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EAU Recommendation

Medical Expulsive Therapy for Ureterolithiasis: The EAU Recommendations in 2016

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Abstract

Medical expulsive therapy (MET), in particular α-blockers, have been recommended as supportive medication if observational treatment of a ureteral stone was an option. Over the years, a considerable number of randomized controlled trials (RCT) as well as several meta-analyses have been published on MET, supporting the use of α-blockers. However, several recently published high quality, large, placebo-controlled randomized trials raised serious doubts about the effectiveness of α-blockers. The contradictory results of meta-analyses of small RCTs versus the findings of large, well conducted multicenter trials show the methodological vulnerability of meta-analyses, in particular if small single center, lower quality, papers have been included. Small single center trials, for instance, tend to show larger treatment effects compared to multicenter RCTs. It also shows the responsibility of careful planning when conducting a RCT. Trial registration as a prerequisite for approval by ethics committees could in addition minimize publication bias. Weighting the current evidence on whether to use MET, or not, it seems that in distal ureteral stones larger than 5 mm, there may be a potential therapeutic benefit for the use of α-blockers. Patients should be informed about the possible, but as yet unproven benefit of using α-blockers in this situation, as well as their off-label use and potential side effects.

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Observational treatment is an option for small ureteral stones in patients with controlled symptoms. In particular, α-blockers have been recommended as supportive, so-called medical expulsive therapy (MET) [1,2]. In 1996, a Russian group demonstrated a positive effect of the α1-adrenoblocker doxazosin on urine outflow disorders [3]. To our knowledge, Cervenakov et al were the first, in 2002, to describe possible acceleration of stone expulsion with the use of the α1-blocker tamsulosin [4]. Since then, many randomized trials and several meta-analyses have been published [5–7]. Most have encouraged the use of α-blockers or calcium channel blockers to facilitate stone expulsion of ureteral calculi. Eventually, most treatment guidelines recommended α-blockers for MET. Nevertheless, some recently published high-quality and large placebo-controlled randomized trials have raised serious doubt

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about the effectiveness of α-blockers. A debate began about the usefulness of MET for conservative management of ureteral stones. This paper summarizes the actual evidence and the related panel and point–counterpoint discussions from the European Association of Urology (EAU) and American Urological Association (AUA) annual meetings and develops a current treatment recommendation.

Searches were carried out using the Cochrane Library Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, Medline, and Embase on the Dialog–Datastar platform up to April 2016. The focus of the searches was identification of meta-analyses of randomized controlled trials (RCTs). In addition, the search was extended to multicenter double-blinded placebo-controlled randomized trials involving >200 patients. They were selected because small single-center RCTs were included in the meta-analyses, and the authors were aware that small single-center RCTs tend to show larger treatment effects than multicenter RCTs usually do [8,9].

1. Evidence from meta-analyses

Various meta-analyses support the use of MET for ureteral stone management. Hollingsworth et al [6] included 693 patients from nine trials and found that patients given calcium channel blockers or α-blockers had a 65% greater likelihood of stone passage compared with those without MET.

Seitz et al pooled 2419 patients in a meta-analysis of 47 RCTs assessing the role of different substances evaluated for MET; only α-blockers and calcium channel blockers demonstrated higher and faster expulsion rates compared with controls, suggesting that MET with α-blockers or calcium channel blockers improves stone expulsion rates, reduces the time to stone expulsion, and reduces analgesic requirements for ureteral stones ≤10 mm [5]. In another meta-analysis focusing on α-blockers only, Campschroer et al compared α-blockers with alternative medications and placebo; they included 32 randomized trials with a total of 5864 participants and showed a noticeably shorter stone expulsion time with fewer pain episodes for MET with α-blockers [7].

Focusing on the comparison of an α-blocker (tamsulosin) and a calcium channel blocker (nifedipine), Wang et al performed a comprehensive search and meta-analysis including 12 RCTs with 4961 patients; they calculated a higher expulsion rate with the use of tamsulosin (risk ratio: 1.29; 95% confidence interval [CI], 1.25–1.33), reduced expulsion time (standard mean difference: −0.39; 95% CI, −0.72 to −0.05), and fewer complications compared with nifedipine and concluded that tamsulosin showed overall superiority to nifedipine [10].

In a recent systematic review and meta-analysis, Özsoy et al compared two α-blockers, silodosin and tamsulosin, as MET. They included three RCTs, two of them double blinded, and showed significantly higher stone expulsion rates and faster expulsion times in favor of silodosin compared with tamsulosin [11].

A major problem with most studies included in meta-analyses performed to date is the difference in primary outcomes used and the lack of information about how outcomes were measured. Stone passage rate and stone expulsion time are described in many studies, but it is not clear how they were measured (very few studies used computed tomography [CT] imaging, and expulsion time relied on patient recall).

2. Evidence from large placebo-controlled double-blinded randomized multicenter trials

In 2015, Pickard et al published a large, multicentric, double-blinded, three-way RCT comparing tamsulosin, nifedipine, and placebo. The authors defined as their primary end point the necessity of interventional stone removal and involved 1167 patients in 24 UK hospitals. The authors noticed no difference among tamsulosin, nifedipine, and placebo in terms of need for intervention, stone passage rate, or pain reduction [12]. Furyk et al recently performed a randomized, double-blinded, placebo-controlled, multicenter trial including 403 patients to compare tamsulosin and placebo for patients with distal ureteral stones only and stone size up to 10 mm. Only the subgroup analysis of stones 5–10 mm showed an increased passage rate in the tamsulosin group; in the overall analysis and in the subgroup of stones <5 mm, there was no significant difference [13].

A double-blinded study by Sur et al involving 27 locations randomized 246 patients to silodosin or placebo. There was no statistically significant difference in terms of overall stone passage, but the passage rate of distal ureteral stones was significantly higher with silodosin than placebo (69% vs 46%, respectively) [14].

3. Guidelines and medical expulsive therapy

In 2007, the EAU and AUA cooperative working group on guidelines on ureteral stones performed and published a meta-analysis of MET. The conclusions drawn were that α-blockers facilitate stone passage, that the positive impact of nifedipine was marginal, and that α-blockers may be the preferred agents for MET [15].

In 2016, the AUA published new guidelines on the management of ureteral stones. Based on its own meta-analysis focusing on distal ureteral stones <10 mm (n = 1215; 27 papers included, mean number of patients was 45), the AUA panel showed superior stone-free rates for those patients treated with α-blockers (77.3%) compared with placebo or no treatment (54.4%) [16]. This resulted in a statement that patients with uncomplicated ureteral stones <10 mm should be offered observation, and those with distal stones of similar size should be offered MET with α-blockers. Due to insufficient data, the AUA panel did not endorse calcium channel blockers as MET [16].

Through the years, the EAU guidelines on urolithiasis reported increased efficacy of MET for distal ureteral stones based on the meta-analyses published. The panel was aware

that meta-analyses based on randomized trials represent one of the highest levels of evidence [17], but meta-analyses depend on the quality of the included RCTs. The majority of published RCTs used for meta-analyses are very heterogeneous, include small numbers of patients (ie, are underpowered), and have known publication bias. The continued use of poor-quality data in each "new" meta-analysis calls the validity and reliability into question.

Nevertheless, the available evidence resulted in a grade A recommendation for MET using α-blockers [18]. In the 2016 issue of the EAU guidelines, the recommendations have been downgraded to grade C, recognizing the recent publications of multicenter, randomized, double-blinded and placebo-controlled studies. The EAU guidelines continue to recommend offering α-blockers as MET as one of the treatment options after informing the patient about the lack of efficacy in recent studies [19].

4. Discussion

The contradictory results of meta-analyses, on the one side, and large high-quality trials, on the other side, show the dilemma of defining and valuing best evidence. Well-performed, large, multicenter, placebo-controlled RCTs are assigned the highest level of evidence. In contrast, meta-analyses of small RCTs help generate hypotheses for more reliable RCTs rather than providing the best possible evidence [20].

The primary outcomes of the paper by Furyk et al were stone expulsion on CT at 28 d and time to stone expulsion [13]. Pickard et al defined the primary end point of their study as the difference in the need for further urologic interventions [12]. They avoided proving stone passage with CT imaging because it was not standard clinical practice in the United Kingdom and would have involved additional costs and radiation doses for study participants. One can argue that this appears to be a less precise surrogate marker to evaluate the true efficacy of MET for stone expulsion; however, in both studies, the event rates were almost identical, showing that stone passage occurred in almost 80%.

The study by Pickard et al [12] was not powered to assess the efficacy of MET in stones >5 mm in the upper or middle ureter. In addition, there were no significant differences in pain scales or number of rescue pain medications. These were secondary outcomes assessed with patient surveys, which suffered from decreased follow-up rates compared with the primary outcome (62% vs 97%).

The question is whether to base treatment decisions on meta-analyses composed of single-center, small, mainly low-quality trials favoring MET or on a few large high-quality trials with findings of no significant effect.

Further work is required to investigate the phenomenon of large, high-quality trials showing smaller effect size than meta-analyses of several small, single-center, lower quality studies. Results of meta-analyses should be subjected to careful sensitivity analyses to test the robustness of the findings and interpreted on principle with caution, even if the pooled effect is statistically significant. The question also arises as to whether all available evidence must be included in meta-analyses.

During both the AUA and EAU annual meetings, a panel discussion on the topic was held. At the EAU meeting, the panel agreed that the largest high-quality study, by Pickard et al [12], was not powered for stones >5 mm, and the EAU debate resulted in the recommendation for further high-quality multicenter and double-blinded RCTs with a well-controlled end point of stone passage rate. In contrast, at the AUA annual meeting, the conclusion was to continue offering α-blockers in particular for informed patients with distal ureteral stones of 5–10 mm, obviously in view of the AUA guidelines work.

5. Conclusions

The contradictory results of meta-analyses of small RCTs compared with large multicenter trials show the vulnerability of meta-analyses, which always have to be taken into account. This vulnerability emphasizes the responsibility of careful planning for RCTs. To minimize publication bias, trial registration should be a prerequisite of ethics committees for the approval of studies.

The current evidence on whether or not to use MET indicates that a potential benefit of MET (α-blockers) is most likely for distal ureteral stones >5 mm. For smaller ureteral stones (i.e., the majority of ureteral stones), there is no proven benefit. It is important to inform patients about the possible but as yet unproven benefit using α-blockers as well as their off-label use and possible side effects.

Further well-designed, double-blinded, placebo-controlled, multicentric RCTs with clearly agreed-upon end points are suggested to address the clinical question.

Conflicts of interest: The authors have nothing to disclose.

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