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ORIGINAL ARTICLE

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

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Ureter;
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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 kidneys, ureters and bladder;
MET, medical expulsive therapy;
NCCT, noncontrast computed tomography;
NO, nitric oxide;
PDE5, phosphodiesterase 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.

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