Medical therapy to facilitate urinary stone passage: a meta-analysis

CRD summary
This review assessed the efficacy of calcium-channel or alpha blockers to treat urinary stone disease. The authors concluded that medical therapy appeared to be an option for patients amenable to conservative management, potentially obviating surgery, but a high-quality randomised trial was necessary. The conclusion appears reliable with the reservation that medical therapy was not directly compared with surgery within the reviewed studies.

Authors' objectives
To assess the efficacy of calcium-channel blockers or alpha blockers to treat urinary stone disease.

Searching
MEDLINE, PREMEDLINE, CINAHL and EMBASE were searched from 1981 to July 2005; the search terms were reported. In addition, abstracts from the annual meetings (1999 to 2005) of the World Congress of Endourology, the European Association of Urology, and the American Urological Association were screened, and authors and drug manufacturers were contacted for unpublished or ongoing trials. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. Non-research reports (editorials or commentaries) and observational studies were excluded.

Specific interventions included in the review
Studies in which a calcium-channel blocker or an adrenergic alpha-antagonist was used as main therapy for ureteral stone disease were eligible for inclusion. Studies in which medical therapy was investigated as an adjuvant to surgery were excluded. Studies in which the control groups had received any medical therapy to ease urinary stone passage, including vasodilators, antispasmodics, anticholinergic therapy or corticosteroids, were also excluded. The patients in the included studies were treated with nifedipine, tamsulosin, terazosin or doxazosin. All patients were treated on an outpatient basis; the treatment duration ranged from 7 days to 6 weeks, or until stone passage if before 6 weeks. In some studies the treatment and the control group received additional non-steroidal anti-inflammatory drugs.

Participants included in the review
Studies of patients with urolithiasis were eligible. The patients in the included studies suffered from mean stone sizes of 3.9 to 7.8 mm. In all but one study the stones were located in the distal third of the ureter.

Outcomes assessed in the review
Studies that reported the proportion of patients who passed stones were eligible. The studies had to have a minimum follow-up period of 1 week to be eligible for inclusion. Mean time to stone passage and side-effects were also extracted, as were other outcomes reported in the individual studies.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The method of randomisation, concealment of allocation, blinding, loss to follow-up and intention-to-treat analysis were assessed. The authors did not state how the validity assessment was performed, although it might have been part of the duplicate data extraction.
Data extraction
Two reviewers independently extracted the data using standardised forms. One was blinded to the source of publication and the authors' names. Inconsistencies were resolved through discussion until consensus was reached. Authors were contacted for clarification and to identify duplicate publications. The reviewers extracted the proportion of patients taking medical therapy who passed stones and the proportion of those not taking medical therapy who passed stones. This was based on an intention-to-treat analysis with the assumption that drop-outs failed to pass stones.

Methods of synthesis
How were the studies combined?
The effect sizes of the individual studies were combined in fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) meta-analyses: as both gave similar results, only those of the fixed-effect analysis, together with 95% confidence intervals (CIs), were reported. The number-needed-to-treat (NNT) was also calculated with 95% CIs (Newcombe-Wilson hybrid score method). Publication bias was assessed using the Rosenthal and Rosenberg fail-safe numbers; the latter is weighted by study variance. Fail-safe numbers of less than 5n+10 (with n being the number of studies in the meta-analysis) were considered indicators of publication bias.

How were differences between studies investigated?
Statistical homogeneity was assessed using Cochran's Q test and the I-squared statistic. The effects of each study on the pooled estimates were computed in an influence analysis. Sensitivity analyses were undertaken based on quality criteria. Subgroup analyses by drug type used a priori defined treatment groups. Identified trials without non-treatment control groups were used in a sensitivity analysis to examine the effect of their inclusion on the overall risk ratios.

Results of the review
Nine RCTs (n=693) were included in the review.

The randomisation method in the included studies was computer-generated sequence, coin toss, or not stated (5 out of 9). All but one study was not blinded. The loss to follow-up ranged from none (n=6) to 1 to 10%, with equal distribution among treatment and control groups.

Patients given calcium-channel or alpha blockers had a 65% greater likelihood of stone passage than those not given such treatment. The pooled risk ratio in favour of the treatment group was 1.65 (95% CI: 1.45, 1.88, p<0.0001), based on 9 trials, with no indication of statistical heterogeneity (p=0.196); the absolute risk reduction was 0.31 (95% CI: 0.25, 0.38) and the NNT was 4. In all trials the primary outcome of interest (the proportion of patients who passed stones) occurred more often in the treatment group than in the control group. In 5 out of 6 trials the treatment groups had shorter mean times to stone expulsion than the control groups.

The pooled risk ratio for alpha blockers was 1.54 (95% CI: 1.29, 1.85; p<0.0001; based on 5 studies); the respective value for calcium-channel blocker with steroids was 1.90 (95% CI: 1.51, 2.40, p<0.0001; 3 studies).

The noted side-effects included dyspepsia, nausea, vomiting, drowsiness, euphoria, transient hypotension, systolic blood-pressure of less than 100 mmHg and palpitations, headaches, asthenia and dizziness in the treatment groups; and nausea, vomiting, drowsiness, headaches, dizziness, diarrhoea and abnormal ejaculation in the control groups. There were 7 drop-outs in the treatment groups and 5 in the control groups.

The Rosenthal and Rosenberg fail-safe numbers were 175 and 105, respectively, which represents the number of additional non significant studies required to reduce the pooled risk ratio to non significance (p=0.05).

Cost information
The discussion stated that potential cost-savings of expulsive medical therapies in lieu of surgical interventions is large and, in the USA alone, the total annual expenditure associated with urolithiasis increased by 50% between 1994 and 2000. Surgical interventions were costly, with estimates ranging from $2,645 for ureteroscopy to $4,225 for shockwave lithotripsy, and repeated interventions were common. Expulsive medical therapy was inexpensive and costs would
range from $10.74 for a 28-day course of doxazosin to $104.41 for a 42-day course of tamsulosin (based on drug cost data from the University of Michigan pharmacy).

**Authors’ conclusions**
The results suggested that medical therapy is an option for facilitation of urinary stone passage for patients amenable to conservative management, potentially obviating the need for surgery, but a high-quality randomised trial is necessary to confirm the efficacy.

**CRD commentary**
The review stated a clear question and well-defined inclusion criteria. The search aimed to identify published and unpublished relevant literature and no language restrictions were applied; this helped to prevent language and publication bias being introduced into the review. Care was taken throughout the review process to reduce errors and bias, but no such measures were reported at the study selection stage. The quality of the included trials was assessed and quality criteria were used for sensitivity analyses.

Details of the included studies were provided and these enabled an overview of the existing evidence; all included trials employed only relatively small samples. The statistical analyses were thorough and included comparisons with pertinent studies not meeting the inclusion criteria. The conclusion appears reliable, but it should be noted that the reviewed studies did not include direct comparisons between expulsive medical therapy and surgery.

**Implications of the review for practice and research**
Practice: The authors stated that the potential cost-savings of expulsive medical therapies in lieu of surgical interventions are large. Surgical procedures exposed patients to anaesthetic and surgical risks that might be unnecessary.

Research: The authors stated that a definitive high-quality RCT trial is necessary to confirm the efficacy of calcium-channel blockers and alpha blockers in patients with urolithiasis. The sample should involve 113 patients in each treatment arm to show a significant effect (using the lower CI limit of the pooled relative risk 1.45, a background occurrence of stone passage of 0.47, a two-sided alpha error of 0.05 and a power of 0.90); if the occurrence of stone passage in the controls was lower (30%), the required sample would be 532 patients in total; if the occurrence was higher (60%), the study would require 110 patients.

**Bibliographic details**

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**Other publications of related interest**
This additional published commentary may also be of interest. Curhan GC. Review: medical therapy with calcium channel blockers or alpha blockers helps patients to pass urinary stones. Evid Based Med 2007;12:15.

**Indexing Status**
Subject indexing assigned by NLM

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