

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

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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.

Furthermore, only 5 more patients in the tamsulosin group passed stones compared with the placebo group (30 versus 25); these small numbers provide only marginal results and questionable benefit.

The benefits of α -blockade for stones greater than 5 mm have been primarily observed in secondary analyses of larger studies. There is a conspicuous lack of dedicated randomized controlled trials examining the effectiveness of medical expulsive therapy for larger stones. A recent meta-analysis seeking to address this deficiency found that in 8 studies of distal ureteral stones, tamsulosin increased stone passage, but this effect had high heterogeneity. In the subgroup analysis, tamsulosin was effective for stones greater than 5 mm (number needed to treat=5) and had no effect in stones less than 5 mm. The authors suggest that the subgroup analysis was likely to be real because it was an a priori hypothesis based on the study by Furyk et al,⁴ and it is biologically plausible (small stones have a high rate of passage, whereas large ones are less likely to pass, and it seems plausible that tamsulosin mainly benefits patients with more recalcitrant stones). Limitations of this analysis include the heterogeneity and lack of comprehensive subgroup data from all trials.⁷

In the trial from China, two thirds of the enrolled patients (>2,000) had stones between 5.1 and 7 mm, and one third had stones that measured 4 to 5 mm. This distribution of stone size differs markedly from that of other trials and raises concerns about the accuracy of stone assessments and lack of a formal protocol for stone size measurement on CT imaging. This is particularly concerning, given that small size differences (a few millimeters) are associated with potential benefit.

There are data in the literature in regard to the method for stone measurement on CT scan. Jendeberg et al⁸ published an article comparing the measurement of ureteral stones performed by an automated 3-dimensional algorithm and by manual measurement performed by 3 radiologists and its prediction rates of spontaneous passage. They found that, although at the distal ureter the discrepancy of the measurement is smaller compared with that at the upper ureter, it still occurs. The authors stated that “[a]n analysis of three radiologists’ stone measurements reveals that relatively small interindividual variations among

the three readers’ measurements result in large discrepancies in the predicted probability of spontaneous stone passage.”

The lack of precise protocols, tools, and software for stone measurement on all these randomized trials comparing α -blocker versus placebo for ureteral stone is a huge limitation. A 1-mm error can shift a patient from the smaller stone group analysis to the larger group analysis and can obviously affect the final result.

In summary, according to the available data, α -blockers appear to be ineffective for stones less or equal to 5 mm and those above the level of the sacroiliac joint. For stones greater than 7 mm, the data supporting medical expulsive therapy with α -blockers are very weak and therefore untrustworthy. For stones between 5.1 and 7 mm at the distal ureter, the data seem to show some benefits, but because of lack of precision of the stone measurement, these assessments are clinically unreliable, and for this reason, α -blockers may provide limited benefit in the treatment of ureteral stones.

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