Re: What is the Role of α-Blockers for Medical Expulsive Therapy? Results From a Meta-analysis of 60 Randomized Trials and Over 9500 Patients

Whether alpha-blockers should be recommended as medical expulsive therapy in patients with symptomatic ureteral stones is much debated. Earlier trials supported the role of alpha-blockers, but most of them were limited by sample size and/or methodological shortcomings. Recent high-quality trials did not find evidence for the use of alpha-blockers to improve stone clearance[1-3] and therefore the role of alpha-blockers has been questioned again.

With interest we read the meta-analysis of Aboumarzouk et al (2018). The authors confirmed the beneficial effect of alpha-blockers on stone expulsion, specifically in stones >5 mm and those distally located. Interestingly, approximately in the same timeframe (March 2018), as part of the Cochrane Collaboration, we updated the earlier version of the Cochrane Review on this same topic.[4-5] In general, we show the same positive effects of alpha-blockers on stone passage rate and various other secondary outcome criteria as Aboumarzouk et al does. The authors used the same methodology for systematic reviews as proposed by the Cochrane handbook for their meta-analyses, like we did. However, small differences can be found when comparing both articles.

First of all, Aboumarzouk et al excluded data from abstracts or conference proceedings. In our latest Cochrane review we chose not to exclude possible significant abstracts and include the abstract we could interpret sufficiently to extract the necessary data from or we asked the authors by e-mail to give the essential raw data. Although usually abstracts do not give a thorough description of the methodology, they were assessed accordingly and possible bias was taken into account. Additionally, sensitivity analyses were performed, based on risk of bias, in which the conference proceedings were extracted, due to their high or unclear risk of bias.

Second, in line with the latest recommendation of the Cochrane Collaboration we applied the GRADE approach[6] (Grading of Recommendations Assessment, Development and Evaluation by using the GRADEpro Guideline Development Tool[7]) to rate the quality of evidence. Criteria related to both internal and external validity were considered. The GRADE approach has been endorsed by many international scientific communities to rate the quality of evidence. By doing so, one does not only take risk of bias of the included studies into account, but looks beyond to aspects such as inconsistency, indirectness, and imprecision. We believe that a quality of evidence assessment, such as GRADE, is crucial in adequately understanding the results of the systematic review.

Another difference between the 2 meta-analyses is the way adverse events were reported. Adverse events of alpha-blockers are an essential topic in this discussion, because cessation of therapy might result in surgical intervention and (re)hospitalization, resulting in higher health care costs. Aboumarzouk et al reported significantly more adverse events (RR 1.81, CI 1.47-2.28) in the alpha-blocker group compared with the control group. However, a substantial percentage of the reported adverse events were retrograde ejaculation, which could be considered reversible. In our opinion, this small increase of reversible adverse events caused by the alpha-blockers does not weigh against the potential benefits on stone passage. Therefore, we defined major adverse events (eg orthostatic hypotension, collaps, syncope, palpitations, or tachycardia) as one of the primary outcomes and studied the frequency of cessation of therapy due to adverse events. We did not find statistically significant difference between the alpha-blocker group and control group (RR 1.25, CI 0.80-1.96). Moreover, cessation of therapy was rarely seen. Therefore, we opt for stratification of the outcome adverse events into: (1) major adverse events; and / or (2) all adverse events, including the reversible events.

Fourth, the subgroup analysis based on stone location was categorized in 3 groups in the Aboumarzouk et al study (distal, mid, and proximal ureter), while we defined 2 groups (distal and mid- or proximal) as different definitions are applied for the term mid-ureter. We found only a borderline significant effect of alpha-blockers on stone expulsion for mid—and proximal stones (RR 1.28, CI 0.99-1.66) whereas Aboumarzouk et al found a significant effect (RR 1.25, CI 1.09-1.43) for the proximal stones. Therefore, we were not able to recommend the use of alpha-blockers for mid—or proximal ureteral stones.

Although we agree with the fact that a methodological risk of bias assessment is prone to subjective assessment, we have downgraded the studies more strictly. As described by the Cochrane handbook, one should not make any assumptions whenever the study authors fail to describe methodological issues. Consequently, we have downgraded many studies due to "unclear risk of bias." Lastly, Aboumarzouk et al (2018) reported a "subgroup analysis"(which actually should be considered as a sensitivity analysis) by including only studies with low risk of

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bias. They included 15 RCTs, all with low risk of bias on almost all domains. We were more strict with grading of these studies while we only found 5 studies with a low risk of bias on all domains. The results were however similar.

In conclusion, we would like to congratulate Aboumarzouk et al and colleagues for making great efforts to show the readers of this journal what the overall evidence on this topic is. Small differences in the methodology and the execution of the review steps can be found between his review and our 2018 Cochrane paper. However, the overall conclusion stays the same: alpha-blockers have beneficial effects on stone passage, have in general only minor adverse effects, and their use is most effective in distal ureteral stones of >5mm. If this answer was already available, one could wonder the need of a tremendous effort as Aboumarzouk et al has conducted, given that new research is expected to provide some (new) form of benefit to the patient.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.02.020.

References

1. Furyk JS, Chu K, Banks C, et al. Distal ureteric stones and tamsulosin: a double-blind placebo-controlled, randomized, multicenter trial. *Ann Emerg Med*. 2016;67:86–95.
2. Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;386:341–349.
3. Sur RL, Shore N, L'Esperance J, et al. Silodosin to facilitate passage of ureteral stones: a multi-institutional, randomized, double-blinded, placebo-controlled trial. *Eur Urol*. 2015;67:959–964.
4. Campschroer T, Zhu Y, Duijvesz D, Grobbee DE, Lock MT. Alpha-blockers as medical expulsive therapy for ureteral stones. *Cochrane Database Syst Rev* 2014:CD008509.
5. Campschroer T, Zhu X, Vernooij RW, Lock MT. Alpha-blockers as medical expulsive therapy for ureteral stones. *Cochrane Database Syst Rev*. 2018;4:CD008509.
6. Schünemann H, Brożek J, Guyatt G, Oxman A, eds. *GRADE handbook for grading quality of evidence and strength of recommendations*. The GRADE Working Group; 2013. Updated October 2013.
7. *GRADEpro Guideline Development Tool [Software]*. McMaster University; 2015. developed by Evidence Prime, Inc.

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Re: Comparing Off-clamp and On-clamp Robot-assisted Partial Nephrectomy: A Prospective Randomized Trial

Letter to the Editor:

We commend with Anderson and coworkers for their efforts. They performed a prospective randomized trial addressing the comparison of on-clamp vs off-clamp technique for robotic partial nephrectomy (RPN).[1] Recent systematic literature reviews already showed no impact of the technique used to manage the renal pedicle on either surgical or oncological outcomes.[2] This is debatable and based on pooled analyses of mostly small sample size studies, affected by several confounders, including selection bias (off-clamp approach is more likely performed in low complexity tumors) and heterogeneity in the surgical techniques used. Porpiglia et al reported on 87 patients who underwent laparoscopic partial nephrectomy by on-clamp or off-clamp approach.[3] Dr. Laguna referred to the study as the one with the closest design to a quasi-randomized controlled trial comparing laparoscopic partial nephrectomy with and without arterial clamping.[4] Notably, the strength of the study relied on the use of renal scan, assessing the operated kidney function at baseline and third month postoperatively, including both the percent reduction in split renal function and the estimated renal plasma flow (that unfortunately the authors did not include in the present study). Bertolo et al recently contributed to this field, performing a head-to-head comparison between 2 high-volume centers[5]: 400 on-clamp vs 200 off-clamp patients were analyzed after propensity-score matching for many potential confounders. They found no significant differences in key perioperative outcomes, confirming the literature trend once again. Finally, another randomized trial (the CLOCK trial, NCT02287987[6]) closed the recruitment with 301 patients who underwent RPN at 7 referral institutions. Results are awaited to be published next.

As stated by the authors themselves, the significance was not achieved in the present study due to the fact that the observed difference in the % change in estimated glomerular filtration rate (eGFR) between the treatment groups was much less than what the authors hypothesized at the time of the power analysis. Sample size was initially calculated considering the absolute change in eGFR (we would have some perplexities in basing the sample size calculation on an expected difference equal to 7 mL/min of eGFR), but surprisingly the authors used the % change (not the absolute difference) in eGFR as primary outcome. Thirty-seven vs 34 patients were actually analyzed. With a 5% alpha error and a power of 80%, the minimum effect size (Cohen's *d*) detectable by the study is 0.67, that approximately equals a 10% absolute difference between groups. Thus, the study would be unable to detect any variation below 10% as statistically significant. On the other