

# Recent advances in management of ureteral calculi

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## Abstract

The management of patients with urinary tract stone disease has changed dramatically over recent years, with current treatment modalities focused on their minimal invasiveness. In this article we will discuss the recent advances in the field of urolithiasis management, with a focus on medical expulsive therapy, extra-corporeal shockwave lithotripsy and ureteroscopy.

## Introduction and context

Urinary tract stone disease is common; in Europe and in the USA the lifetime risk of developing a stone is between 5 and 12%, more often affecting men than women. The peak incidence is between the ages of 20 and 50 years. Unfortunately, within 5 years of their first bout of renal colic, 50% of patients will have stone recurrence. Not all renal tract calculi need active intervention as distal ureteric calculi of  $\leq 5$  mm in size have a spontaneous passage rate of 71-98%.

Stone size and location are important when considering conservative management, and analgesia is essential for such patients, as the passage of a calculus is associated with severe pain. Non-steroidal anti-inflammatory drugs are commonly used for this, however, patients placed on 'watchful waiting' may benefit from adjuvant treatment in the form of medical expulsive therapy (MET).

This article briefly reviews some of the current issues in the management of ureteric calculi, including MET, extra-corporeal shockwave lithotripsy and ureteroscopy. Some of the latest developments, including the use of isoproterenol and the application of robotics to flexible ureterorenoscopy, are also discussed.

## Recent advances

### Medical expulsive therapy

In recent years there has been a growing trend in administering medication (in addition to analgesia) to

patients with distal ureteric calculi in order to help with expulsion of a calculus. There have been many trials demonstrating the efficacy of such an approach, highlighted below.

### Alpha adrenoceptor antagonists

Tamsulosin, alfuzocin and terazocin have all been used in MET. The rationale behind the use of  $\alpha 1$ -antagonists in MET has been that they are capable of decreasing the resting tone of the ureter and interfering with ureteric contractions, thereby decreasing the frequency of peristaltic contractions. Several studies have demonstrated that alpha blockers expedite stone passage, decrease pain, and hence, reduce analgesic requirements [1].

A recent study by Sigala *et al.* [2] looked at gene and protein expression of alpha adrenoceptors in the proximal, middle and distal ureters. They demonstrated that  $\alpha 1$ -d mRNA was the most common overall (and is expressed in all portions of the ureter), and that  $\alpha 1$ -mRNA was found in greater abundance in the distal ureter than more proximally.

Tamsulosin has been the most commonly studied alpha blocker in MET and has equal affinity for  $\alpha 1$ -a and  $\alpha 1$ -d. Cervenàkov *et al.* [3] were one of the first to carry out a double blind randomised trial using tamsulosin. In their series the rate of expulsion was 80.4% in the tamsulosin group versus 62.8% with standard therapy without tamsulosin. Since this study, the Italian authors

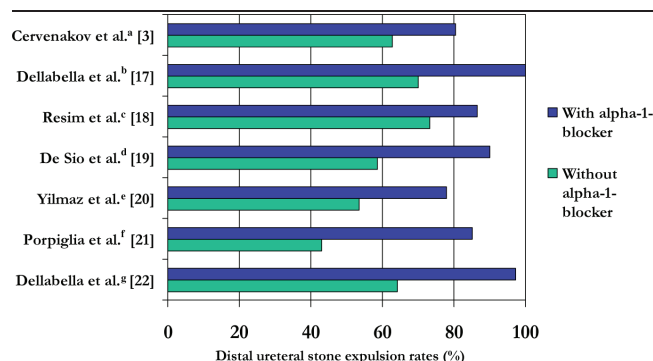
Dellabella and Porpiglia have been two key researchers in this field. Dellabella *et al.* [4] showed the effectiveness of tamsulosin in improving overall stone expulsion rates whilst reducing the patient's analgesic requirements and risk of readmission to hospital, particularly when combined with a corticosteroid (which also reduced the time to expulsion). More recently, Porpiglia *et al.* [5] have reported the use of a second 10-day course of tamsulosin for patients who had not yet passed their stone after an initial treatment period of similar length. In this study, a further 80% of patients successfully passed a stone (compared with just under half of patients who passed them spontaneously without additional treatment). Figure 1 shows the effectiveness of alpha blocker MET in seven randomized controlled trials for distal ureteric stones.

Pedro *et al.* [6] performed a double blind randomised trial using alfuzosin. The alfuzosin group demonstrated a reduced time to distal stone expulsion and reduced analgesic requirements but the rate of expulsion was not increased. This may be an indication that alfuzosin is not as effective as the other alpha blockers.

#### Calcium channel blockers

The use of calcium channel antagonists such as nifedipine has also proved useful. Borghi *et al.* [7] carried out a double blind randomised trial involving 86 patients who received methylprednisolone with either

**Figure 1. Effectiveness of MET with alpha-blocker drugs for distal ureteral stones**



The graph shows that spontaneous passage rates vary from 43-73%. These increase from 76-100% with the addition of MET using an alpha-blocker drug, and these improvements are generally statistically significant. <sup>a</sup>P-value not available; <sup>b</sup>P = 0.001; <sup>c</sup>P = 0.196; <sup>d</sup>P = 0.01; <sup>e</sup>the expulsion rate shown here is the mean rate recorded in this study between tamsulosin (79.31%, P = 0.03), terazosin (78.57%, P = 0.03) and doxazosin (75.86%, P = 0.04); <sup>f</sup>P < 0.001; <sup>g</sup>P < 0.000. Taken together, the meta-analysis by Hollingsworth *et al.* [16] demonstrated that patients given medical therapy (with either a calcium channel antagonist or alpha-blocker) had a 65% greater likelihood of stone passage without intervention. MET, medical expulsive therapy.

placebo or nifedipine. The nifedipine cohort had a significantly higher rate of stone passage at 87 versus 65%. Other studies comparing nifedipine against tamsulosin seem to indicate that both drugs are useful, but tamsulosin is more efficacious [1,6].

#### Corticosteroids

Steroids have also been used to aid stone passage. The rationale for this treatment is that it reduces stone-induced oedema and hence allows a calculus to pass. Steroids combined with an alpha blocker proved more efficacious than either a steroid or alpha blocker alone. Porpiglia *et al.* [8] compared tamsulosin; deflazocort; a combination of tamsulosin and deflazocort; and analgesics (taken when required). The groups were comparable in terms of age, sex, and stone size and location. The rate of expulsion for the four groups was 60%, 37.5%, 84.8%, and 33.3%, respectively. Surprisingly, deflazocort on its own was not very efficacious compared to tamsulosin or combination therapy. Patients benefit greatly from combination therapy (84.8% expulsion rate) but if steroids are contraindicated (that is, because of diabetes or history of peptic ulceration) then adjuvant alpha blocker therapy will be of benefit (60% expulsion rate).

MET has been shown to be cost-effective by reducing the number of ureteroscopic procedures that would be required following observation alone. Provided that ureteroscopy is not extremely cheap and MET is not very expensive, or spontaneous stone passage rates are not extremely high (and therefore need neither MET nor ureteroscopy) or extremely low (and therefore require a ureteroscopy whether treated by MET or not), MET is a cost-effective treatment. In the USA, this approach would result in a theoretical \$1,132 cost saving per patient over observation, a saving that is related to the very high cost of ureteroscopy in the USA and the relatively low cost of tamsulosin. In fact, due to the cost differences between the two treatments, if only one ureteroscopy per 100 treated patients is avoided because of MET, then it would still be a cost effective treatment in the USA [9].

#### Extra-corporeal shockwave lithotripsy

Extra-corporeal shockwave lithotripsy has been used for many years and is an effective treatment modality for a select group of patients. It has been shown to be very efficacious for upper ureteric stones of  $\leq 10$  mm in size. Multiple large series have shown stone-free rates of over 80% for proximal ureteric calculi. In a series of 397 patients with an upper ureteric stone, 91% had a calculus diameter of  $\leq 14$  mm and this cohort had an 84.3% stone-free rate at 3 months. However, with increasing

stone diameter the success rate decreases. For the Dornier Compact Delta lithotripter the success rate at 3 months was reported as 96% for calculi  $\leq 10$  mm and 90% for those 11-20 mm in diameter [10].

### Ureteroscopy

Along with ongoing development of safety/working wires and basket design and size, one of the key advances in ureteroscopy relates to the improved image quality itself, with the development of digital ureteroscopes with 'chip in the tip' technology. Such systems can be illuminated by LEDs (light-emitting diodes) in the tip of the scope, and an external light source may not therefore be required. In addition to the remarkable improvement in image quality, such scopes are lighter (there is no need for an external camera to be attached), inherently safer (there is no risk of drape or patient burns from the external light source), and possibly more durable (there are no fragile fibre-optics within the scope since the image is transmitted digitally) [11,12].

It has been suggested that the considerable improvement in image quality over conventional analogue scopes may allow the earliest stages of stone formation to be better appreciated, and hence improve our understanding of the pathogenesis of calcium oxalate stone formation [13].

### Isoproterenol and ureteroscopy

Through its effect on relaxation of ureteric tone, the use of endoluminal isoproterenol in the irrigation fluid has been shown to reduce pelvic pressure compared with saline irrigation without affecting heart rate or mean arterial blood pressure. Significant increases in intra-renal pressure do occur during ureteroscopy (especially during injection of contrast) and these may be associated with complications, including urinary sepsis due to pyelovenous and pyelolymphatic reflux. The reduction of intra-pelvic pressure, without associated cardiovascular side effects, therefore offers a potentially useful safety step in ureteroscopy [14].

### Robotics

Whilst not reported for the treatment of ureteric calculi as yet, the extension of robotics to ureteroscopy deserves a mention. Desai and colleagues [15] have recently described the use of a modified robotic catheter system for ureterorenoscopy that had been originally developed for intra-cardiac applications.

In this feasibility study using a pig model, they were able to inspect 98% of calyces using a steerable guide catheter controlled remotely via a three-dimensional joystick. They reported that the robotic method was 'stable,

easily manoeuvrable, and ergonomically superior' to conventional ureterorenoscopy. Intra-renal therapeutic manoeuvres were also possible, including the complete fragmentation of small stones. They found that the combination of the precise positioning of the catheter tip and its subsequent stability allowed the system to be 'parked' in a calyx for prolonged periods, improving the ability to target small fragments for further fragmentation. However, they identified significant extravasation of irrigation fluid following these procedures, and have subsequently reduced the size of the prototype ureterorenoscope to 7.5 F [15].

### Implications for clinical practice

Although already in widespread use, and supported by the 65% relative increased chance of stone passage compared with non-treatment, MET still requires a well-designed randomized trial to confirm its effectiveness and best practice in the management of ureteric stones. Until then, MET is useful in patients who do not require more urgent intervention, but its 'off-label' use should be emphasized.

The ability to treat large, proximal ureteric stones, with a good chance of being stone-free in one procedure, continues to be the goal of ureteroscopic stone management. The use of isoproterenol, the first report of pharmacological manipulation of the ureter intra-operatively [14], could potentially reduce the risk of septic complications following ureteroscopy; if so, then it may not be long before this strategy is taken up by others, and, if proven to be effective in randomized trials in humans, could become as standard a step in ureteroscopy as the insertion of a safety wire.

Using their robotic system, Desai *et al.* [15] were able to decrease the time required for a complete examination of the kidney down to under a minute; however, the learning curve for this is likely to be greater for those without as much robotic or ureterorenoscopic experience. Further improvements to the method, and details of its use in a clinical setting, will no doubt reach the literature soon, and evidence of wider dissemination of this technique is pending. Inevitably, the cost implications of establishing a robotic ureterorenoscopic programme, relative to the ability of experienced operators to gain access to each calyx, and similarly to 'park' the tip of a conventional flexible ureterorenoscope in the desired calyx for sufficient time to completely treat the stone within, remains to be quantified and will play a significant role in wider acceptance.

### Abbreviations

MET, medical expulsive therapy.

## Competing interests

The authors declare that they have no competing interests.

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