*Credit to Dr. Christopher Carpenter

Critical Review Form
Meta-analysis

Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. Ann Emerg Med. 2007 Nov;50(5):552-63.

Objective: **"To critically evaluate the cu rrent body of evidence on medical therapy with α -antagonists and calcium channel blockers to facilitate spontaneous passage of distal ureteral calculi in adults." (p.553)**

Methods: **Two investigators reviewed abstracts resulting from a multi-faceted search of PUBMED, EMBASE, and the Cochrane Controlled Trials Register. Studies were limited to human subjects in randomized or controlled trials comparing the proportion of subjects receiving α-antagonist or calcium channel blockers (CCB) with successful kidney stone expulsion with the expulsion rate in those not receiving these agents. A secondary outcome was time to stone expulsion.**

When a likely article was identified by PUBMED, investigators used the "Related Articles" link to identify additional research evidence. The investigators also conducted a hand-search of the literature (seven prominent Urology journals), reviewed Urology conference scientific abstracts for the last seven years, and electronically contacted abstract authors to ascertain the status of unpublished abstracts.

Studies included had to be randomized or controlled, recruit subjects over 18 years of age, have clinically and radiographically confirmed acute ureteral colic, and use either an α-antagonist or CCB as medical expulsion therapy. Individual studies were assessed for quality using the CONSORT principles and the Jadad scale.

Investigators calculated a pooledrisk ratio with 95%, CI for both α-antagonists and CCB by using random effects model. Heterogeneity was assessed via Cochrane's Q-test, τ2 and I2 statistic. NNT was calculated from the point-estimate of RR. Publication bias was assessed with funnel plots, Egger regression asymme try test and the Begg adjusted rank correlation tests. An influence analysis was performed by re-calculating the pooled estimate by omitting one study at a time.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes – what is the effect of distal kidney stone passage successfully with medical therapy compared with routine pain management alone?
2.	Was the search for relevant studies detailed and exhaustive?	Yes – the investigators conducted a well described, reproducible search of various sources.
3.	Were the primary studies of high methodological quality?	No, as demonstrated in Tables 1-2 (p.555) the Jadad scores ranged 0-3 with a me dian score of 2 for both α - antagonist and CCB. Absence of double-blinding was the most common deficiency.
4.	Were the assessments of the included studies reproducible?	Yes, since the authors used the validated Jadad score.
II.	***What are the results?***	
1.	What are the overall results of the study?	• MEDLINE search yielded 4,443 articles and additional search strategies yielded 15 more articles. Ultimately, 22 articles were included in this meta-analysis. • No study followed the revised CONSORT standards. • Five abstracts were included, but no original investigator responded to electronic communication for more information. **α-antagonists** • The median follow-up period was 4-weeks. • The average stone size was >5mm in all but five trials. • A total of 1,235 patients were reported in 16 trials. • Tamsulosin was used in 13/16 trials. • Mild heterogeneity was identified by I2 (30%), though the Cochrane Q-statistic was not significant (p=0.13). • Evidence for *publication bias* favoring beneficial effects was detected by funnel plot (Fig 3, p.577) and Egger's test (p=0.02). • Point estimate favored addition of α-antagonist to standard therapy with RR 1.59 (95%, CI 1.44 – 1.75) and NNT 3 (95%, CI 2.1 – 4.5). • Nine trials assessed time to expulsion with a 2-6 day

		improvement (upper limit 14-days by 95%, CI). • Adverse effects occurred in 4% but were inconsistently reported. Dizziness was the most common adverse effect. Only one patient (0.2%) had to discontinue therapy for asthenia • Influence analysis of higher quality (Jadad ≥ _3) studies vs. lower quality studies did not alter the point estimate (RR = 1.66). Removal of one study significantly reduced heterogeneity (I2 30% → _5%) but did not significantly reduce the treatment effect (RR 1.54). **CCB** • A total of 686 patients were reported in nine trials. • Nifedipine was used in all trials. • No heterogeneity was noted between studies via Cochrane's Q-statistic (p=0.566) and I2 statistic (0%). • The funnel plot demonstrated mild asymmetry (Fig 5 p.559), but Egger's test revealed no evidence of publication bias (p=0.31). • For stone expulsion time, the upper limit of 95% CI was 28-days. • 15% of subjects reported adverse effects (led by nausea and asthenia) and 2.9% had to discontinue therapy. • CCB improved stone expulsion rates with RR 1.50 (95%, CI 1.34 - 1.68) and NNT 3.9 (95%, CI 3.2 – 4.6). • Influence analysis of higher quality studies improved the treatment effect slightly RR 1.60 (95%, CI 1.28 – 2.01). • No trials assessed α-antagonists versus or in conjunction with CCB. • Evaluation of various trials using concurrent anti-cholinergic agents or steroids did not significantly alter the point estimates for α-antagonists or CCB (Tables 5 and 6, p 559).
2.	How precise are the results?	Very consistent point-estimates and narrow CI's reported
3.	Were the results similar from study to study?	Yes. See Fig 2 and Fig 4 (pp 557-558).
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?	Both α-antagonists and nifedipine increase the proportion of patients with successful kidney stone passage compared with standard therapy. Medical expulsion therapy should be maintained for 14-28 days.
2.	Were all patient important outcomes considered?	No, adverse effects were not consistently evaluated or reported. Additionally, the SR investigators did not report on re-hospitalization rates, urgent ureteroscopy, analgesic requirements, QOL, or work-days lost though individual trials reported those outcomes.
3.	Are the benefits worth the costs and potential risks?	Yes, if pain can be more quickly alleviated with infrequent side effects.

Limitations

1) **Overall low quality studies with median Jadad score 2. Historically, one-third of meta-analyses have been overturned by subsequent large RCT's so before widespread acceptance of these results a well-done RCT should confirm the findings.**

2) **Publication bias may have skewed the α-antagonist results in favor of benefit.**

3) **Most patients were enrolled from the Urology office. These patients may differ from ED populations with more persistent pain and/or financial means to follow-up, thus limiting external validity.**

Bottom Line

Low-quality RCT's suggest that both α-antagonists (primarily tamsulosin NNT = 3) and nifedipine (NNT = 4) improve moderate sized (more than 5mm) distal kidney stone expulsion rates compared with standard medical therapy. CCB may have more adverse side effects than α-antagonists (4% vs. 15%). Both therapies reduce the time to stone expulsion with upper limit of 95% CI 14-days (α-antagonists) or 28-days (CCB).