Title of the Systematic Review:
The Effectiveness of Lemon Solution versus Potassium Citrate in the Management of Hypocitraturic Calcium Kidney Stones: A Systematic Review

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Program: Master in Clinical Science
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Title of Systematic Review Protocol

The effectiveness of lemon solution versus potassium citrate in the management of hypocitraturic calcium kidney stones: A systematic review

Review Questions/Objectives

The objective of this systematic review is to critically analyse the quantitative research studies and present the best available evidence related to the effectiveness of lemon solution compared with the effectiveness of potassium citrate in the management of hypocitraturic calcium kidney stones for adults. The more specific review question is: Is lemon solution as effective as potassium citrate in the management of hypocitraturic calcium kidney stones for adults?

Background

The prevalence and incidence of kidney stones, has been increasing in many countries across the globe. For example, the prevalence of kidney stones doubled during 1964-1994 in the United States and 1965-2005 in Japan culminating in incidences of 1116 and 1143 per 100,000 affected individuals reported in the USA in 2000 and in Japan in 2005, respectively.1

Kidney stones develop when crystals, predominantly of calcium salts, precipitate and accumulate within the kidney and other components of the urinary tract.2 The definition of nephrolithiasis is the presence of stones within the kidney, whilst urolithiasis is a more general term that means stones anywhere within the urinary tract (the kidneys, ureters, bladder, and urethra).2 The types of stone that lead to kidney stones can be described according to their composition and they include: calcium oxalate stones (59%), calcium phosphate stones (10%), uric acid stones (17%),
struvite or infection stones (12%), and cystine and other stones (2%). The diagnostic criteria for the type of calcium kidney stones is based on stone analysis. This systematic review will focus on studies of adults with calcium oxalate and/or calcium phosphate kidney stones that appear anywhere in the urinary tract and are related to the management of hypocitraturia.

Kidney stones are usually asymptomatic; however, identified manifestations of kidney stones include acute flank pain, loin pain, urine frequency, dysuria, and haematuria. Surgical intervention is required when stones cause obstruction, bleeding, severe pain, and/or serious infection. Almost 50% of people with kidney stones have recurrences within 10 years and it causes pain, distress, and also adds an economic burden.

Risk of kidney stones can be increased by both lifestyle and non-lifestyle factors. Lifestyle factors include low fluid intake, excess intake of foods with sodium, oxalate or animal protein, and long-hours working in hot environments resulting in high fluid loss. Factors unrelated to lifestyle include suffering urinary tract infection, chronic inflammatory bowel disease, bone loss, and metabolic abnormality. The causes of calcium oxalate and calcium phosphate kidney stones include hypocitraturia, hypercalciuria, hyperuricosuria, hyperoxaluria, and low urine volume. Idiopathic low urine citrate, chronic metabolic acidosis, renal tubular acidosis, and inflammatory bowel disease can cause hypocitraturia.

Hypocitraturia is a common metabolic risk factor which occurs in 16-63% of calcium stone formers. Citrate is an important inhibitor in stone formation and low urinary citrate excretion has been related to the development or recurrence of kidney
There is a non-uniform definition of hypocitraturia based on literature review. Hypocitraturia is commonly defined in adults as total daily urinary citrate excretion of less than 320 mg.\textsuperscript{8,9,10,20} Hypocitraturia is also defined as total daily urinary citrate excretion of less than 500mg.\textsuperscript{11} Increasing urinary citrate can act in renal tubules to reduce saturation of both calcium oxalate and calcium phosphate and prevent resultant crystal agglomeration and growth. Increasing urinary citrate may also avoid adhesion of calcium oxalate to renal epithelial cells.\textsuperscript{8}

In the pharmacological treatment of hypocitraturic calcium kidney stones, potassium citrate is a common intervention that is recognised widely by most clinicians. Potassium citrate is given as a solution and achieves its beneficial effect as a result of its citraturic and alkalinising actions.\textsuperscript{3,8,12,13} The average dose of potassium citrate is a total of 40 mEq per day; the dose may be increased or decreased based on monitoring of changes in the levels of urinary citrate.\textsuperscript{12}

Side-effects of potassium citrate including nausea, vomiting, diarrhoea, and stomach ache, which can deter some patients to continue the treatment of potassium citrate. The cost of long-term use of potassium citrate can also be a financial burden to some patients. Therefore, the alternative intervention of consuming citrus fruits, in particular lemons, has been proposed for the management of hypocitraturic calcium kidney stones.\textsuperscript{8}

Increased fluid intake and dietary modification are recommended in the concurrent management of hypocitraturic kidney stones.\textsuperscript{8} Fluid intake (mainly water) is recommended to ensure 24-hour urine output of at least 2,000 ml daily. This is a general intervention for prevention of kidney stone recurrence.\textsuperscript{3} The increased output
of dilute urine subsequently decreases the saturation of stone-forming salts and the concentration of constituent ions.\textsuperscript{14}

Increased consumption of citrus fruits is a type of dietary modification which can increase urinary citrate excretion in people who are predisposed to form kidney stones (hypocitraturic stone formers).\textsuperscript{6} Studies investigating the effectiveness of citrus fruits in the management of hypocitraturic kidney stones however, have shown controversial results.\textsuperscript{14,15,16,17} Blackcurrant juice increases the urinary pH, but cranberry juice decreases the urinary pH.\textsuperscript{14} Grapefruit juice does not alter urinary calcium phosphate, calcium oxalate, and uric acid.\textsuperscript{15} Orange juice reportedly lacks the ability of potassium citrate to reduce urinary calcium oxalate.\textsuperscript{16} Lime powder appears to exert both citraturic and alkalinising actions as efficiently as potassium citrate.\textsuperscript{17}

Two studies demonstrate that lemon interventions reduce urinary calcium level and increases urine output more effectively than potassium citrate.\textsuperscript{11,18} The effect is most likely due to the fact that lemons contain the highest concentration citrate acid and sodium, and the lowest concentration of calcium compared with other citrus fruits.\textsuperscript{19,20} One study shows that lemons in the form of lemonade is better than potassium citrate in assisting patients for maintaining good urine output.\textsuperscript{21} Lemons in solution may also have the added advantage of reduced incidence or severity of side-effects, compared with potassium citrate. The amount of lemon consumption in the management of hypocitraturic calcium kidney stones needs to be clarified as does the effect of sugar concentration within these fruit beverages. High fructose consumption has recently been identified as a risk factor for the development of kidney stones.\textsuperscript{22}
High fructose consumption is associated with urinary environment that predisposes to stone formation, including decreased urinary pH and increased urinary concentration of uric acid, calcium and oxalate.22

There is a need to conduct a systematic review for synthesis of best clinical evidence regarding the effectiveness of lemon solution as an alternative intervention in the management of hypocitraturic calcium kidney stones. The purpose of this systematic review is to compare the effectiveness of an alternatively specific intervention-lemon solution, with potassium citrate in the management of hypocitraturic calcium kidney stones for adults. The systematic review may have great impact on the management of hypocitraturic calcium kidney stones globally due to the preference of patients and easy access to lemon solution in hospitals, communities, and homes. The intervention of lemon solution may be more convenient and cheaper than the intervention of potassium citrate.

The Joanna Briggs Institute Library and Cochrane Library of Systematic Review and the electronic databases of CINAHL, and PubMed were searched and no available systematic review on this topic was found before conducting this systematic review.

**Inclusion Criteria**

**Types of participants**

The participants of interest include adult and elderly patients who are 18 years or above. There is no limitation with gender, ethnicity, and settings. Patients who are required to have surgical intervention or have acute symptoms such as acute pain, obstruction, bleeding, and severe infection are also included. Participants are
diagnosed with the types of calcium oxalate and/or calcium phosphate kidney stones based on stone analysis and presenting total daily urinary citrate excretion of less than 320 mg or 500 mg. Other diagnostic methods for stone analysis are specified by research investigators will be included.

**Types of interventions**

The intervention of interest is lemon solution in the management of hypocitraturic calcium kidney stones. For instance, lemon solution includes commercial beverages of lemonade, and using fresh lemon juice with water only and/or sugar. Approximately 85cc of lemon juice contains 60 mEq (4.2 gm) citrate. The daily dose of lemons’ citrate is given as equal as comparator-potassium citrate. Nursing staff daily make a jug of lemon water (1,000ml – 2,000ml) and delivery to participants. The participants have to finish the jug of lemon water in 24 hours. Lemon water also can be delivered as a single serve (e.g. 250-350 ml) after 3 meals. Participants in communities or homes are trained to administrate this intervention.

**Types of comparator**

The comparator is the drug intervention of potassium citrate administered orally in the management of hypocitraturic calcium kidney stones. A typical dose of potassium citrate for adults is from 40 to 60 mEq daily. The dose of potassium citrate can be increased or decreased based on inpatient monitored changes in urinary citrate level. Nursing staff daily delivery potassium citrate to participants after 3 meals. Participants in communities or homes administrate potassium citrate by themselves based on doctor’s prescriptions. The total daily dose of potassium citrate can be taken 2-3 times based on doctor’s prescriptions. Potassium citrate can be taken for short-term or life time based on the individual’s needs.
Types of outcomes measures

The primary outcome measures of interest are the clinically relevant outcomes:

- pain level (e.g., subjective pain scale/self-reported pain scores) in both management groups
- the rate of stone recurrence in both management groups (new stone formation or growing of the existing stone is considered as stone recurrence)
- total surface area of stones in both management groups
- incidence of stone passage in both management groups

The secondary outcomes:

- the concentration of urinary calcium level in 24-hour urine in both management groups
- the concentration of urinary citrate level in 24-hour urine in both management groups
- the result of urinary pH in 24-hour urine in both management groups
- the result of the total volume of 24-hour urine in both management groups

Types of studies

This systematic review will include randomised controlled trials and quasi-experimental studies that report the effectiveness of lemon solution versus potassium citrate in the management of hypocitraturic calcium kidney stones for adults.

Search Strategy

The search strategy aims to find out both published and unpublished studies in English language. Published studies up to September 2011 will be searched through
computerised databases. A three-step search strategy will be used and followed. Firstly, the initial phase consisting of searches of the PubMed, Scopus, and CINAHL databases will be conducted by using keywords or terms. The initial keywords include lemon or lemonade, potassium citrate, hypocitraturia, kidney stones or nephrolithiasis or ureter stones or ureterolithiasis or bladder stones or cystolithiasis or urolithiasis.

Secondly, a more extensive search will be performed by using the appropriate keywords/phrase and subject headings for each of the databases listed below. Thirdly, the references lists and/or bibliographies of identified articles and reports will be hand searched for additional relevant studies. Searching on selected relevant journal website will be performed.

Databases to search will include:

(1) BioMed Central
(2) CINAHL
(3) Cochrane Central Register of Controlled Trials
(4) Embase
(5) Scopus
(6) PubMed
(7) Web of Science

The grey literature search consisted of:

(1) Current Controlled Trials
   http://www.controlled.trials.com/
(2) Google Scholar
   http://scholar.google.com.au
Hand searching consisted of conducting an online search of relevant journals including:

1. Kidney International (e-journals)
2. Searching reference lists or biographies of included studies

**Assessment of Methodological Quality**

All quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological quality prior to inclusion in the review and it is based on using the standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MASTARI) (Appendix I). Any disagreements between the two independent reviewers will be resolved through discussion with a third reviewer.

**Data Extraction**

All relevant quantitative data will be extracted from papers included in the review based on using the standardised data extraction tool from JBI-MASTARI (Appendix II). The data extracted will include specific details about the populations, interventions, study methods, and outcomes of significance to the objectives of the view.
Data Synthesis

All selected quantitative papers if appropriate will be pooled in statistical meta-analysis based on using JBI-MAStARI. All results will be subjected to double entry. Odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed based on using the standard Chi-square. As fluid administration is also a common adjunct treatment for kidney stones, the intervention or comparator of interest with any large difference in concurrent fluid volume may be the basis for analysis and presentation of subgroups in this review. Consideration of fructose concentration co-administered may also similarly be addressed via subgroups if necessary. Where statistical pooling is not possible, the findings will be presented in narrative form.

Conflicts of Interest

No conflicts of interest are known.

Acknowledgements

As this systematic review forms part of a submission for a MSc Clinical Sciences, a secondary reviewer will only be used for critical appraisal and data entry stages of the review.
References


Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907772/


Appendix I- JBI Critical Appraisal Checklist for Experimental Studies

JBI Critical Appraisal Checklist for Experimental Studies

| Reviewer __________________ | Date __________ |
| Author ____________________ | Year __________ | Record Number _____ |

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<tr>
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<th>Yes</th>
<th>No</th>
<th>Unclear</th>
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<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions?</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include □ Exclude □ Seek further info. □

Comments (Including reasons for exclusion)

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Pei-Ling Yang (Peggy)
Appendix II- JBI Data Extraction Form for Experimental/Observational Studies

JBI Data Extraction Form for Experimental/Observational Studies

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<tr>
<td>Journal</td>
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Study Method
- RCT
- Quasi-RCT
- Longitudinal
- Retrospective
- Observational
- Other

Participants
- Setting
- Population
- Sample size

Interventions
- Intervention 1
- Intervention 2
- Intervention 3

Interventions

Clinical outcome measures

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<th>Outcome Description</th>
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### Study results

#### Dichotomous data

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<thead>
<tr>
<th>Outcome</th>
<th>Intervention ( ) number / total number</th>
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#### Continuous data

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<tr>
<th>Outcome</th>
<th>Intervention ( ) mean &amp; SD (number)</th>
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### Authors Conclusions

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### Comments

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