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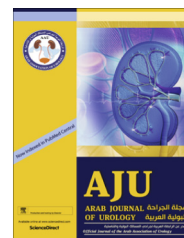
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STONES/ENDOUROLOGY
ORIGINAL ARTICLE

Sildenafil citrate as a medical expulsive therapy for distal ureteric stones: A randomised double-blind placebo-controlled study



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KEYWORDS

Ureter;
Stone;
Sildenafil citrate;
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Medical expulsive therapy

ABBREVIATIONS

cAMP, cyclic adenosine monophosphate;
DUS, distal ureteric stones;
ESWL, extracorporeal shockwave lithotripsy;
cGMP, cyclic guano-

Abstract Objective: To study the effect of sildenafil citrate on spontaneous passage of distal ureteric stones (DUS).

Patients and methods: This was a randomised double-blinded placebo-controlled study of 100 patients with DUS. Inclusion criteria were: male, age 18–65 years, normal renal function, and a single radiopaque unilateral DUS of 5–10 mm. Patients were randomly allocated into two equal groups, one that received placebo and the other that received 50 mg sildenafil citrate once daily. Both investigators and patients were masked to the type of treatment. Patients self-administered the medication until spontaneous passage of the DUS. In patients where there was uncontrolled pain, fever, an increase in serum creatinine of >1.8 mg/dL, progressive hydronephrosis or no further progress after 4 weeks, a decision was taken for further treatment.

Results: In all, 47 and 49 patients were available for analysis in both the placebo and sildenafil citrate groups; respectively. Both groups were comparable for age and stone characteristics. Spontaneous expulsion occurred in 19 of 47 patients (40.4%) in the placebo group and in 33 of 49 (67.3%) in the sildenafil citrate group ($P = 0.014$). The mean time to stone expulsion was significantly shorter in the sildenafil citrate group ($P < 0.001$). A multivariable Cox proportional hazards model showed that

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sine monophosphate;
KUB, plain abdominal
radiograph of the kid-
neys, ureters and blad-
der;
MET, medical expul-
sive therapy;
NCCT, noncontrast
computed tomogra-
phy;
NO, nitric oxide;
PDE5, phosphodies-
terase 5;
RCT, randomised
controlled trial

receiving sildenafil citrate was the only independent factor that had a significant impact on stone passage with a hazard ratio of 2.7 (95% confidence interval 1.5–4.8; $P < 0.001$).

Conclusion: Sildenafil citrate enhances spontaneous passage of 5–10 mm DUS.

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Introduction

Urolithiasis is one of the most common urological diseases and represents a major clinical and economic burden. The risk of stone disease ranges between 5% and 12% worldwide, with males twice as likely to be affected as females [1]. Ureteric stones account for ≈20% of all urinary tract stones and >70% of the ureteric stones are located in the lower third of the ureter, i.e. distal ureteric stones (DUS) [2].

There are multiple management options for ureteric stones, such as conservative, medical expulsive therapy (MET), extracorporeal shockwave lithotripsy (ESWL), and endourological and open surgical procedures. MET includes various drugs, such as α -adrenergic blockers [3], anti-inflammatory drugs [4], and calcium channel blockers [5,6], which have a relaxant effect on the ureteric smooth musculature [7].

Relaxation of the smooth muscles of the lower ureter plays a major role in MET. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important intracellular second messengers mediating cellular responses. An increase in cAMP and cGMP triggers a signal transduction cascade, which leads to smooth muscle relaxation [8]. Cyclic nucleotides (cAMP and cGMP) are degraded by the enzyme phosphodiesterase 5 (PDE5). Thus, using PDE5 inhibitors can play a role in the relaxation of the smooth muscle of the ureter by preservation of cAMP and cGMP. In studies conducted to evaluate three PDE5 inhibitors (sildenafil, vardenafil, and tadalafil) it was found that PDE5 inhibitors could reverse the tension of isolated human ureteric smooth muscles via cGMP-mediated pathways [9].

To investigate whether a PDE5 inhibitor could be used for MET, we conducted a randomised double-blind placebo-controlled study of 100 patients with DUS (5–10 mm), treated using either placebo or PDE5 inhibitor (sildenafil citrate). To the best of our knowledge, the present study is the first on this topic.

Patients and methods

The study was conducted between June 2014 to September 2015 and included patients with DUS presenting at our outpatient clinic. Inclusion criteria were; male, age 18–65 years, normal renal function, and a single radiopaque unilateral DUS located below the common iliac vessels, as assessed by noncontrast CT (NCCT). The stone size ranged between 5 and 10 mm.

Exclusion criteria were: patients with solitary kidney, bilateral ureteric stones, UTI, recurrent fever, serum creatinine of >1.8 mg/dL, multiple, radiolucent stones of >10 mm, patients receiving nitrates, history of open ureteric surgery, and patients who refused an informed consent.

A valid informed consent was obtained from all patients and the study was approved by the Local Ethics Committee. The study was also approved and registered in Clinical Trial. gov (ID number NCT02345980).

The study was designed as a randomised double-blind placebo-controlled trial to compare sildenafil citrate vs placebo as a MET for DUS of 5–10 mm.

The sample size was calculated assuming type I statistical error of 5% and type II statistical error of 20% to obtain a power of 80%. Based on previous studies estimating stone expulsion to be 90% and 65% in patients with and without other MET; respectively a sample size of 42 in each group was accrued. We choose a sample size of 50 patients in each arm to allow for an attrition rate of 19%.

In all, 142 consecutive patients were eligible for the study. Of these, 42 were excluded for various reasons, leaving 100 patients who were randomly assigned into two equal groups to receive either placebo or sildenafil citrate (Fig. 1). Randomisation was carried out using a computer-generated random table, at a ratio of 1:1.

Either placebo or 50 mg sildenafil citrate (Viagra, Pfizer Inc., New York, NY, USA) was given daily. The placebo was prepared to be the same colour, weight, and shape as the effective drug. These medications were

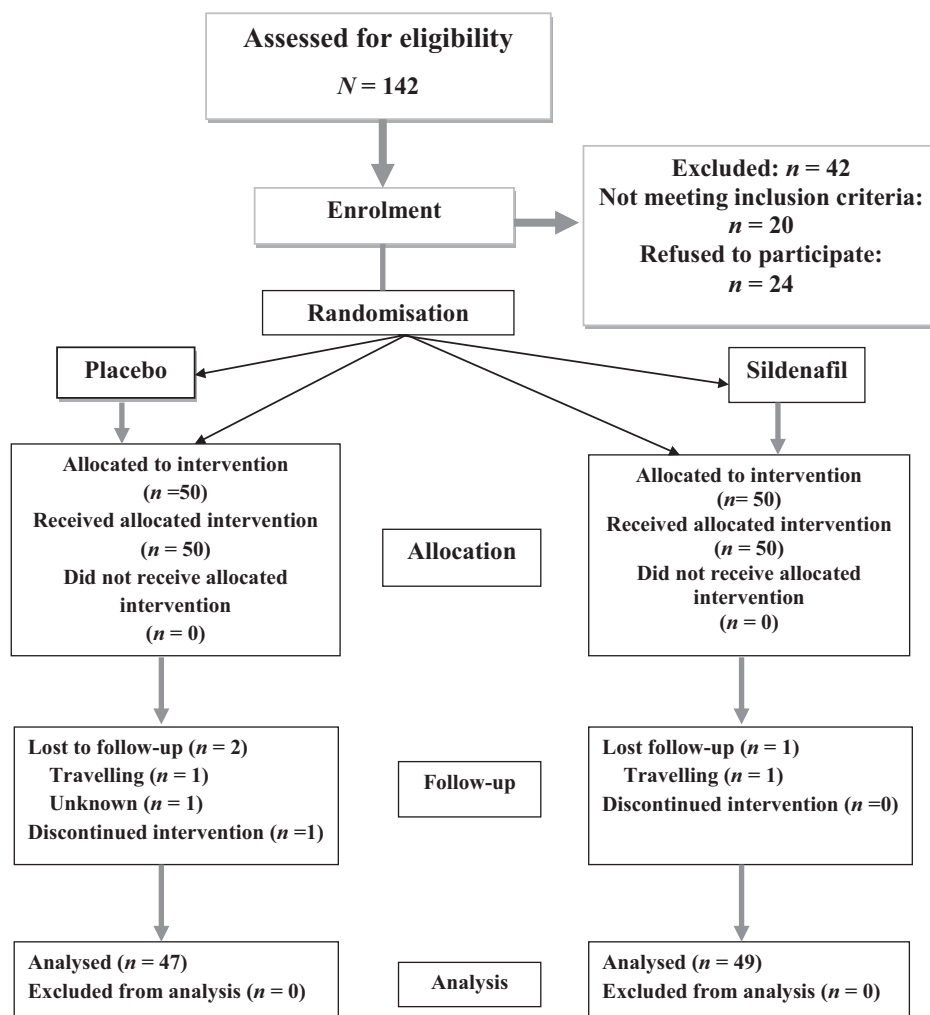


Figure 1 Consolidated Standards Of Reporting Trials (CONSORT) flow chart.

supplied by an independent source that had no further involvement in the trial. Investigators and patients were masked to the type of treatment received throughout the study. Randomisation data were kept strictly confidential by a third party not included in the study. A dose of 75 mg diclofenac sodium was given in cases of severe renal colic. Patients self-administered the medication until spontaneous passage of the stone or a decision was made for further treatment in patients with no further progress after 4 weeks, uncontrolled pain, fever, increase in serum creatinine (>1.8 mg/dL) or progressive hydronephrosis.

Patients were followed-up with plain abdominal radiograph of the kidneys, ureters and bladder (KUB), renal ultrasonography, and urine analysis every week until passage of the stone or cessation of MET. The patients were advised to filter their urine to detect the stones and the expulsion of the stone was confirmed by KUB or NCCT.

The time and frequency of stone passage and the possible side-effects of the medications were recorded in both groups of patients.

Data were stored and analysed using SPSS 8.0 statistical software package (SPSS Inc., Chicago, IL, USA). Nominal data were presented as percentages, while continuous data were presented as the mean (SD). The chi-square test was used for analysis of categorical data and the Student's *t*-test for analysis of continuous data. A receiver operating characteristic (ROC) curve was used to determine the threshold value of age and stone size that may affect the frequency of stone passage. A Kaplan–Meier curve was constructed for recording the rate of spontaneous stone passage. The log-rank test was used for comparison between the stone expulsion rates of both groups. Hazard ratios (HR), 95% CIs and multivariable Cox proportional hazards model were used to determine the independent predictors of stone passage in patients of both groups. A $P < 0.05$ was considered to indicate statistical significance.

Results

One patient in the placebo group discontinued the treatment and two patients were lost during follow-up, thus

Table 1 Baseline data.

Variable	Placebo group	Sildenafil citrate group	<i>P</i>
Number of patients	47	49	
Mean (SD)			
Age, years	45.3 (10.83)	45.8 (13.72)	0.71
Larger stone diameter, mm	8.5 (1.10)	8.1 (1.02)	0.039
Smaller stone diameter, mm	6.6 (1.13)	6.5 (1.12)	0.789
Stone side, <i>n</i>			0.1
Right	20	30	
Left	27	19	
Stone location, <i>n</i>			0.72
Pelvic	37	41	
Intramural	10	8	

47 patients with follow-up data were available for analysis. One patient in the sildenafil citrate group was lost during follow-up; consequently 49 patients were available for analysis (Fig. 1).

Both groups were comparable for age and stone characteristics (Table 1). There was spontaneous expulsion in 19 of 47 (40.4%) in the placebo group and 33 of 49 (67.3%) in the sildenafil citrate group; a difference significantly in favour of the sildenafil citrate group ($P = 0.014$; Table 2).

The mean time to stone expulsion was significantly shorter in the sildenafil citrate group [mean (SD) 11.5 (4.8) days] compared with the placebo group [mean (SD) 17.2 (5.0) days; $P < 0.001$; Table 2].

The Kaplan–Meier curve showed that the stone passage rate was significantly higher in the sildenafil citrate group vs the placebo group ($P < 0.001$; Fig. 2).

The mean pain scale score was comparable between the placebo and the sildenafil citrate groups ($P = 0.07$; Table 2).

Studying the factors predicting stone passage with univariable analyses showed that both a patient age of >40 years and receiving sildenafil citrate were the only factors that significantly affected stone passage (Table 3).

Table 2 Summary of the results.

Variable	Placebo group <i>N</i> = 47	Sildenafil citrate group <i>N</i> = 49	<i>P</i>
Stone expulsion rate, <i>n</i> (%)	19 (40.4)	33 (67.3)	0.014
Mean (SD)			
Time to stone expulsion, days	17.2 (5.0)	11.5 (4.8)	<0.001
Pain scale score (0–10)	6 (1.6)	5.4 (1.5)	0.077
Side-effects, <i>n</i>			–
Headache	0	2	

Both age and receiving sildenafil citrate were studied using multivariable Cox proportional hazards model and showed that receiving sildenafil citrate was the only independent factor that had a significant impact on stone passage with a HR of 2.7 (95% CI 1.5–4.8; $P < 0.001$; Table 4).

In the sildenafil citrate group, only two patients reported the side-effect of headache, which was treated with paracetamol. For the 44 patients in both groups who failed to pass the DUS within 4 weeks or who discontinued MET because of persistent pain, fever, progressive hydronephrosis or an increase in serum creatinine, further management comprised ESWL in 17 and ureteroscopy in 27.

Discussion

MET is one of the treatment approaches for DUS. α -Blockers [3], calcium channels blockers [5] and corticosteroids [4] are used as MET drugs. Decreased ureteric peristalsis, relaxation of the ureteric smooth musculature, and a reduction in ureteric inflammation are the basis for the usage of these drugs. Moreover, it has been shown that α -blockers decrease basal ureteric tone [10], therefore decreasing the tonic contractions of the ureter over the stone and helping its downward expulsion.

α -Blockers are the most frequently used MET by urologists and different types are used based on the subtype of α -receptor. Tamsulosin [11], alfuzosin [12], terazosin [13] and silodosin [14] are the most frequently used α -blockers in the literature. Tamsulosin has been widely studied in the context of MET for patients with DUS of <10 mm. It has been shown that tamsulosin increases stone expulsion rates, decreases pain, reduces mean time to stone expulsion, and decreases analgesic usage when compared with placebo [6,11].

Based on the same principle, we speculated that PDE5 inhibitors could be used for MET. Taher et al. [15] reported the presence of PDE isoenzymes 1, 2, 4 and 5 in cytosolic supernatants prepared from human ureteric tissue. Smooth muscle tone in the lower urinary tract is controlled by various adrenergic, cholinergic, and non-adrenergic non-cholinergic neurotransmitters released from nerve terminals and endogenous factors from vascular endothelial sources. Kühn et al. [16] then confirmed the relaxing properties of inhibitors of PDE4 and PDE5 on isolated human ureteric smooth musculature, and showed that these effects were due to an elevation in intracellular levels of cAMP or cGMP. Later, PDE5 was shown to play a central role in relaxant responses of lower urinary tract tissue mediated by nitric oxide (NO) and cGMP pathways.

In a recent RCT, Doluoglu et al. [17] compared three groups of patients with DUS of ≤ 6 mm for the frequency of spontaneous passage. Patients in the first group were asked to have sexual intercourse at least

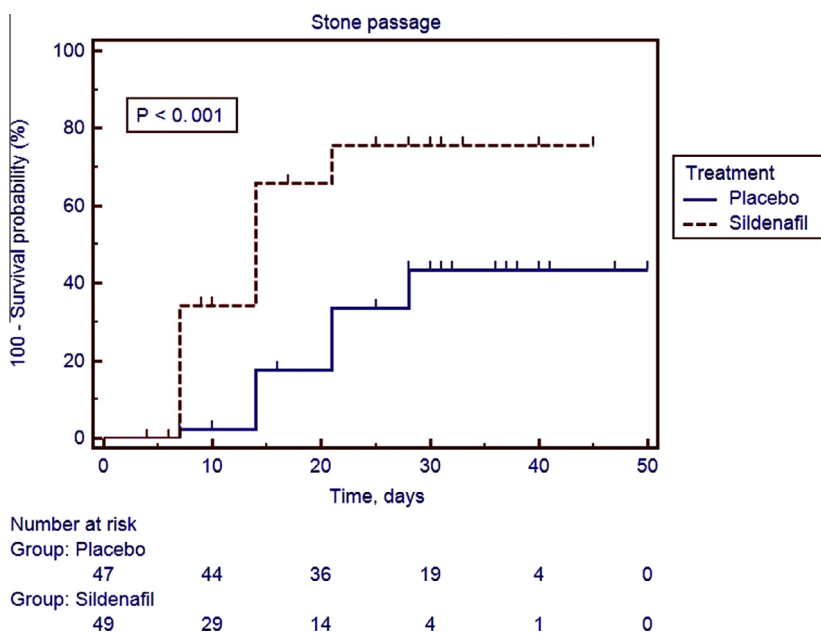


Figure 2 Kaplan–Meier curve comparing the rate of spontaneous passage of ureteric stones in both groups.

Table 3 The stone passage probabilities for patients with stones at the pelvic ureter in the study groups.

	Stone passage probabilities				<i>P</i> ^{**}
	7-Day	14-Day	21-Day	28-Day	
Age, years [*]					0.03
≤40	0.15	0.24	0.37	0.44	
>40	0.19	0.51	0.63	0.67	
Stone size ^{*#} , mm ²					0.1
≤38	0.22	0.48	0.62	0.67	
>38	0.143	0.34	0.46	0.51	
Stone location					0.4
Pelvic	–	0.25	0.375	0.5	
Intramural	0.19	0.43	0.56	0.6	
Treatment					<0.001
Placebo	0.02	0.17	0.33	0.43	
Sildenafil citrate	0.34	0.659	0.75	0.75	

* Threshold values were determined using a ROC curve.

** *P* values calculated using the log-rank test.

Stone size was calculated using the formula: $0.785 \times \text{length}_{\text{max}} \times \text{width}_{\text{max}}$.

Table 4 Multivariate Cox proportional hazards model for independent predictors of stone passage in patients treated with sildenafil citrate or placebo.

Potential predictor	HR (95% CI)	<i>P</i>
Age, years		
≤40	Referent	
>40	1.6 (0.908–3.095)	0.1
Treatment		
Placebo	Referent	
Sildenafil citrate	2.7 (1.553–4.862)	<0.001

3–4 times/week. Patients in the second group received tamsulosin 0.4 mg/day, and those in the third group were considered as controls and received standard medical therapy alone. The authors concluded that sexual intercourse 3–4 times/week significantly increased the probability of spontaneous stone passage. The authors postulated that release of NO, which is the main chemical mediator of penile erection, could be the mechanism of increase of spontaneous passage of ureteric stones. Thus, we hypothesise that the use of sildenafil citrate in the present study enhances release of NO, which in

turn induces relaxation of the distal ureter, and thus increases spontaneous passage of ureteric stones.

A limitation of the present study is the absence of assessment of the impact of sildenafil citrate on the frequency of sexual intercourse of the study population. Therefore, we cannot define the exact mechanism of action of sildenafil citrate, whether it is due to an increase in sexual intercourse or due to direct effects on the musculature of the distal part of the ureter. Moreover, the type of neural stimulus that is delivered to the distal ureter during sexual intercourse still needs to be clearly defined.

To best of our knowledge, this is the first RCT evaluating the effect of a PDE5 inhibitor (sildenafil) as a MET. Our present results show that sildenafil citrate had a stone expulsion rate comparable with the results of tamsulosin in this context [11,13,18,19].

In our present RCT, sildenafil citrate significantly improved spontaneous stone expulsion compared with placebo. There were no serious complications in the patients on sildenafil citrate during the study period and only two patients in the sildenafil citrate reported the side-effect of headache, which was treated with analgesic. On multivariable analysis, receiving sildenafil citrate was the only independent variable that sustained statistical significance for stone expulsion frequency.

Additional studies with more patients are invited to consolidate the results of the present study. Further investigation into the types of neurotransmitters active in the distal ureter are needed, as knowing the exact types of these transmitters will open a new horizon for MET.

In conclusion, in the present randomised double-blind placebo-controlled study, a PDE5 inhibitor (sildenafil citrate) was a safe and effective MET for DUS of 5–10 mm.

Conflict of interest

None of the authors have a conflict of interest

Source of Funding

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