

Medical Expulsive Therapy for Ureteral Stone Passage

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor's Note that summarizes important concepts. Participation as an authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

Editor's Note: Medical expulsive therapy, using α -blocking agents such as tamsulosin, has been advocated as a means of enhancing ureteral stone passage, but clinical trials have produced equivocal results. In this installment of *Clinical Controversies*, pro and con advocates present evidence and arguments relating to the use of medical expulsive therapy and discuss opposing perspectives that should be considered in deciding whether to use it in the treatment of ureteral stones.

BACK TO THE FUTURE: MEDICAL EXPULSIVE THERAPY FOR LARGE DISTAL STONES



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Among the controversial topics in urology, medical expulsive therapy is a popular topic that continues to attract interest and foment the development of new studies. It is an example of how concepts and treatment recommendations may change according to the results of randomized controlled trials, meta-analyses, and systematic reviews and illustrates the potential limitations of statistical methods when they are contaminated by methodological biases, even when they are minimal. The pathophysiologic basis for medical expulsive therapy is that α -antagonists may inhibit contraction of ureteral smooth muscle, resulting in less severe ureterospasm, facilitating stone passage. The distal ureter has the highest density of α_1 -adrenergic receptors. Distal ureteral stones should thus benefit most from medical expulsive therapy.

Medical expulsive therapy soon achieved widespread acceptance based on the early report of limited trials^{1,2} and systematic reviews of these trials.^{1,2} However, the quality of the studies included was poor: randomization, blinding, and follow-up were suboptimal. It exemplifies that systematic reviews and meta-analyses are as good as the original studies that go into them. Even so, according to the European Association of Urology Guidelines on conservative management of urolithiasis, medical expulsive therapy has demonstrated a positive effect on stone expulsion rates, with level of evidence 1b.³

α -Blockers had been widely used until the release of the Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial, a large, multicenter, randomized controlled trial by Pickard et al,⁴ who showed that tamsulosin was not superior to placebo in decreasing intervention rates to clear ureteral stone. The trial used the need for urologic intervention as the main outcome measure and, since that study, medical expulsive therapy has been jeopardized.

Despite the high quality of the trial, concerns about possible study biases were raised, such as the lack of confirmation of the stone passage with computed tomography scans or any other imaging to avoid costs and radiation; there is no doubt that clinical assessment of stone passage of small calculi is imprecise. Furthermore, there is a high rate of nonintervention in the placebo arm and a predominance of stones less than 5 mm and located in the distal ureter, which can underpower the study. To elucidate the discrepancies between some meta-analyses of mostly small trials^{5,6} and a high-quality randomized controlled trial, new multicenter, randomized, double-blind, placebo-controlled trials were performed. Furyk et al⁷ conducted a randomized controlled trial with 403 patients and found no benefits of medical expulsive therapy with tamsulosin for patients with distal ureteral stones. However, the subgroup of patients with stones of 5 to 10 mm had an increased rate of stone passage. The Tamsulosin for Urolithiasis in the Emergency Department (STONE) study, conducted by Meltzer et al,⁸ randomized 512 patients to receive tamsulosin or placebo and failed to

show a benefit of medical expulsive therapy. The largest randomized controlled trial so far was conducted by Ye et al,⁹ who included 3,296 patients and showed increased passage of distal stones on medical expulsive therapy; moreover, subgroup analyses showed superior results for distal stones greater than 5 mm.

Although the initial results of medical expulsive therapy from the pioneer small studies were never duplicated in larger well-conducted trials, the latest studies seem to confirm the efficacy of the therapy in facilitating stone passage for 5- to 10-mm distal stones. Wang et al¹⁰ recently performed a systematic review and meta-analysis that included these latest studies about stone size and passage using medical expulsive therapy; despite its being a subgroup analysis, it seems to be valid and strong, suggesting the efficacy of using α -blockers in patients with large distal stones (5 to 10 mm). The number needed to treat seems to be approximately 5, which is higher than previously described by Hollingsworth et al² (4 patients). However, considering that this is a highly prevalent condition and medical expulsive therapy is a low-cost and well-tolerated therapy, it may have a role in the treatment of distal ureteral stones.¹⁰

<https://doi.org/10.1016/j.annemergmed.2018.06.023>

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MEDICAL EXPULSIVE THERAPY FOR URETERAL STONES: IS IT STILL WORTHWHILE?



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Nephrolithiasis has become epidemic in the United States, with a prevalence approaching 9% in the general population.¹ It has been estimated that there are 226 stone-related emergency department (ED) visits for every 100,000 patients per year.² The majority of visits are prompted by symptoms arising from the passage of ureteral stones.

Medical expulsive therapy with α -blockers has been promoted as an effective option for conservative medical treatment, especially for patients with small ureteral stones less than 5 mm in diameter. However, the SUSPEND trial, comparing placebo with α -blockers, recently showed no difference in stone passage, raising concerns about the effectiveness of medical expulsive therapy.³ An Australian multicenter study corroborated the SUSPEND trial, showing no difference in passage for stones overall, but did find increased rates of passage for stones between 5 and 10 mm (83% with α -blocker versus 61% with placebo).⁴ Similarly, Meltzer et al,⁵ in a randomized trial of 512 patients with ureteral stones between 1 and 8 mm, found no difference in stone passage rates between patients receiving tamsulosin compared with placebo (52% versus 49%).⁵ More recently, a large prospective randomized trial comparing tamsulosin with placebo for 4- to 7-mm distal ureteral stones in greater than 3,200 patients showed results similar to those of the Australian trial: no difference for stones 5 mm or less and increase in stone passage in the group with 5.1- to 7-mm stones (87% versus 75%), with a small overall benefit when all sizes were considered (4 to 7 mm; 86% versus 79%).⁶

Careful examination of the data from the Australian trial reveals that only one fourth of the patients had stones greater than 5 mm, and of those, 20% did not have 4-week posttreatment computed tomography (CT) scans, making a definitive assessment of stone passage impossible.