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Medical Expulsive Therapy for Distal Ureteral Stones

Vassilios Tzortzis,[1] *Charalampos Mamoulakis*,[2] *Jorge Rioja*,[2] *Stavros Gravas*,[1] *Martin C. Michel*[3] and *Jean J.M.C.H. de la Rosette*[2]

1 Department of Urology, University of Thessaly School of Medicine, Larissa, Greece
2 Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
3 Department of Pharmacology and Pharmacotherapy, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

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Abstract

Although minimally invasive treatments for ureteral stones are efficacious, they are not free of complications and are associated with high cost. Medical expulsive therapy (MET) has recently emerged as an alternative strategy for the initial management of small distal ureteral stones. A MEDLINE search was undertaken to evaluate all currently available data on efficacy and safety of MET therapy in such patients. The specific mechanism of action on the ureteral smooth muscle and the emerging evidence of the efficacy (defined as

either an increase in expulsion rate or a decrease in time to expulsion) and low-risk profile suggest that α-adrenergic receptor antagonists (α-blockers) and calcium channel antagonists should be the initial medical treatment in patients amenable to conservative therapy. NSAIDs and anticholinergics have not shown efficacy as single agents or in combination with α-blockers or nifedipine. Corticosteroids may provide a small additive effect when combined with either α-blockers or nifedipine.

Technological advances in endoscopic instrumentation and in shock wave machinery have allowed urinary stones to be treated with efficacy and low morbidity using minimally invasive techniques. However, the significant cost and the need for highly specialized equipment and specialist expertise raise the question of whether these treatments are indeed the most attractive therapeutic options.

Alternatively, watchful waiting policies have been proposed in patients with uncomplicated ureteral stones <10 mm, normal renal function and pain that is controllable with oral medications.[1] Observation can avoid invasive procedures but may be associated with pain, uncertainty and anxiety, potential risks to renal function and lost time at work.[2]

The understanding of ureteral pathophysiology associated with urinary stone obstruction and the growing evidence that pharmacotherapy facilitates spontaneous stone passage has led to the wide clinical application of such treatments. Evidence has suggested that relaxing the ureter in the region of the stone and increasing hydrostatic pressure proximal to the stone may help to facilitate ureteral stone passage.[3] Such relaxation can be accomplished with α-adrenergic receptor antagonists (α-blockers) and calcium channel antagonists (or calcium channel blockers; CCB), which work through α_1-adrenergic receptor and L-type calcium channels, respectively, in the ureteral smooth muscle.[4,5]

A MEDLINE search of the English language literature was conducted using as medical subject headings (MESH® keywords) 'medical expulsive treatment', 'calcium channel blockers', 'nifedipine', 'α-adrenergic receptors blockers', 'tamsulosin', 'terazocin', 'doxazocin', 'alfuzosin', 'corticosteroids', 'NSAIDs', 'anticolinergics' and 'ureteral calculi' or 'ureteral lithiasis'. The search criteria included randomized controlled trials (RCTs) and meta-analyses, and revealed 27 relevant references (24 RCTs and 3 meta-analyses) to December 2008.

This review provides a critical assessment of all currently available medical expulsive treatments (METs) for distal ureteral stones, with a particular focus on efficacy (increase in expulsion rate and/or decrease in time to expulsion) and safety data.

1. Urolithiasis

1.1 Epidemiology

The prevalence of urinary tract stones in otherwise healthy adults varies between countries. It seems to be lower in Asia (1–5%) than in Europe (5–9%) and the USA (13%). The highest prevalence is reported for Saudi Arabia (20.1%) and the lowest in Greenland and the coastal areas of Japan.[6] However, numerous reports have suggested an increasing frequency of kidney stone disease in Westernized societies.[7] The annual incidence of stone formation is generally considered to be 1500–2000 cases per million persons.[8]

1.2 Natural History

Although the chemical composition of stones varies widely among different populations, a common denominator is the high risk of stone recurrence.[9] A relapse rate of 50% in 5–10 years and 75% in 20 years has been reported. Features associated with recurrence include a young age of onset, a positive family history, infection stones and those secondary to underlying medical conditions. Thus, urolithiasis is considered a chronic disease with substantial economic consequences and a significant impact on public health.[10]

The likelihood of a stone passing through the ureter is dependent on several factors, including stone dimensions and ureteral conditions. A wide range of spontaneous passage rates have been reported in the literature, from 71% to 98% for distal-ureteral stones <5 mm and from 25% to 53% for those between 5 mm and 10 mm.[11]

In a meta-analysis, Hübner and colleagues[12] reviewed the data from 2704 patients and found that the rate of spontaneous stone passage, irrespective of their position in the ureter, was 38% for those <4 mm compared with 1.2% for those >6 mm. Calculi located in the distal, mid and proximal thirds of the ureter showed a spontaneous passage rate of 45%, 22% and 12%, respectively. Two-thirds of the stones passed spontaneously within 4 weeks after the onset of symptoms. The rate of complications, such as kidney obstruction, sepsis or unremitting colic, was directly related to the duration of symptoms, reaching 20% when symptoms lasted >4 weeks compared with 7% if symptoms were <4 weeks in duration.

A prospective study has provided further evidence that size and location are the two most important factors in predicting stone passage.[2] Stones that are smaller and more distal in location are more likely to pass spontaneously. Interestingly, size has been also reported to be related to stone-passage interval, with right-sided calculi passing earlier. Overall, approximately 95% of ureteral stones of 2–4 mm pass spontaneously. However, the passage may take as long as 40 days.[2]

Finally, according to the recent European Association of Urology and American Urological Association guidelines[1,13] on the management of ureteral stones, 68% of distal ureteral stones ≤5 mm and 45% between 5 mm and 10 mm pass spontaneously, and may only require observation if symptoms can be controlled.

1.3 Physiology of the Ureter

Even though almost a century has passed since the first reports of *in vitro* studies on ureteral function, the controlling mechanisms of ureteral smooth-muscle contractility have yet to be clarified. Today, it is believed that ureteric peristalsis arises from spontaneous depolarization of the pacing cells at the pelvicalyceal junction, which creates a depolarization wave (peristaltic wave) counting down the ureter. Ureteric smooth-muscle cell depolarization results in Ca^{2+} influx from the extracellular space to trigger and maintain spontaneous rhythmic activity of the ureter (co-ordinated peristaltic contraction).[14]

Sympathetic, parasympathetic and non-adrenergic noncholinergic nerve fibres have been found in the epithelial, submucosal, muscular and adventitial layers of the upper urinary tract.[15] However, since ureteral peristalsis can also be observed in the transplanted ureters, the ureteral contractions are believed to be primarily myogenic in origin, with neural innervations having some modulatory influences.[16] In fact, various locally released endogenous substances, including prostaglandins, nitric oxide, local renin-angiotensin system products and endothelins, have been implicated as the modulators of ureteral contractility.[17-19]

2. Medical Expulsive Treatments (METs)

2.1 Rationale for MET

Ureteral calculi induce irritation and stress stimulation, resulting in ureteral spasm, preventing organized antegrade peristalsis and inducing increased, disorganized, uncoordinated (anti)peristalsis, which arrests stone passage. An effective pharmacological agent should ideally inhibit spasm without significantly affecting ureteral peristalsis because the latter is considered to promote stone passage. CCBs and α-blockers mainly produce relaxation of the distal human ureter *in vitro* by reducing ureteric smooth-muscle tone rather than by completely ablating its activity. These drugs may work by preventing the increased, uncoordinated muscular activity seen in renal colic while maintaining peristalsis. This mechanism may facilitate spontaneous urinary stone passage.[20]

In addition to ureteral spasm, oedema is recognized as an important factor arresting ureteral stone passage. The rationale for using corticosteroids or NSAIDs is based on the principle that

the presence of a stone in the ureter creates an inflammatory reaction of the mucosa, which causes various grades of oedema. Use of these drugs can prevent and treat this inflammatory reaction and facilitate stone expulsion.[21]

2.2 Calcium Channel Antagonists

2.2.1 In Vitro Studies

Quite recently, results on measurements of Ca^{2+} signals in the human ureter obtained during phasic contractions and in response to agonists have been reported for the first time.[22] It was found that fast propagating Ca^{2+} waves, dependent on L-type Ca^{2+} channel entry, spread rapidly throughout the muscle bundles, producing regular contractions. L-type Ca^{2+} channels were detected in ureteral smooth-muscle cell membranes, carrying the α_{1C} subunit ($Ca_V1.2$ channel). Drugs that interfere with Ca^{2+} entry (e.g. nifedipine) had profound effects on Ca^{2+} signalling and contractility. Sarcoplasmic reticulum Ca^{2+}-adenosine triphosphatase (SERCA)-2 and SERCA3, inositol 1,4,5-trisphosphate receptor and ryanodine receptor 3 were also detected in the human ureter. However, it was found that sarcoplasmic reticulum calcium stores had little role in modulating contraction. In another study, it has been demonstrated that nifedipine and 5-methyl-urapidil (an α-ARA) produced greater ureteric relaxation than diclofenac in human ureteric strips. It has also been found that the predominant relaxation effect of CCBs and α-blockers is actioned on the distal third rather than the proximal third of the ureter. Conversely, NSAIDs predominately affect the proximal ureter, albeit to a lesser degree.[23]

2.2.2 Clinical Studies

A total of seven clinical trials assessing the potential benefit of MET with CCBs on ureteral stone passage have been published.[24-29] Until now, nifedipine is the only CCB that has been evaluated in this respect. In six studies, which included a total of 598 patients, the efficacy of nifedipine as the main treatment option was evaluated (table I), whereas one study evaluated the same endpoints with nifedipine as an adjuvant after shock wave lithothripsy (SWL).[30]

The results of these aforementioned clinical trials have been the subject of meta-analyses by two independent investigator groups.[31,32] Both meta-analyses excluded trials investigating MET as an adjuvant to non-medical treatments such as SWL. Only RCTs[31] or controlled clinical trials regardless of randomization[32] were included.

Hollingsworth and co-workers[31] included five RCTs studies in their main analysis,[25,26,28,33,34] and conducted a separate sensitivity analysis based on the data of studies with a lack of a 'true' control[24,28,35] to examine the effect of their inclusion on the overall risk ratio (RR). A total of 408 patients were randomized. There were no significant differences between treatment arms of the individual RCTs regarding sex or age. In all but one study,[25] treated patients had stones located in the distal third of the ureter. Mean stone size ranged from 2 mm to 10 mm, with no significant differences between treatment arms of the individual trials. All patients were treated on an outpatient basis for a period ranging from 7 to 28 days. Nifedipine was administered in 179 patients, tamsulosin in 48 patients and 181 patients served as controls. Patients were followed up for a period of 20–42 days. The main outcome of this meta-analysis[31] was the proportion of patients who passed stones. In all five individual RCTs, the proportion was found to be statistically greater for the nifedipine compared with the control arm. The difference in expulsion rates ranged from 27.0%[33] to 43.8%.[26] However, only two studies[26,33] detected a significantly shorter expulsion time in patients who received nifedipine compared with the controls. The pooled results suggested that nifedipine has a consistent beneficial effect on the passage of distal ureteral stones and that there might be a small additive effect when combined with corticosteroids.[31] The effects of nifedipine and tamsulosin were directly compared in three studies.[28,29,34] Two of these reported no significant difference in stone expulsion/expulsion time,[28,34] but one study[29] noted that tamsulosin was better (RR 1.26; 95% CI 1.10, 1.44). A possible benefit that seems to be associated with the use of nifedipine is the need for significantly lower doses of analgesics reported in two studies.[26,28]

Table I. Efficacy of medical expulsive therapy for ureteral stones: clinical trials of nifedipine published

Study (year)	Medical expulsive treatment	Administration regimen	No. of patients included	Stone size [mm]		Stone location (no. of patients)	Follow-up (days)	Expulsion rate (%)	Expulsion time [mean (range), days]
				range	mean (SD)				
Borghi et al.[24] (1994)	Nifedipine, methylprednisolone	20 mg bid (45 days max) 8 mg bid (45 days max)	43	≤5.0	6.7 (3.0)	NA	45	34/43 (79.1)[a,b]	11.2 (NA)[a]
	Placebo, methylprednisolone	bid (45 days max) 8 mg bid (45 days max)	43	≤15.0	6.8 (2.9)			24/43 (55.8)[a,b]	16.4 (NA)[a]
Cooper et al.[25] (2000)	Nifedipine XL, ketorolac	30 mg od (7 days only) 10 mg qid (5 days)	35	2.0–6.0	3.9 (NA)	Upper 6, middle 7, distal 22	42	31/35 (88.6)[a]	12.6 (1–48)[c]
	Prednisone, ketorolac	10 mg bid (5 days only) 10 mg qid (5 days)	35	2.0–6.0	3.9 (NA)	Upper 6, middle 5, distal 24		19/35 (54.3)[a]	11.2 (1–42)[c]
Porpiglia et al.[26] (2000)	Nifedipine XL, deflazacort	30 mg od (28 days max) 30 mg od (10 days max)	48	3.5–10.0	5.8 (1.8)	Distal	28	38/48 (79.2)[a]	7 (2–10)[a]
	Control		48	3.0–10.0	5.5 (1.4)			17/48 (35.4)[a]	20 (10–28)[a]
Saita et al.[27][d] (2004)	Nifedipine XL, prednisolone	30 mg od (20 days max) 25 mg od (20 days max)	25	≤15.0	12.0 (NA)	NA	20	15/25 (60.0)[b]	6 (2–10)
	Prednisolone	25 mg od (20 days max)	25	≤15.0	12.8 (NA)			12/25 (48.0)[b]	10 (5–15)
Porpiglia et al.[28] (2004)	Nifedipine XL, deflazacort	30 mg od (28 days max) 30 mg od (10 days max)	30	3.5–10.0	4.7 (1.5)	Distal	28	24/30 (80.0)[a,e]	9.3 (3–20)
	Tamsulosin, deflazacort	0.4 mg od (28 days max) 30 mg od (10 days max)	28	3.0–10.0	5.4 (1.5)			24/28 (85.6)[a,e]	7.9 (1–15)[a]
	Control		28	≤10	5.4 (1.5)			12/28 (42.9)[a]	12 (3–20)[a]
Dellabella et al.[29] (2005)	Nifedipine XL, deflazacort	30 mg od (28 days max) 30 mg od (10 days max)	70	4.0–11.0	6.2 (1.5)[a,d]	Distal	28	54/70 (77.1)[a,e]	5 (3–8)[a,e,f,g]
	Phloroglucinol, deflazacort	80 mg od (28 days max) 30 mg od (10 days max)	70	4.0–11.8	6.2 (1.7)[a,e]			45/70 (64.3)[a,e]	5 (3–7)[a,e,f,g]
	Tamsulosin, deflazacort	0.4 mg od (28 days max) 30 mg od (10 days max)	70	4.0–18.0	7.2 (2.4)[a]			68/70 (97.1)[a]	3 (1–5)[a,f,g]

a Statistically significant differences detected between treatment arms.

b Denominator adjusted to reflect worst-case scenario principle.

c Statistically significantly fewer work days were lost in the nifedipine arm [1.76 (0–8)] than in the prednisone arm [4.96 (0–28)].

d Non-randomized controlled clinical trial.

e The difference between the nifedipine and phloroglucinol arms is not statistically significant for expulsive rate and time.

f Value expressed as median (interquartile range).

g Statistically significantly fewer work days were lost in the tamsulosin arm [2 (1–2)] than in the nifedipine arm [3 (1–5)] and the phloroglucinol arm [5 (2–6.25)]. The difference between nifedipine and phloroglucinol is also significant for work days lost.

bid = twice daily; **max** = maximum; **NA** = not available; **od** = once daily; **qid** = four times daily; **XL** = extended release.

The results of using the meta-analysis study methodology to address clinical questions must be interpreted with caution. Up to one-third of meta-analyses reporting on a beneficial therapy are later discredited after a large-scale, well performed RCT is completed.[36] In this case in particular,[31] there are limitations, which were recognized by the authors, including the following: (i) limited number of studies with a small overall number of patients analyzed; (ii) potential publication bias and heterogeneity, although there is no clear evidence for that and; (iii) poor overall quality of RCTs reviewed (median Jadad score <3) mainly as a result of the absence of blinded methodology in all but one study[24] and the lack of a detailed description of randomization procedures in the majority of the RCTs. Therefore, it was stressed by the authors that a definitive high-quality RCT would be necessary to confirm these results.[31]

In the meta-analysis conducted by Singh and co-workers,[32] pooled data included 686 patients from nine trials,[24-29,33-35] with an average stone size >5 mm in all but three trials.[25,28,35] All studies evaluated stones in the distal ureter, except three[24,25,27] that included stones within the upper and middle sections of the ureter as well. Little heterogeneity existed among the clinical trials, with no evidence of a publication bias.

The pooled analysis of all nine trials suggested that the addition of nifedipine compared with standard therapy significantly improved the spontaneous stone expulsion rate in patients with moderately sized distal ureteral stones. The RR was 1.50 (95% CI 1.34, 1.68), and the number to treat 3.9 (95% CI 3.2, 4.6). A pooled analysis of 380 patients from 'best quality' trials (Jadad score ≥3)[24,26,28,29] resulted in an RR of 1.60 (95% CI 1.28, 2.01). Sequential exclusion of each study from the analysis resulted in minimal changes in the pooled RR or precision. All nine trials evaluated time to stone expulsion. When compared with standard therapy, a reduction in time to stone expulsion was observed in the majority of these trials. The mean time to stone expulsion in the treatment arm, including the upper limit of the 95% CI, was <28 days.

With the restriction that adverse effects were in general poorly categorized in these RCTs, in the meta-analysis of Hollingsworth et al.,[31] nifedipine seemed to be well tolerated (table II). According to the analysis of Singh and co-workers,[32] adverse effects were not consistently reported in all trials. However, adverse effects were observed in around 15% of patients in the nifedipine arm. Mild adverse effects included nausea/vomiting (n = 11), asthenia (n = 10), dyspepsia (n = 6), headache (n = 3), euphoria (n = 2), drowsiness (n = 4), transient hypotension not requiring discontinuation of therapy (n = 3) and undefined effects (n = 3). A total of 11 patients discontinued therapy (hypotension/palpitations, n = 4; erythema, n = 6; headache, n = 1). The mean decrease in systolic blood pressure was 15 mmHg (10–25 mmHg), the mean decrease in diastolic blood pressure was 8 mmHg and the mean increase in pulse rate was 8 beats/min.[24,26]

2.2.3 Calcium Channel Antagonists and Shock Wave Lithotripsy (SWL)

Porpiglia et al.[30] investigated the possibility that combined medical therapy (nifedipine plus deflazacort) increases the success rate of first-SWL treatment for ureteral stones and reduces the necessity for SWL retreatment or secondary procedures. A total of 80 patients were randomized into two equal groups after receiving a single SWL session. Group 1 received oral nifedipine extended release 30 mg/day plus deflazacort 30 mg/day for 10 days, while group 2 served as the control group, using only symptomatic therapy in case of colic. The groups did not differ significantly in stone size, stone location or double J stent use before the procedure. The average stone size was 11.6 mm in group 1 and 10.1 mm in group 2. Patients were evaluated 45 days after SWL and all of them completed the study. There was no significant difference between groups regarding the number of patients who experienced colic (35.5% in group 1 vs 42.5% in group 2); however, there was a statistically significant difference in diclofenac consumption (100 mg per person in group 1 vs 202 mg per person in group 2). Only slight adverse effects were attributed to the medical treatment, such as headache and asthenia in

Table II. Safety of medical expulsive therapy for ureteral stones: clinical trials of nifedipine

Study (year)	Medical expulsive treatment	Withdrawal rate (%)	No. of patients who reported (R) an adverse effect or who withdrew (W) as a result of a adverse effect potentially attributed to drugs
Borghi et al.[24] (1994)	Nifedipine Methylprednisolone	4/43 (9.3)	Hypotension,[a] palpitations (W1),[a] headache (W1), peri-malleoral oedema (W1), stomach ache (W1)
	Placebo Methylprednisolone	6/43 (14.0)[b]	Stomach ache (W2)
Cooper et al.[25] (2000)	Nifedipine XL Ketorolac Prednisone	0/35 (0.0)	Dyspepsia (R4), nausea (R5), vomiting (R6), drowsiness (R4), euphoria (R2)
	Ketorolac	0/35 (0.0)	Nausea (R8), vomiting (R4), drowsiness (R2)
Porpiglia et al.[26] (2000)	Nifedipine XL Deflazacort	2/48 (4.2)	Hypotension (W1),[c] palpitations (W1), headache (R3), asthenia (R8)
	Control	2/48 (4.2)[d]	
Saita et al.[27][e] (2004)	Nifedipine XL Prednisolone	6/25 (24.0)	Erythema (W5), stomach ache (W1)
	Prednisolone	7/25 (28.0)[f]	Stomach ache (W4)
Porpiglia et al.[28] (2004)	Nifedipine XL Deflazacort	1/30 (3.3)	Hypotension with palpitations (W1), undefined minor adverse effects (R3)
	Tamsulosin Deflazacort	1/28 (3.6)	Asthenia (W1), undefined minor adverse effects (R3)
	Control	0/28 (0.0)	
Dellabella et al.[29] (2005)	Nifedipine XL Deflazacort	0/70 (0.0)	Undefined minor adverse effects (R, NA)[g]
	Phloroglucinol Deflazacort	0/70 (0.0)	
	Tamsulosin Deflazacort	0/70 (0.0)	

a Significant decrease in mean systolic and diastolic blood pressure and significant increase in mean heart rate compared with baseline. These parameters were unchanged with placebo. No patient interrupted treatment as a result of hypotension.

b Two patients withdrew as a result of the development of urinary tract infections and two were lost during follow-up.

c Significant decrease in mean blood pressure compared with baseline. No variation observed in the control arm.

d One patient withdrew as a result of the development of a urinary tract infection and one because of repeated urinary colic.

e Non-randomized clinical control trial.

f Three patients withdrew as a result of the development of acute renal colic.

g Similar frequency of reported minor adverse effects among the three treatment arms.

NA = not available; **XL** = extended release.

one and three patients, respectively. The stone-free rate was significantly higher in group 1 (75% vs 50%). However, when patients were stratified according to stone location (upper or lower ureter), the benefit of the combined adjuvant therapy did not reach statistical significance.

2.3 α-Adrenergic Receptor Antagonists

2.3.1 In Vitro Studies

In 1970, Malin et al.[37] first described the presence of α- and β-adrenergic receptors in the entire length of the human ureter and the physiological response (increased tone and frequency of contractions) of the ureter when exposed to α-adrenergic receptor agonists. Later, it was found that α-adrenergic receptor agonists have a stimulatory effect on the ureteral smooth muscle, whereas β-adrenergic receptor agonists have an inhibitory affect. In this regard, the α_1-adrenergic receptor-mediated contractile activity prevails over the relaxing effects induced by the β-adrenergic receptor stimulation.[38] More

recently, α_1-adrenergic receptor gene and protein expression in the proximal, middle and distal ureter was studied. The authors found that the human ureter was endowed with each subtype of α_1-adrenergic receptor, although α_{1D} and α_{1A} were expressed in significantly greater amounts than the α_{1B} receptor subtype; these authors also demonstrated that the distal ureter expressed the greatest quantity of α_1-adrenergic receptor messenger RNA.[39]

2.3.2 Clinical Studies

Since the first study by Cervenàkov et al.,[40] many studies have been published on the efficacy of α-blockers to facilitate the passage of distal ureteral stones. Although the available trials on the use of α-blockers in the treatment of urolithiasis did not always reach statistical significance with regard to overall expulsion rates, they have consistently shown α-blockers to be more effective than standard treatments with regard to expulsion time, colic episodes, pain, use of analgesics and quality of life. The results of RCTs using only α-blockers as MET are displayed in table III.[41-47] These studies are clinically interesting, although they do have limitations and differences in their design. For example, different α-blockers were used including tamsulosin 0.4 mg (six studies), terazosin 5 mg (two studies), doxazosin 4 mg (two studies) and alfuzosin (one study) [drug dose was not reported]. Furthermore, stone size also varied between the published reports. The treatment time ranged from a minimum of 8 days to a maximum of 6 weeks. Specific recommendations for pain control and adjunctive drugs in the conservative therapy arm also differed. In addition, studies have been criticized for the relatively low patient numbers resulting in limited statistical power, and the need for well conducted, randomized, multicentre trials has been stressed.[48]

In the meta-analysis by Hollingsworth et al.,[31] subgroup analysis of the four studies in which treatment groups were given tamsulosin (without a CCB) demonstrated that patients had a 52% greater likelihood of stone passage than controls (pooled RR 1.52; 95% CI 1.23, 1.86). When all studies in which an α-blocker was used (n = 5) were summarized, the pooled RR was 1.54 (95% CI 1.29, 1.85).

Recently, another meta-analysis provided a high level of evidence for the clinical benefit of α-blocker therapy in patients with distal ureteral calculi.[49] A pooled analysis of 11 trials with 911 patients showed that the use of α-blockers was associated with a significantly increased rate of distal ureteral stone expulsion compared with conservative management alone, resulting in a 44% higher likelihood of expelling the stones (RR 1.44, 95% CI 1.31, 1.59). When a subgroup analysis was carried out based on the α-blocker type and prior use of SWL, a population of 664 participants from nine trials receiving tamsulosin without prior SWL was identified as the single largest subgroup in the analysis and produced effect estimates similar to the overall pooled treatment effect for all studies (RR 1.44, 95% CI 1.32, 1.58).

Are all α-blockers equal? Most of the studies have used tamsulosin, probably because of its excellent tolerability and the lack of need for dose titration upon initiation of treatment.[48] However, limited direct comparative data indicate that doxazosin and terazosin may have similar efficacy to tamsulosin.[42,47] In the only study comparing three α-blockers, Yilmaz et al.[42] included 114 patients divided into four groups (control, tamsulosin 0.4 mg, terazosin 5 mg and doxazosin 4 mg). There were no differences between the groups with respect to patient age, weight, height, sex and stone size. The calculi passed through the ureter spontaneously in 53.57%, 79.31%, 78.57% and 75.86% of patients, respectively. In the groups receiving an α-blocker, the number of pain episodes, expulsion time and analgesic dosage were found to be lower than those in the control group. Despite the small number of patients included, this is the first study indicating similar efficacy of the available α-blockers in MET. In addition, in a recent study on the efficacy of tamsulosin and terazosin as MET for patients with symptomatic lower ureteral stones, no statistically significant difference between the two α-blockers was found.[47]

In an RCT, the efficacy of low-dose (0.2 mg/day) tamsulosin was evaluated in the Asian population.

Table III. Efficacy of medical expulsive therapy for ureteral stones: clinical trials of α-blockers

Study (year)	Medical expulsive treatment (stone size)	No. of patients included	Stone size mean [mm (SD)]	Follow-up (days)	Expulsion rate (%)	Expulsion time [mean (SD), days]
Küpeli et al.[41] (2004)	ST1	15	4.9 (NA)	15	3/15 (20.0)	NA
	ST1 + tamsulosin	15	4.7 (NA)		8/15 (53.3)	
Yilmaz et al.[42] (2005)	ST2	28	6.1 (1.4)	30	15/28 (53.6)	10.5 (2.1)
	ST2 + tamsulosin	29	6.0 (1.3)		23/29 (79.3)[a]	6.3 (0.9)[a]
	ST2 + terazosin	28	6.0 (0.8)		22/28 (78.6)	5.8 (0.9)
	ST2 + doxazosin	29	5.9 (0.9)		22/29 (75.9)	5.9 (0.6)
Resim et al.[43] (2005)	ST2	30	7.8 (2.2)	42	22/30 (73.3)	NA
	ST2 + tamsulosin	30	7.8 (2.3)		26/30 (86.6)	
De Sio et al.[44] (2006)	ST3	46	6.4 (1.3)	14	27/46 (58.7)	7.5 (1.8)
	ST3 + tamsulosin	50	6.9 (1.0)		45/50 (90.0)[a]	4.4 (2.1)[a]
Liatsikos et al.[45][a] (2007)	ST1 (<5 mm)	15	3.0 (1.5)	28	9/15 (60.0)	8.8 (1.1)
	ST1 (5–10 mm)	16	7.7 (1.4)		7/16 (43.8)	12.1 (1.4)
	ST1 + doxazosin (<5 mm)	20	3.2 (1.3)		17/20 (85.0)[b]	7.6 (0.8)[b]
	ST1 + doxazosin (5–10 mm)	22	7.8 (1.4)		16/22 (72.7)[c]	7.1 (1.3)[c]
Pedro et al.[46] (2008)	Placebo	35	4.1 (1.1)	28	27/35 (77.1)	8.5 (7.0)
	Alfuzosin	34	3.8 (0.9)		25/34 (73.5)	5.2 (4.8)[d]
Wang et al.[47] (2008)	ST4 + tamsulosin	32	6.5 (1.3)	14	26/32 (81.2)[a]	6.3 (2.4)[a]
	ST4 + terazocin	32	6.5 (1.5)		25/32 (78.1)[a]	6.3 (2.1)[a]
	ST4	31	6.5 (1.4)		17/31 (54.8)	10.1 (3.0)

a Statistically significant difference versus arm with ST alone.

b Statistically significant difference versus ST1 and stone size <5 mm arm.

c Statistically significant difference versus ST1 and stone size 5–10 mm arm.

d Statistically significant difference versus placebo arm.

NA = not available; **ST** = standard therapy; **ST1** = diclofenac; **ST2** = tenoxicam; **ST3** = diclofenac and horse chestnut extract (aescin); **ST4** = ketorolac and buprenorphine.

The authors[50] found that both low and standard dosages of tamsulosin increased the stone-expulsion rate and decreased expulsion time compared with the control.

In the published studies on MET, adverse effects with α-blockers were uncommon (table IV). However, not all trials systematically reported on the adverse effects of the administered α-blocker; whereas in some trials, adverse events, particularly those defined as minor, were not qualitatively described.[20] Another parameter that should be taken into account is that in some cases, the exclusion criteria included patients who had hypotension or were receiving antihypertensive treatment. On the other hand, the concomitant administration of other drugs, such as corticosteroids, horse chestnut extract (aescin) and phloroglucinol, may have contributed to adverse events.[20] It is also interesting that abnormal ejaculation associated with use of tamsulosin was not reported, probably because of the short observation time and the decrease in coitus frequency due to colicky pain.[51]

2.3.3 α-Adrenergic Receptor Antagonists and SWL

Potentially, a further application of expulsion therapy might be the passage facilitation of the fragments after SWL. There are four available prospective trials on the efficacy of tamsulosin as adjunctive treatment in patients with stones who underwent SWL (table V).[41,52-54] Again, there is variability in stone size, number of shocks

Table IV. Safety of medical expulsive therapy for ureteral stones: clinical trials of α-blockers

Study (year)	Medical treatment expulsive treatment	Withdrawal rate due to adverse events (%)	Adverse events: number and type (%)
Küpeli et al.[41] (2004)	ST1	0/15 (0.0)	None
	ST1 + tamsulosin	0/15 (0.0)	1/15 (6.6) slight dizziness
Yilmaz et al.[42] (2005)	ST1		No hypotension presented[a]
	ST1 + tamsulosin	0/29 (0.0)	
	ST1 + terazosin	0/28 (0.0)	
	ST1 + doxazosin	0/29 (0.0)	
Resim et al.[43] (2005)	ST2	0/30 (0.0)	11/30 (36.6) headache, dizziness, nausea and vomiting
	ST2 + tamsulosin	0/30 (0.0)	12/30 (40.0) headache, dizziness, diarrhoea, abnormal ejaculation, nausea and vomiting
De Sio et al.[44] (2006)	ST3	0/46 (0.0)	2/46 (4.3) malaise, diarrhoea
	ST3 + tamsulosin	0/50 (0.0)	3/50 (6.0) transient hypotension, asthenia and dizziness
Liatsikos et al.[45] (2007)	ST1		No hypotension presented[a]
	ST1		
	ST1 + doxazosin		
	ST1 + doxazosin		
Pedro et al.[46] (2008)	Placebo	0/35 (0.0)	None
	Alfuzosin	4/34 (11.8)	4/34 (11.8) dizziness and orthostatic hypotension
Wang et al.[47] (2008)	ST4 + tamsulosin	0/32 (0.0)	1/32 (3.1) undefined
	ST4 + terazocin	0/32 (0.0)	5/32 (15.6) transient hypotension, asthenia, syncope, palpitations
	ST4	0/31 (0.0)	None

a Unknown if other adverse events were recorded.

NA = not available; **ST** = standard therapy; **ST1** = diclofenac; **ST2** = tenoxicam; **ST3** = diclofenac and horse chestnut extract (aescin); **ST4** = ketorolac and buprenorphine.

delivered, type of lithotripter used and follow-up period. Conflicting evidence regarding efficacy has been reported: Küpeli et al.[41] found significantly enhanced clinical success using tamsulosin after SWL, whereas another trial[53] indicated no clinical benefit in terms of the expulsion rate. Interestingly, the administration of tamsulosin seems to be particularly effective in the presence of large stones treated with SWL. When patients were stratified according to stone size, the success rate was significantly greater in the tamsulosin group than in the control group for stones >10 mm, whereas this improvement was not achieved for smaller stones.[52] Expulsion time was not commonly included in the trials endpoints. In studies without prior SWL where only pharmacological treatment was given to facilitate stone passage, calculi were intact and patients could precisely record the time of stone expulsion. In the adjunctive tamsulosin studies, fragmentation of the stones made it difficult for patients to recognize the expulsion time.

Additional clinical benefits associated with the administration of tamsulosin after SWL included reduced painful episodes and less analgesic requirement.[51] Furthermore, the use of tamsulosin for the management of patients who developed a steinstrasse after SWL did not result in a significant improvement of the spontaneous passage rate (65.7% and 75% for the conservative and tamsulosin group, respectively) and expulsion time (10 days vs 9 days, respectively), although less pain, as measured by visual analogue scores and number of colic episodes, was experienced during resolution.[54]

2.4 Combination Treatments

2.4.1 α-Adrenergic Receptor Antagonists and Corticosteroids

In Vitro Studies

Corticosteroids inhibit transcriptional activity of several genes that encode proinflammatory proteins, including phospholipase A2 and cyclooxygenase 2 (COX-2), both of which are important for the synthesis of prostaglandins.[55-57] Prostanoids (prostaglandins, thromboxanes, prostacyclin) play a major role in the modulation of ureteral contractility.[58,59] In fact, prostaglandins can have either an excitatory or inhibitory action on the smooth-muscle contractility of the upper urinary tract, depending on the type and concentration and on the tissue and species involved.[60] It has also been found that the main site of prostaglandin production is likely to be located in the urothelium because its removal produces a 50% reduction in the amount of released prostaglandin.[61]

In human ureteric preparations, prostaglandin (PG)-E_1 decreased the spontaneous contractions, while $PGF_2\alpha$ increased muscle contractility.[62] The effects of PGE_2 are more inconsistent. Researchers have reported a decrease,[63] an increase[17] and no change[64] in ureteric contractility. Recently, it was found that PGE_2 increased contractility in obstructed ureters while relaxing normal and nonobstructed ureters and, therefore, may be a unique target for pharmacological modulation in the treatment of symptoms associated with acute urinary obstruction.[65]

Clinical Studies

There are only two studies fulfilling our inclusion criteria. Dellabella et al.[66] evaluated the additional benefit of corticosteroids to tamsulosin for the treatment of distal stones. Group 1 received tamsulosin for 28 days and group 2 received tamsulosin for 28 days plus deflazacort 30 mg daily for 10 days. The authors reported that the only noted benefit was in expulsion time. The expulsion rate was not affected and was similar in the two groups. In a similar study, Porpiglia et al.[67] found that the use of corticosteroids proved to be effective only when administered together with α-blockers.

Table V. Efficacy of medical expulsive therapy after shock wave lithotripsy for ureteral stones: clinical trials of tamsulosin

Study (year)	Medical expulsive treatment	No. of patients included	Stone size [mm]		Stone location (no. of pts)	Follow-up (days)	Expulsion rate (%)
			range	mean (SD)			
Küpeli et al.[41] (2004)	Diclofenac	24	6.0–15.0	8.2 (NA)	Distal	15	8/24 (33.3)
	Diclofenac + tamsulosin	24	6.0–16.0	8.6 (NA)			17/24 (70.8)[a]
Gravina et al.[52] (2005)	Methylprednisolone + diclofenac	65	NA	14.2 (5.3)	Kidney	90	Overall (60)[a] stones 4–10 mm (68) stones 11–20 mm (55)[a] overall (78.5) stones 4–10 mm (75)
	Methylprednisolone + diclofenac + tamsulosin	65	NA	14.6 (5.4)	Kidney		Stones 11–20 mm (81)
Gravas et al.[53] (2007)	Diclofenac	31	6.0–12.0	8.3 (NA)	Distal	28	18/31 (58.06)
	Diclofenac + tamsulosin	30	6.0–13.0	8.5 (NA)			20/30 (66.66)
Bhagat et al.[54] (2007)	Dextropropoxyphene + placebo	29	6.0–24.0	NA	Kidney (21) Upper (6) Distal (2)	30	Overall (79.3)[a] stones 6–10 mm (94.1) stones 11–24 mm (58.3)
	Dextropropoxyphene + tamsulosin	29			Kidney (20) Upper (5) Distal (4)		Overall (96.6)[a] stones 6–10 mm (100) stones 11–24 mm (93.3)[a]

a Statistically significant difference detected versus other treatment arm.

NA = not available.

Short-term use of corticosteroid therapy avoids many of the adverse effects associated with prolonged corticosteroid therapy. Thus, in all studies, deflazacort was administrated for 10 days. However, two patients in the corticosteroid group experienced a high degree of dyspepsia in the study of Dellabella et al.[66] Porpiglia et al.[67] reported that during the treatment period, two patients receiving tamsulosin experienced hypotension. However, no patients were reported to have withdrawn from either study.

2.4.2 α-Adrenergic Receptor Antagonists and Anticholinergics

In Vitro Studies

Although the role of the parasympathetic nervous system in the control of ureteral peristalsis is undefined, muscarinic cholinergic receptors and acetylcholinesterase containing nerve fibres have been demonstrated in the ureter and especially in the distal and intravesical part.[68] It has been reported that all five types of muscarinic receptors (M_{1-5}) are immunohistochemically identified in the human ureter, although reverse transcriptase polymerase chain reaction confirms the presence of only M_2, M_3 and M_5,[69] possibly because of false-positive immunohistochemistry results with muscarinic receptor antibodies. Potentially more reliable radioligand binding studies have mainly identified M_2 receptors in the porcine ureter.[70] The M_3 receptor was found to mediate rhythmic contraction in a preparation of canine ureter, whereas relaxation was probably mediated mainly via the M_4 receptor.[71] In another study, cholinergic receptor stimulation by the muscarinic agonist carbachol in anesthetized dogs had a suppressive effect on pressure and peristalsis in obstructed ureters in contrast to its activation of bladder smooth muscle.[72]

Clinical Study

There is only one RCT dealing with the efficacy of tolterodine in medical expulsion therapy. Erturhan et al.[73] compared the efficacy of tamsulosin and tolterodine in 120 patients with distal ureteral stones. Patients were divided into four groups. Group 1 patients received tamsulosin 0.4 mg/day, group 2 patients received tamsulosin 0.4 mg/day plus tolterodine 2 mg (twice a day), group 3 patients received tolterodine 2 mg (twice a day) and group 4 was the control group. The study showed that the stone expulsion rate was 73.3%, 70%, 46.6% and 40% for these groups, respectively. The comparison between groups revealed that the use of tolterodine was not effective in increasing the expulsion rate or reducing the expulsion time, and did not contribute significantly in reducing pain episodes. All treatments were well tolerated.

2.5 NSAIDs

2.5.1 In Vitro Studies

It has been demonstrated that COX-2 mRNA and protein levels are up-regulated in chronically obstructed human ureters, and the use of selective COX-2 inhibitors may be useful for treating prostanoid-induced effects associated with ureteral obstruction.[74] Nørregaard et al.[75] showed that COX-2 expression is significantly increased in the ureteral wall in response to obstruction in the rat and human ureter, and COX-2 activity contributes to increased pelvic pressure after obstruction. It has also been shown that COX-1 and COX-2 receptors are expressed in the urothelium, smooth-muscle cells and in the blood vessels of the human ureter, and that the non-selective COX inhibitor diclofenac induces a concentration-dependent decrease in the amplitude of contractions of the ureter in contrast to valdecoxib (a COX-2 inhibitor), which had no effect.[76] Furthermore, diclofenac and NS-398 (a selective COX-2 inhibitor) have been found to inhibit ureteric contractions.[77] Similarly, celecoxib (a selective COX-2 inhibitor) and indomethacin (a non-selective COX inhibitor) both inhibit prostaglandin release in the ureter, even in the presence of COX-2 induction.[78]

2.5.2 Clinical Study

There is only one published clinical study satisfying our inclusion criteria, in which Laerum et al.[79] assessed the efficacy of diclofenac as expulsive treatment. A total of 41 patients received oral diclofenac 50 mg three times a day for 7 days and 39 patients received a placebo. No statistically

significant difference in the stone-passage rate was detected between the two groups. In addition, the mean time to stone expulsion was nearly identical. However, a highly statistically and clinically significant decrease in colic recurrence was demonstrated in the diclofenac group. No intergroup differences were reported in adverse effects, which were minor and primary gastrointestinal.

3. Cost Effectiveness of MET

Comparative studies on costs have inherent difficulties and may never be carried out in a reliable manner. Effective treatment regimens aimed at resolving ureteral stones while minimizing cost are highly desirable.

The total annual expenditure on stone disease in the US in 2000 was estimated to be nearly $US2.1 billion, including $US971 million for inpatient services, $US607 million for physician office and hospital outpatient services, and $US490 million for emergency room services; values that are almost certainly underestimated.[80]

Lotan et al.[81] reported that surgical intervention costs for urolithiasis ranged from $US2645 for ureteroscopy to $US4225 for SWL per patient (year 2001 values), and repeated therapy is often needed.

On the other hand, based on drug-cost data obtained from the University of Michigan pharmacy, Hollingsworth et al.[31] reported that the costs for MET would range from $US10.74 for a 28-day course of doxazosin to $US104.41 for a 42-day course of tamsulosin, the only non-generic medication.

A recent study found that MET with α-blockers was a cost-effective strategy for the management of ureteral stones compared with watchful waiting and surgery. MET was associated with a $US1132 cost saving over observation ($US1493 vs $US2625, respectively; year 2007 values). Cost effectiveness was more noticeable when compared with surgery. Indeed, because of the high cost of ureteroscopy ($US4773) in the US and the low cost of medication ($US28), even a 1% greater likelihood of stone passage with MET makes this strategy cost saving.[82]

4. Conclusions

Patients given MET with α-blockers or CCBs are more likely to pass their stones, and MET should be considered as first-line treatment for patients with distal ureteral calculi who are amenable to waiting management. Benefits associated with MET compared with placebo or with standard treatments include shortened time to stone passage, fewer pain episodes and less need for analgesics, hospitalization and/or endoscopic treatment. MET is generally well tolerated with minor adverse effects causing few patients to discontinue their treatment. α-Blockers seem to be more effective than CCBs, and the benefit of adding corticosteroids or anticholinergics is insignificant. Moreover, MET with α-blockers is cost effective for the management of distal ureteral stones. Although NSAIDs are very useful in treating colics, they have no effect on stone passage.

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Correspondence: Prof. Dr *Jean J.M.C.H. de la Rosette*, Chairman Department of Urology, AMC University Hospital, Meibergdreef 9 (G4-105), 1105 AZ Amsterdam, the Netherlands.
E-mail: J.J.Delarosette@amc.uva.nl