Medical Expulsive Therapy of Ureteral Calculi and Supportive Therapy After Extracorporeal Shock Wave Lithotripsy

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1. Introduction

Stone size, location, and symptom duration are the most important parameters to predict spontaneous stone expulsion in addition to patient-dependent factors such as pain tolerance and the development of infection that determine the need for active stone removal or decompression of the renal collecting system [1–3]. Miller and Kane reported the time to spontaneous stone passage of stones <2 mm, 2–4 mm, and 4–6 mm was an average of 8.2, 12.2, and 22.1 d, respectively, and 95% of those that passed did so by 31, 40, and 39 d, respectively [2]. A meta-analysis of studies in which spontaneous ureteral stone passage was assessed reported a median probability of stone passage of 68% for stones <5 mm (n = 224) and 47% for those >5 mm and <10 mm (n = 104) [4]. These studies had certain
limitations including nonstandardization of the stone size measurement methods and lack of analysis of stone position, stone-passage history, and time to stone passage. According to the European Association of Urology guidelines, observation as initial treatment is an option for patients with controlled symptoms harboring ureteral stones <10 mm.

2. Evidence acquisition

2.1. Ureteral pathophysiology

An increase of cytoplasmatic free calcium concentration is one principal mechanism initiating ureteral contraction. It was demonstrated that calcium channel inhibitors counteract the phasic-rhythmic activity in isolated human caliceal segments [5] and in the ureter [6]. Endogenous prostaglandin synthesis and calcium influx induce spontaneous rhythmic contractions of the human ureter, which are inhibited by the calcium channel blockers nifedipine and verapamil [7]. This negative effect on ureteral contractility has evoked interest in using calcium channel blockers to facilitate medical-induced stone passage.

Three different subtypes of adrenergic receptors (ARs) have been pharmacologically identified: $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$ [8]. A heterogeneous distribution of $\alpha_1$ AR binding sites was detected, with the highest density in the distal ureter [9]. The distribution of ARs throughout the inner and outer smooth muscle of the ureter was highest for $\alpha_{1D}$ especially in the distal ureter, followed by $\alpha_{1A}$ and $\alpha_{1B}$ ARs [10]. Of interest, heterodimers $\alpha_{1B}/\alpha_{1A}$ and $\alpha_{1B}/\alpha_{1D}$ do occur, whereas $\alpha_{1A}/\alpha_{1D}$ ARs do not heterodimerize, suggesting a possible regulatory role of $\alpha_{1B}$ [11]. This ability to oligodimerize could influence future drug development.

The exact pathophysiology of ureteral colic and stone passage is not completely understood. A ureteral stone tends to induce a ureteral inflammatory response by ureteral stone obstruction and ureteral wall tension stimulating prostaglandin synthesis. Prostaglandins have a dilating effect on afferent arterioles resulting in an increased renal blood flow, further increasing ureteropelvic pressure, inflammation, and edema [12]. A subsequent increase of smooth muscle contraction impairs propulsive antegrade peristalsis aggravating ureteral obstruction, impaction, and pain [13,14]. Therefore the ideal agent to facilitate stone expulsion would reduce ureteral inflammation, edema, ureteral spasm, and uncoordinated ureteral contractions without altering propulsive peristalsis.

2.2. Medical expulsive therapy

A rational approach to expulsion therapy would be to increase peristaltic activity with high fluid intake increasing the volume transported through the ureter and thereby augmenting the hydrostatic pressure above the stone. In cases of obstruction, a high diuresis is likely to counteract the passage of the stone and to cause more pain. A systematic review evaluating the effect of fluids and diuretics found no credible evidence supporting a diuretic approach in terms of pain relief and stone expulsion [15]. A recent randomized comparison between high and normal diuresis during the primary session of shock wave lithotripsy (SWL) for removal of ureteral stones did not demonstrate a beneficial effect [16].

An improved understanding of ureteral physiology has led to an anti-inflammatory and antiedematous treatment by nonsteroidal anti-inflammatory drugs (NSAIDs), decreasing agonist-induced contractions in pig ureters [17]. Cyclooxygenase (COX)-2 inhibitors were able to inhibit prostaglandin release and ureteral contractility [18]. NSAIDs have proved effective by inhibiting prostaglandin synthesis and reducing vasodilatation with subsequent reduction of inflammation, glomerular filtration rate, and intrarenal pressure [12]. However, stone expulsion rates were not affected in double-blind placebo-controlled trials [19,20].

Terpenes were reported to have diuretic anti-inflammatory analgesic and spasmodic properties. Among the reported properties the anti-inflammatory effect is achieved by the suppression of arachidonic acid metabolism and cytokine production [21]. In a prospective randomized placebo-controlled single-blind trial for prostatitis/chronic pelvic pain syndrome, Rowatinex demonstrated more improvement in the numerical value for pain score than ibuprofen [21]. Rowatinex was reported in recent randomized controlled trials (RCTs) to accelerate stone-free rates and reduce symptoms during stone passage in patients undergoing SWL for renal stones. No significant adverse events leading to discontinuation of the drug were reported [22]. Rowatinex will continue to be evaluated in the medical treatment of upper urinary stone disease.

Another potent analgesic and antipyretic drug that has been proposed to inhibit COX enzyme activity is dipyrone. Studies in animal and human ureters demonstrated a significant reduction of renal pelvic pressure with dipyrone and the NSAID indomethacin that alleviated colic pain [23]. Holmlund and Sjödin had already shown the effect of indomethacin in 1978 [24]. However, so far no study has reported an accelerated stone expulsion.

Antimuscarinics might relax genitourinary smooth muscle and thus reduce colic pain [25]. However, a randomized placebo-controlled trial determining whether N-butylscopolamine (Buscopan) reduces the amount of opioid analgesia required in renal colic showed no favorable effect [26]. N-butylscopolamine failed to reduce renal pelvic pressure significantly [23] and was less effective than dipyrone. The addition of spasmodytic agents (eg, hyoscine) to dipyrone did not improve its analgesic efficacy [27]. Those regimens have failed so far to demonstrate an increase in stone expulsion rates, but it might be interesting to explore the effects further in randomized studies.

Phosphodiesterases (PDEs) regulate intracellular cyclic nucleotide turnover influencing smooth muscle tension. Kühn et al found relaxing effects on potassium chloride-induced tension of ureteral smooth muscle by PDE4 and PDE5 inhibitors in vitro [28]. Gratzke et al demonstrated the ureteral smooth muscle relaxing effects of different PDE5 inhibitors in vitro. Results were similar to those reported for tamsulosin, suggesting the potential of using PDE inhibitors in the treatment of ureteral colic [29]. Another drug that
interferes with the PDE enzyme is papaverine, which results in an increase of adenosine monophosphate that causes ureteral smooth muscle relaxation. Its analgesic potential is similar to that of pethidine and diclofenac, and its superiority to hyoscine butylbromide was demonstrated in recent randomized trials [30,31]. Further studies are necessary to assess their potential role in expulsion therapy.

Corticosteroids have been reported to facilitate stone expulsion [32,33]. However, publications in peer-reviewed journals are necessary. So far no further evidence has confirmed whether corticosteroids alone are capable of facilitating stone expulsion.

\(\alpha\)-Adrenoreceptor antagonists (\(\alpha\)-blockers) inhibit contractions of ureteral musculature, reduce the basal tone, and decrease peristaltic frequency and colic pain facilitating ureteral stone expulsion. Davenport et al found a beneficial effect of both nifedipine and 5-methylurapidil on human ureteric activity with a median reduction in proximal versus distal ureteral tone of 47% versus 57% and 33% versus 65%, respectively [34]. These data suggest a beneficial effect for MET further supported by a pilot study investigating the in vivo effect of nifedipine and tamsulosin on ureteral contraction frequency, pressure, and velocity using a ureteric pressure transducer in humans. Both drugs allowed peristalsis to continue, which is important for successful stone expulsion [35].

### 3. Evidence synthesis

A recent meta-analysis offered evidence for an overall increased stone expulsion rate and reduced time to stone expulsion using an \(\alpha\)-blocker or calcium channel blocker compared with a standard therapy or placebo control group (Fig. 1) [36]. A class effect for \(\alpha\)-blockers was suggested after similar expulsion rates for tamsulosin, terazosin, and doxazosin were observed [37]. Similar results were obtained using terazosin, doxazosin, and the \(\alpha_1\)-blocker naftopidil, further confirming the concept of a class effect [38–43]. Only one alfuzosin trial reported an inferior numerical outcome for the treatment group [44]. However, the time to stone

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**Total (95% CI): 1333 1085 100.0% 1.45 (1.34, 1.57)**

**Total events: 1074 590**

**Heterogeneity: Tau² = 0.02; Chi² = 46.99 df = 28 (P = 0.01); I² = 49%**

**Test for overall effect: Z = 9.40 (P < 0.00001)**

**Fig. 1 – Forest plot of comparison: \(\alpha\)-blockade versus control; outcome: stone free. Risk ratios (RRs) in each square with area proportional to the number of events comparing outcome in patients allocated to an \(\alpha\)-blocker group with outcome in patients allocated to a control group, along with 95% confidence intervals (CIs) as the horizontal line. Overall RRs and CIs are plotted as a diamond. A square or diamond to the right of the vertical line of no effect indicates a benefit with \(\alpha\)-blockers. This benefit is significant (p < 0.05) only if the horizontal line or diamond does not overlap the vertical line. Adapted from Seitz et al. [36]. M-H = Mantel-Haenszel test.**
expulsions and pain scores were significantly in favor of the treatment group.

3.1. Stone size and medical expulsion therapy

Due to the high likelihood of spontaneous passage for stones up to about 4 mm, one would expect that the efficacy for medical expulsion therapy (MET) would decrease because of the high spontaneous expulsion rate.

Of interest, three high-quality double-blinded RCTs failed to demonstrate a significant higher expulsion rate for MET using alfuzosin or tamsulosin [44–46]. In addition to a possible lower effectiveness of alfuzosin, a small mean stone size of 3.8 mm could have accounted for high spontaneous stone passage rates leading to an underestimation of alfuzosin in promoting stone passage [44]. The same applies for the study of Vincendeau et al including distal ureteral stones with a mean stone size of 2.9 mm and 3.2 mm for the treatment and control groups, respectively [45]. In the study from Hermanns et al. [46], 76% and 84% of the patients in the tamsulosin and control groups harbored distal ureteral stones <5 mm. Tamsulosin did not improve expulsion rates in stones >5 mm (Table 1). However, as the authors stated, the study was not powered for this subgroup analysis [46]. Although the limited numbers of patients might account for the undetectable significant differences in the treatment of smaller stones, results might as well indicate that with decreasing stone size an additional benefit for MET is less likely owing to the high spontaneous expulsion rate. Nevertheless, a numerically accelerated expulsion rate and significant analgesic effect within the treatment of smaller stones, results might as well account for the undetectable significant differences leading to an underestimation of alfuzosin in promoting stone passage [44].

It is reasonable to assume that the stone expulsion rate of MET using alfuzosin or tamsulosin [44–46]. However, the “ideal” stone size for MET is not known. Due to the high likelihood of spontaneous passage for stones up to about 4 mm and found a significantly higher expulsion rate (p < 0.001) and shorter expulsion time (p < 0.0001) in the tamsulosin group, although stones in the tamsulosin group were significantly larger (7.2 vs 6.2 mm). Notably, stone size and expulsion time did not correlate, a finding that might be attributable to the concomitant administration of a corticosteroid [50]. Hospitalizations, loss of workdays, auxiliary measures, and the amount of rescue medication were significantly in favor of the tamsulosin group.

3.2. Tamsulosin versus nifedipine in medical expulsion therapy

Three studies compared the efficacy of tamsulosin compared with nifedipine for distal ureteral stones [48–50]. Keshvary et al found no statistical difference in expulsion rates between tamsulosin and nifedipine [48]. Porpiglia et al evaluated the effectiveness of tamsulosin versus nifedipine in combination with deflazacort for stones <10 mm. Expulsion rates and expulsion time were in favor of the tamsulosin group, although differences were not significant [49]. Dellabella et al compared the efficacy of tamsulosin and nifedipine in combination with deflazacort for stones >4 mm and found a significantly higher expulsion rate (p = 0.001) and shorter expulsion time (p < 0.0001) in the tamsulosin group, although stones in the tamsulosin group were significantly larger (7.2 vs 6.2 mm). Notably, stone size and expulsion time did not correlate, a finding that might be attributable to the concomitant administration of a corticosteroid [50]. Hospitalizations, loss of workdays, auxiliary measures, and the amount of rescue medication were significantly in favor of the tamsulosin group.

<table>
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Table 1: Efficacy and safety data from recent randomized controlled trials at different formulations for medical expulsive therapy.

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3.3. Shock wave lithotripsy and medical expulsion therapy

It would be reasonable to assume that MET is effective after SWL for renal stones because the fragments have to pass the ureter. Pooled data for α-blocker after SWL suggested a treatment benefit for ureteral stones [36]. All tamsulosin 0.4 mg, doxazosin, and terazosin trials demonstrated a treatment benefit, suggesting a class effect. Colic episodes or analgesic doses in the α-blocker groups were significantly lower in six [42,51–55] of seven trials. Only one tamsulosin 0.2 mg trial after extracorporeal shock wave lithotripsy (ESWL) reported unfavorable outcomes for the treatment group, although differences were not significant. Nevertheless, the mean time to stone expulsion was significantly in favor of the treatment group (15.7 ± 6.1 vs 35.5 ± 53.7; \( p = 0.04 \)) [56].

Four studies available for renal stones treated with ESWL showed a beneficial effect for α-blockade [52,57–59]. Additionally, the double-blind RCT from Romics et al also demonstrated a significant higher expulsion rate and decreased expulsion time with a special combination of terpenes (Rowatinex) after ESWL [60]. This is discussed in detail elsewhere in this supplement. α-Blockers also could prove beneficial for proximal ureteral stone locations because they mediate a reduction in proximal ureteral tone of 33% [34]. All fragments have to pass the distal ureter; therefore, stone passage might be facilitated with decreased expulsion time and fewer colicky episodes. Indeed, findings suggest a beneficial effect. Han et al administered tamsulosin for upper ureteral stones after ESWL and found a significant increased expulsion rate and significant decreased analgesic requirements versus a control group [61]. Porpiglia et al demonstrated a relatively higher expulsion rate for upper ureteral stones compared with a control group using nifedipine in conjunction with a corticosteroid. The expulsion rate in the treatment group was equal for upper and distal ureteral stones [62]. However, one single-centre nonblinded RCT including <15 mm proximal ureteral stones failed to demonstrate a significant treatment effect after SWL [63].

Similar to patients undergoing MET, stone size could also influence the efficacy of MET after SWL. Observations from SWL studies suggested an adjunct role of α-blocker to ESWL. Gravina et al and Bhagat et al found no significant difference in stone-free rates in 6- to 10-mm ureteral stones but with increasing stone size of ≥11 mm the difference became significant [52,57]. Similar findings were reported by Küpeli et al. [64]. The difference in expulsion rates between treatment and control groups for stones <5 mm was not significant. In contrast, stone-free rates in patients treated for stones >5 mm were significantly in favor of the treatment group. In patients receiving nifedipine after ESWL, Porpiglia et al demonstrated that the average stone size of the stone-free versus non–stone-free patients was not significantly different (11.8 vs 11.4 mm). In contrast, average stone size in stone-free versus non–stone-free patients in the control group was significantly different (8.8 vs 11.5 mm; \( p = 0.002 \)), suggesting facilitated stone passage for larger stones in the nifedipine group [62].

3.4. Adverse events in medical expulsion therapy

Adverse events (AEs) rarely led to dropouts of patients and were reversible after discontinuation of the drug. Dropout rates might have been low in trials with previous exclusion of patients prone to side effects of the drugs used (eg, hypotensive patients) [6,49,65]. Inclusion of various drugs for standard treatment or steroids added to the treatment group possibly accounted for additional AEs, although a 10-d course of corticosteroids seems to be only associated with a low AE profile.

3.5. Cost effectiveness of medical expulsion therapy

Bensalah et al conducted an elaborate evaluation of the cost effectiveness of MET compared with conservative therapy for distal ureteral stones in five countries [66]. Calculations were based on the pooled risk ratio (RR) for treatment with an α-blocker (RR: 1.54; 95% confidence interval, 1.29–1.85) reported by Hollingsworth et al. [67]. It was assumed that failures underwent ureterorenoscopy, which was shown to be more cost effective than ESWL for ureteral stone treatment of any location in most of the countries investigated including the United States [68]. However, obvious but inevitable limitations of any cost analysis are intra- and international variations in the degree of reimbursement and subsidization of services and pharmaceutical costs.

4. Conclusions

In a patient who has a newly diagnosed ureteral stone <10 mm and whose symptoms are controlled, observation with periodic evaluation is an option. Patients may be offered an appropriate MET to facilitate stone passage. There is evidence that MET reduces additional analgesic requirements and accelerates the spontaneous passage of ureteral stones <10 mm as well as renal stone fragments generated with SWL. With decreasing stone size, an increased stone-free rate after MET is less likely because of the high spontaneous expulsion rate. Evidence suggests that MET can be suggested as an effective treatment option. However, large-scale placebo-controlled RCTs and the investigation of promising new substances is still needed to better define the future and optimized role of MET.

Conflicts of interest

In recent years, the author has received consultancy or lecturer honoraria from Rowa Pharmaceuticals.

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References


