Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis

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Authors' objectives
The authors aimed to compare the rates of recurrent calcium renal stone formation for medical treatment versus placebo or no treatment.

Searching
MEDLINE was searched from 1980; the keywords were stated. The reference lists in identified studies were also checked.

Study selection
Study designs of evaluations included in the review
Only studies that presented adequate data were eligible for inclusion. All of the included studies were randomised controlled trials (RCTs).

Specific interventions included in the review
Studies of medical treatment used for secondary prevention were eligible for inclusion. The drugs used in the included studies were thiazide diuretics (trichlormethiazide, hydrochlorothiazide, bendroflumethiazide, chlorthalidone), indapamide, allopurinol, magnesium (various doses), alkali citrate, phosphate (sodium acid, sodium and orthophosphate formulations) and a non-thiazide diuretic.

Participants included in the review
Studies of patients who had repeatedly formed renal stones were eligible for inclusion. Some of the included studies selected only stone formers with hypercalcuria; other studies were of unselected stone formers.

Outcomes assessed in the review
Studies that assessed calcium renal stone formation were eligible for inclusion. The included studies measured stone formation as stones/patient per year or as remission rates.

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 authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Information on the drug treatment, hypercalcuric or unselected patients, study duration and sample size were tabulated. The authors estimated the stones/patient per year and remission rates for both treatment groups for each individual RCT, and tested the statistical significance of the results.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the drug studied, with indapamide being included with the thiazide diuretics, and a narrative synthesis was initially undertaken. Then, a random-effects model was used to estimate the pooled risk differences (RDs) and 95% confidence intervals (CIs) for studies that reported the number of patients with and without stone formation for all treatments versus no treatment combined, and then for each treatment group where possible.
How were differences between studies investigated?
Statistical heterogeneity was not formally tested. Forest plots were used to display the RD and 95% CIs for individual RCTs for all treatments versus placebo or no treatment, and for thiazide diuretics versus placebo.

Results of the review
Fourteen RCTs (939 patients) were included.

All RCTs combined (12 RCTs): medical treatment significantly reduced stone recurrence; the RD was -22.6% (95% CI: -29, -16.3, P<0.001).

Thiazide diuretics plus indapamide (8 RCTs, 496 people): 6 RCTs found that thiazides significantly reduced stone recurrence. Two RCTs with a treatment duration of less than 2 years found no significant difference between thiazides and control. Thiazides significantly reduced stone recurrence; the RD (6 RCTs) was -21.3% (95% CI: -29.2, -13.4, P<0.001).

Allopurinol (4 RCTs, 134 people): one RCT (60 people, the largest RCT) found that allopurinol significantly reduced stone recurrence compared with placebo or no treatment in hyperuricosuric, normocalcuric patients. The other 3 RCTs found no significant difference between allopurinol and placebo.

Phosphate (3 RCTs, 103 patients): none of the RCTs found any significant difference in stone recurrence between phosphate and placebo or no treatment.

Magnesium (2 RCTs, 89 patients): neither RCT found any significant difference in stone recurrence between magnesium and placebo or no treatment in unselected patients.

Alkali citrate (3 RCTs, 117 patients): the results differed. One RCT found that potassium citrate significantly reduced stone recurrence compared with placebo or no treatment in patients with isolated hypocitraturia. Another RCT found that potassium magnesium citrate significantly reduced stone recurrence compared with placebo or no treatment in unselected patients. The remaining RCT found no significant difference between sodium potassium citrate and no treatment in unselected patients.

Authors' conclusions
Medical treatment reduced calcium renal stone recurrence. Thiazide diuretics significantly reduced stone recurrence; there were insufficient studies and data to assess the effect of other individual medical treatments.

CRD commentary
The review question was clear in terms of the participants, intervention and outcomes, although the inclusion criteria were not explicitly defined. Only one database was searched and this may have resulted in the omission of other relevant studies. The search dates were not specified clearly and it was unclear whether any language restrictions had been applied. No attempt was made to locate unpublished studies, thus raising the possibility of publication bias. The methods used to select the studies, assess validity and extract the data were not described. Hence, efforts made to reduce errors and bias cannot be judged. Validity was not formally assessed and study quality was not discussed in the text.

Some relevant information on the included studies was tabulated, but the methods used to measure stone formation in the individual studies were not described. The studies were appropriately grouped by drug treatment and, initially, a narrative synthesis was undertaken. Studies with sufficient data were then combined in meta-analyses without a formal assessment of statistical heterogeneity. The forest plot clearly showed significant heterogeneity for all treatments combined versus placebo, but the authors did not explore potential reasons for this. This significant heterogeneity suggests that a meta-analysis may not have been appropriate for all treatments versus placebo, and that no firm conclusions were possible for all medical treatments combined. The evidence presented supports the authors' conclusions regarding the effectiveness of thiazide diuretics and the lack of sufficient data to reach conclusions about other medical treatments.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that clinical trials should be standardised with respect to study design, inclusion criteria for the participants, and the reporting of outcomes in terms of stones/patients per year or stone remission rate.

Bibliographic details


PubMedID

10608521

Indexing Status

Subject indexing assigned by NLM

MeSH

Allopurinol /therapeutic use; Benzothiadiazines; Calcium Oxalate /metabolism; Citrates /therapeutic use; Diuretics; Humans; Kidney Calculi /drug therapy /metabolism /prevention & control; Phosphates /therapeutic use; Randomized Controlled Trials as Topic; Secondary Prevention; Sodium Chloride Symporter Inhibitors /therapeutic use

AccessionNumber

12000000110

Date bibliographic record published

30/06/2004

Date abstract record published

30/06/2004

Record Status

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