Critical Review Form

Meta-analysis

Medical therapy to facilitate urinary stone passage: a meta-analysis, *Lancet* 2006; 368:1171-1179

Objective: **"To derive a quantitative estimate of ureteral-stone expulsion associated with medical therapy." (p. 1171)**

Methods: **Investigators searched MEDLINE, CINAHL, and EMBASE from 1981-2005 for randomized controlled trials of medical management with CCB or α-antagonists for urolithiasis with no language restrictions. Control groups were determined *a priori* to not receive any other medical intervention which might facilitate stone passage. In addition to the electronic search, investigators hand-searched the scientific abstracts from 3 international Urology conferences from 1999 – 2005. Additionally, major drug manufacturers were contacted.**

The primary endpoint was proportion of subjects with spontaneous stone passage. Studies were analyzed by random-effects and fixed effects models, but the latter was used because no difference was noted between the analytical strategies. Heterogeneity was assessed with Cochrane's Q-test and I^2 statistic. Publication bias was assessed using a modification of Rosenthal's fail-safe number (the number of non-significant unpublished studies that would need to be published to reduce a statistically significant observed result to non-significant). An influence analysis was conducted by omitting one-study at a time and re-calculating the effect size. Individual study quality was assessed using criteria suggested by the Cochrane collaboration: method of randomization, allocation concealment, blinding, less to follow-up, and intention to treat analysis.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. What is the quantitative benefit of α-antagonists or CCB to facilitate non-surgical expulsion of symptomatic kidney stones?
2.	Was the search for relevant studies details and exhaustive?	Yes, using multiple electronic search engines, as well as contacting industry and scientific leaders.

3.	Were the primary studies of high methodological quality?	No. Eight trials non-blinded and six did not describe randomization procedures.
4.	Were the assessments of the included studies reproducible?	No, because the authors did not use a validated quality assessment tool like the Jadad scale.
II.	***What are the results?***	
1.	What are the overall results of the study?	• 434 studies were identified, 38 reviewed in detail and nine included with 693 patients in this analysis. Five additional studies lacked a true control group so results were calculated with and without these studies. • In those studies included, the mean age ranged 34-46 years and stone size 3.9 – 7.8 mm. Across all nine studies only 12 dropouts were reported. • Treatment duration ranged from seven days to six weeks and follow-up from 15 days to 48 days. • For α-antagonists and CCB combined, the fixed effects treatment effect was risk ratio 1.65 (95%, CI 1.45 – 1.88, $p< 0.001$) with NNT = 4 and no significant heterogeneity (Cochrane's Q-test p=0.196, $I^2 = 28\%$). • The Rosenthal fail safe number was 175 studies and the Rosenberg was 105 studies to reduce significance under 0.05 so significant publication bias was unlikely. • The risk ratio for tamsulosin alone was 1.52 (1.23 – 1.86, $p<0.0001$). Authors don't report NNT for this safe group, but calculated NNT 3.6 (95%, CI 2.7-5.7). • Subgroup analysis of those treated with and without NSAID's indicated no significant NSAID related stone expulsion rate. • When only published studies were analyzed the risk ratio did not change 1.68 (1.42 – 1.97). • The summary effect did not change with influence analysis. • Side-effects were not rigorously reported but ranged 3.3 – 4.2%. • Multiple trials showed that MET reduced need for analgesics, lost workdays, repeat ED visits, and need for surgical interventions.

2.	How precise are the results?	Narrow CI does not alter findings, so significantly precise.
3.	Were the results similar from study to study?	Yes, as pictured in Fig 3 (p.1174) every study favored therapy and 95% CI's widely overlapped.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	Medical therapy can benefit kidney stone patients with small to medium distal kidney stones and may represent safer, cheaper first line therapy.
2.	Were all patient important outcomes considered?	No assessment of QOL which some of the referenced studies did report.
3.	Are the benefits worth the costs and potential risks?	Yes, by the author's calculations based upon UM pharmacy costs, a 28 day course of doxazosin costs $10.74 and a 42 day course of tamsulosin is $104 compared with single-intervention therapies like ureteroscopy $2,645 and lithotripsy $4,225 which often also require repeat interventions.

Limitations

1) **Clinical heterogeneity may cloud interpretation of these results. Patients were recruited from a variety of locales (ED, Urololgy Clinic, PCP office) and likely received heterogeneous co-interventions. In particular, there may be an additive effect of corticosteroids.**

2) **Overall, low quality of studies. Unfortunately, the authors do not report the Jadad score to permit rapid quantitative, valid and reproducible quality assessment of the individual trials.**

3) **Industry sponsored meta-analysis authors, although their sponsors don't currently produce any renal colic related agents.**

Bottom Line

Low quality RCT's suggest that MET with either CCB or α-antagonists may be a cheap, effective addition to routine pain management with watchful waiting. For tamsulosin, the NNT = 4 (95%, CI 3-6) and multiple studies report enhanced stone passage, reduced analgesia requirement, and less lost workdays with MET. Compared with ureteroscopy and lithotripsy, MET may save $2,000 - $4,000 per patient. Future large RCT's will need to identify subjects of patients unlikely to respond to MET, adverse event rates, and the optimal MET agent, dosing, and duration of therapy.