteral stones? A prospective, randomized, controlled study. *Urology*. 2015;86:19-24.
6. Yucel S, Baskin LS. Neuroanatomy of the ureterovesical junction: clinical implications. *J Urol*. 2003;170:945.
7. Iselin CE, Ny L, Larsson B, et al. The nitric oxide synthase/nitric oxide and heme oxygenase/carbon monoxide pathways in the human ureter. *Eur Urol*. 1998;33:214.
8. Jayant K, Agrawal R, Agrawal S. Tamsulosin versus tamsulosin plus tadalafil as medical expulsive therapy for lower ureteric stones: a randomized controlled trial. *Int J Urol*. 2014;21:1012.
9. Kumar S, Jayant K, Agrawal MM, et al. Role of tamsulosin, tadalafil, and silodosin as the medical expulsive therapy in lower ureteric stone: a randomized trial (a pilot study). *Urology*. 2015;85:59.

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