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INVITED REVIEW

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Preventive treatment of nephrolithiasis with alkali citrate—a critical review

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Abstract Using the keywords "urolithiasis and citrate treatment", "nephrolithaisis and citrate treatment", "kidney stones and citrate treatment", a Medline search revealed 635 articles published between 1 January 1966 and 1 December 2004. For the present analysis, only studies meeting all of the following criteria were included: (1) publications in English or German, (2) studies on preventive alkali citrate treatment in patients with calcium oxalate, uric acid and infection stone disease, (3) clinical studies including at least ten subjects, and (4) treatment phases of at least 1 week duration. A total of 43 studies met the inclusion criteria and were further subclassified according to intermediate or ultimate endpoints as well as to study design. With stone recurrence as the ultimate endpoint, 21 uncontrolled studies in almost 1,000 patients demonstrated a reduction in stone forming rate by 47–100%. In four randomized controlled trials including 227 patients, 53.5% on alkali citrate vs 35% on placebo remained stone-free after at least 1 year of treatment ($P < 0.0005$). Similar values (66% vs 27.5% for alkali citrate vs placebo, $P < 0.0005$) were obtained in 104 patients from two randomized trials with dissolution/clearance of residual stones as endpoint. Unfortunately, up to 48% of alkali citrate treated patients left the studies prematurely, primarily due to adverse effects such as eructation, bloating, gaseousness or frank diarrhea.

Keywords Urolithiasis · Nephrolithiasis · Calcium oxalate · Uric acid · Citrate · Alkali citrate treatment

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Introduction

Citrate retards the crystallization of stone-forming calcium salts in urine [1] and mediates the inhibitory effects of macromolecular modulators of calcium oxalate crystallization [2, 3]. Therefore, low urinary citrate (hypocitraturia) is a pathogenetically important risk factor for calcium nephrolithiasis [1] which occurs in 20–60% of calcium stone formers [4]. Incomplete renal tubular acidosis is the most prevalent pathogenic factor causing hypocitraturia [5]; other conditions associated with low urinary citrate are dietary acid load, reduced intake of vegetable fibres, low urine volume, hypokalemia, thiazide diuretics and acetazolamide [4, 5].

Changes in intracellular acid-base homeostasis are the predominant determinants of proximal tubular reabsorption and urinary excretion of citrate [4, 5, 6]. Acid loads favor tubular reabsorption of citrate and thus hypocitraturia, whereas alkali loads reduce tubular reabsorption and increase urinary citrate excretion [4, 5. 6]. Indeed, urinary citrate is positively related to net gastrointestinal absorption of alkali [1]. Therefore, treatment with alkali, usually in the form of potassium citrate or magnesium potassium citrate, is widely used to increase urinary citrate and reduce rates of stone formation in patients with hypocitraturic calcium nephrolithiasis [1, 4]. In addition, due to its alkalinizing effect, alkali citrate has successfully been used to raise urine pH and reduce rates of stone formation in patients with uric acid stones [4]. Moreover, initiation of urease induced crystallization in urines of healthy volunteers taking oral potassium citrate is markedly delayed [7], suggesting that alkali citrate treatment could also be beneficial in infection stone disease.

The purpose of this paper is to critically review available clinical studies on alkali citrate treatment of calcium, uric acid and infection stone disease in adults.

Materials and methods

Selection of published studies

A Medline search for articles on the treatment of nephrolithiasis with alkali citrate published between 1 January 1966, and 1 December 2004 was performed. We used the key words "urolithiasis and citrate treatment", "nephrolithaisis and citrate treatment", "kidney stones and citrate treatment", respectively, and found 635 published papers. For the present review, we included articles meeting all of the criteria listed in Table 1. Excluded were all reviews, case reports, studies in children (< 18 years), physiologic/clinical studies including only healthy volunteers, and articles in other languages than English or German.

According to the endpoints stated in the published articles, studies were first classified into those with "weak" (intermediate) and those with "hard" (ultimate) endpoints. "Weak" endpoints are defined as changes in urinary chemistry and/or urinary supersaturation, whereas changes in rates of stone recurrence or rates of dissolution/clearance of preexisting (residual) stones are considered "hard" endpoints.

In addition, we categorized all articles according to the study design, as originally presented by Churchill [7]:

1. One-group design: no comparison group, clinical outcome measures before and during intervention in the same individuals.
2. One-group design with a non-equivalent, i.e. not randomly allocated comparison group, with clinical outcome measures before and during intervention.
3. Randomized controlled trial (RCT).

Thus, all articles were first categorized according to their "hard" or "weak" endpoints. Thereafter, they were subdivided according to study design: for instance, a RTC with stone recurrence rate as ultimate endpoint was labelled as "hard end-point, RCT on stone recurrence rate", and a non-randomized study of treatment effects on urine chemistries, where patients serve as their own controls, was catagorized as "weak endpoint, one-group design".

Statistics

Success rates and frequencies of side effects of placebo and alkali citrate treatments in randomized trials were compared by using χ^2 statistics.

Results

Among the 635 published articles, we found 43 meeting our predefined criteria [9–51]. Thirty articles (70%) focused on "hard" and 13 on "weak" endpoints. Figures 1 and 2 depict the subclassification of all studies with "hard" and "weak" end-points, respectively. Out of all 43 studies, only eight (19%) were carried out as randomized controlled trials, six with "hard" [35, 37, 39, 41, 47, 48] and two [29, 33] with "weak" endpoints. The following analysis mainly focuses on studies with "hard" end-points, with the primary emphasis on randomized controlled trials.

Table 1 Inclusion criteria for the analysis of articles published on the treatment of nephrolithiasis with alkali citrate

Alkali citrate literature review—inclusion criteria
Publications in English or German
Studies on preventive alkali citrate treatment in patients with calcium oxalate, uric acid and infection stone disease
Clinical studies including at least ten subjects
Treatment phases of at least 1 week duration

Studies with stone recurrence rate as "hard" endpoint

Studies with one-group design

In 16 prospective studies [13, 14, 16, 17, 19, 20, 21, 23, 24, 26, 31, 36, 40, 43, 48, 49] lasting between 1 and 4.4 years, a total of 777 patients (groups of ten to 134) served as their own historical controls. The daily administered dose of alkali citrate ranged from 35 to 109 mEq. During this treatment, stone forming rates were reduced by between 47 and 99% of pretreatment values.

Studies with one-group design and non-equivalent comparison groups

In five mainly retrospective studies [18, 34, 39, 44, 50], alkali citrate treatment was administered to a total of 208 stone formers, divided into alkali citrate-treated patients and comparison groups of non-equivalent stone formers. These studies lasted between 1.5 and 7 years. The daily administered dose of alkali citrate, as far as it can be determined from the published data, ranged from

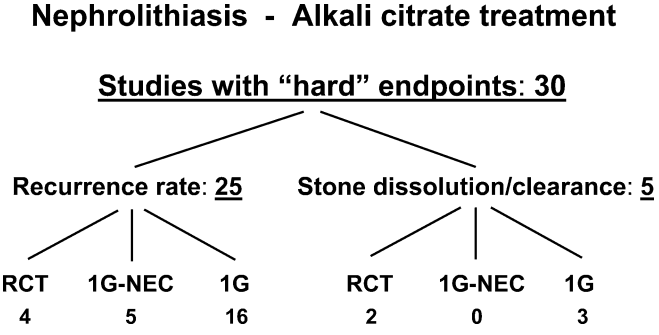

Fig. 1 Summary of the number of studies in nephrolithiasis demonstrating a treatment effect of alkali citrate on "hard" (ultimate) endpoints. *RCT*: randomized controlled trial; *1G-NEC*: study with one-group design and non-equivalent comparison group; *1G*: study with one-group design (patients serve as their own controls)

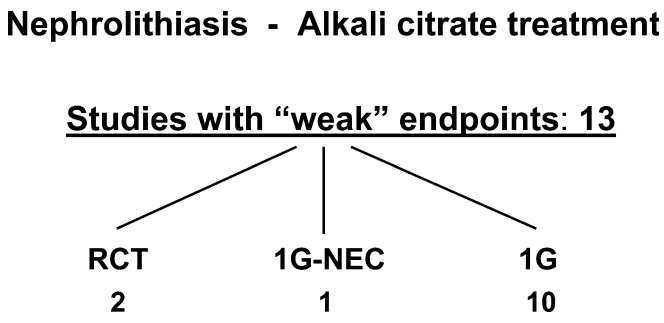

Fig. 2 Summary of the number of studies in nephrolithiasis demonstrating a treatment effect of alkali citrate on "weak" (intermediate) endpoints

33 to 90 mEq. This resulted in reductions of stone forming rates of between 62 and 100%.

RCTs on stone recurrence rates

Four RCTs [35, 37, 41, 47] on stone recurrence rates have been published. They all focus on treatment of calcium nephrolithiasis with alkali citrate vs placebo or "general prophylaxis" in unselected calcium stone patients or patients with hypocitraturic calcium nephrolithiasis. Whereas three studies [35, 37, 41] exclusively report on stone recurrence rates, the article by Soygür et al. [47] is somewhat special in that: (1) 20 out of 110 calcium stone patients after stone treatment were excluded for various reasons before randomization to treatments took place, and (2) it included both stone-free patients and patients with residual stones after ESWL. For the present discussion, we only included those 56 patients who were stone-free at randomization into the study [47].

Table 2 summarizes the four RCTs lasting either 12 [47] or 36 months [35, 37, 41]. It is remarkable that all current sound evidence on the therapeutic effect of alkali citrate is derived from only 227 randomly treated patients! The daily administered dose of alkali citrate in the four studies amounted to 60–90 mEq. When analyzing the four studies on an intention-to-treat basis, 53.5% of alkali citrate treated patients remained stone-free after at least 1 year of treatment, significantly more than on placebo (35%, $P < 0.0005$ vs alkali citrate). Our overall stone-free percentage of 53.5% on citrate treatment clearly contrasts with the 72% and 87% of stone-free patients published by Barcelo et al. [35] and Ettinger et al. [41]. However, their calculations were based on patients who actually finished the study, not on an intention-to-treat analysis. Also of note is the fact that 17% of subjects in the placebo, but 30% in the alkali citrate group ($P < 0.0005$ vs placebo) prematurely dropped out after randomization; the highest drop-out rate of 48% was observed on potassium magnesium citrate treatment in the study by Ettinger et al. [41]. Except for patients' non-compliance, drop-outs were primarily due to adverse effects such as eructation/bloating/gaseousness (26%) or diarrhea (12%) [41].

Studies with stone/fragment dissolution or clearance as "hard" endpoint

Studies with one-group design

Three studies [9, 10, 11] report on alkali citrate treatment of uric acid stones. A total of 216 patients were studied for up to 5 years and served as their own historical controls. The percentage of stone-free patients during treatment ranged from 62 to 83%.

Studies with one-group design and non-equivalent comparison groups

No such studies on stone dissolution or clearance are available.

RCTs on stone/fragment dissolution or clearance

Published data on stone/fragment dissolution or clearance could be gathered from three published studies [38, 46, 47]. However, we could not include the data from Premgamone et al. [46] into our analysis, since this study reported only on stone size reduction over time, as measured by repeated ultrasound examination, but did not mention numbers of stone-free patients. Furthermore, the study was not placebo-controlled, since patients were randomized to either sodium potassium citrate or a tea based on the herbal plant *Orthosiphus grandiflorus* which is known to increase urinary citrate excretion [46].

Table 2 Summary of randomized controlled trials on the effects of alkali citrate treatment on stone recurrence rate as a "hard" (ultimate) endpoint. *$P < 0.0005$ vs placebo, $^{+}$ drop-outs excluded before randomization to treatment [47]

First author (Reference no.)		Barcelo [35]	Hofbauer [37]	Ettinger [41]	Soygür [48]	Total
Started	Placebo	29	25	33	28	115
	Alkali citrate	28	25	31	28	112
Drop-outs	Placebo	9	3	8	0^{+}	20
	Alkali citrate	10	9	15	0^{+}	34*
Finished	Placebo	20	22	25	28	95
	Alkali citrate	18	16	16	28	78
No new stones	Placebo	9	6	9	20	44
	Alkali citrate	14	5	14	28	61*

For our analysis of RCTs on clearance/dissolution of residual stones, we thus included the data from Cicerello et al. [38] on alkali citrate treatment of calcium and infection stone formers with residual stones as well as the subgroup of patients with residual stones/fragments in the study by Soygür et al. [47]. Therefore, as depicted in Table 3, a total of 104 stone patients have been randomly studied vs placebo with stone dissolution/clearance as ultimate endpoint. The daily administered dose of alkali citrate amounted to 60–80 mEq. When analyzing the data on an intention-to-treat basis, 66% of alkali citrate-treated patients became stone-free after 1 year of treatment, significantly more than in the placebo group (27.5%, $P < 0.0005$ vs alkali citrate). Drop-outs were very rare; however, this finding is influenced by the fact that Soygür et al. [47] excluded 20 stone patients for various reasons before randomization took place.

Studies with "weak" endpoints

Studies with one-group design

Ten short-term studies [12, 15, 22, 25, 27, 28, 30, 32, 42, 45] report on alkali citrate treatment of calcium or uric acid stone formers. A total of 313 patients were studied for between 1 and 12 weeks. As far as mentioned in the studies, urine pH increased by between 1% and 14% from pretreatment values. The same was true for urinary citrate which increased by between 27% and 94%. Urinary oxalate changed between +24.5% and −32.7% from pretreatment values, whereas urinary calcium decreased by between 8% and 40% in all studies except one in which an increase by 15.4% was noted on combined magnesium citrate/magnesium oxide treatment [25]. In some studies, changes in relative urinary supersaturations (calculated as formation product ratios) from baseline values were reported; they ranged from +5% [26] to −49% [15] for calcium oxalate and from −24% [25] to +67% [22] for calcium phosphate, indicating trends for reduced calcium oxalate and for increased calcium phosphate supersaturations on alkali citrate treatment.

Table 3 Summary of randomized controlled trials on the effects of alkali citrate treatment on clearance or dissolution of residual stones/fragments as a "hard" (ultimate) endpoint. * $P < 0.0005$ vs placebo, $^{+}$ drop-outs excluded before randomization to treatment [47]

First author (Reference No.)		Cicerello [38]	Soygür [48]	Total
Started	Placebo	35	16	51
	Alkali citrate	35	18	53
Drop-outs	Placebo	1	0^{+}	1
	Alkali citrate	1	0^{+}	1
Finished	Placebo	34	16	50
	Alkali citrate	34	18	52
Stone-free	Placebo	12	2	14
	Alkali citrate	27	8	35*

Study with one-group design and non-equivalent comparison group

There is only one recent study [51] reporting 61 stone patients treated for 1 month in four treatment subgroups: (1) potassium chloride, (2) potassium sodium citrate, (3) magnesium glycine, and (4) potassium magnesium citrate (63 mEq/day). Urine pH and citrate significantly increased only in patients treated with either potassium citrate or potassium magnesium citrate, whereas potassium chloride and magnesium glycine induced a fall in urine pH without a change in citraturia. The latter clearly increased urinary supersaturation of uric acid, whereas all four supplements left calcium oxalate supersaturation unchanged [51].

RCTs

Two RCTs have been reported [29, 33], both short-term studies lasting 1 week. Pak et al. [29] sequentially studied five normal subjects and five calcium stone formers during a placebo phase as well as during treatments with potassium citrate (50 mEq/day) and potassium magnesium citrate (73.5 mEq citrate/day). In comparison with placebo, potassium magnesium citrate induced more pronounced increases in urinary citrate and pH than potassium citrate. This was accompanied by a greater decline in the amount of daily excreted undissociated uric acid and a more pronounced increase in urinary citrate excretion. Consequently, the activity product of calcium oxalate declined significantly more during potassium magnesium citrate (from 1.49×10^{-8} to 1.03×10^{-8} mol^2) than during potassium citrate therapy (to 1.14×10^{-8} mol^2) [29].

Using a similar trial design, Wabner and Pak [33] studied eight healthy men and three hypocitraturic calcium stone formers in three phases, each lasting 1 week. Compared with placebo, 1.2 l of orange juice per day (190 mEq citrate) and potassium citrate (60 mEq/day) caused similar increases in urine pH and citrate. This was associated with comparable decreases in urinary undissociated uric acid levels. On the other hand, because orange juice increased urinary oxalate without changing urinary calcium, only potassium citrate significantly reduced urinary saturation of calcium oxalate [33].

Discussion

Success or failure of any medical treatment is ascertained by the comparison of outcomes in active treatment and control groups. Placebo or sham control groups are clearly preferred, although historical controls are often used as less desirable alternatives [52]. The

main finding of the present literature review is that alkali citrate treatment of nephrolithiasis has been investigated in a prospective randomized manner in only 352 subjects in eight studies [29, 33, 35, 37, 39, 41, 47, 48]. When solely considering studies with "hard" (ultimate) endpoints, the respective number falls to 331 stone formers, studied with either stone recurrence rate (227 patients) or dissolution/clearance of residual stones (104 patients) as endpoints. This is rather surprising, given the fact that prevalences of nephrolithiasis are increasing and now reach 11.7% in Europe [53] and 11.1% in the US [54] in men in their mid-sixties; respective values for women are 7.7% [53] and 5.6% [54].

The uncontrolled studies with "weak" (intermediate) endpoints included in our analysis suffer from a wide variability in study design. Nevertheless, they generally reveal what can theoretically be expected, namely that urine pH and citrate increase in patients treated with either potassium citrate or potassium magnesium citrate. Altogether, data from 374 subjects treated for between 1 and 12 weeks demonstrate increases in urine pH of up to 14% and in urinary citrate of up to 94% from pretreatment values. This is generally accompanied by decreases in urinary calcium oxalate supersaturation of up to 49%, but increases in calcium phosphate supersaturation of up to 67% may occur.

Consequently, 21 uncontrolled studies with stone recurrence as "hard" (ultimate) endpoint [13, 14, 16, 17, 18, 19, 20, 21, 23, 24, 26, 31, 34, 36, 39, 40, 43, 44, 48, 49, 50] in almost 1,000 patients have demonstrated that stone forming rate was reduced by between 47% and 100% of pretreatment values. Four randomized controlled trials including 227 patients, when analyzed on an intention-to-treat basis, also reveal that more than half of all alkali citrate treated patients remain stone-free after at least 1 year of treatment, significantly more than on placebo treatment (35%). Of at least equal importance appear data from two randomized, placebo-controlled trials with clearance or dissolution of preexisting (residual) stones as ultimate endpoint. After 1 year of treatment, 66% of alkali citrate-treated patients became stone-free, again significantly more than on placebo (27.5%). This may appear highly relevant for thousands of patients undergoing shock-wave lithotripsy who might profit from routine administration of alkali citrate for improved clearance of residual fragments. Indeed, it can be anticipated that more complete fragment clearance would be associated with a reduced likelihood of residual fragments becoming niduses for newly growing stones.

The overall percentage of stone-free patients (53.5%) on alkali citrate in the present analysis of published studies with stone recurrence as endpoint contrasts with considerably higher numbers of 72% and 87% in some of the studies [35, 41]. However, these latter calculations were based on patients who actually finished the studies, whereas we strongly believe that a more realistic summary should strictly be based on an intention-to-treat analysis (Table 2). Unfortunately, we were not able to perform a thorough intention-to-treat analysis of all published data, since some patients were excluded before randomization to alkali citrate or placebo in one study [47].

Alkali citrate treatment not only raises urinary citrate levels in patients with calcium nephrolithiasis [1, 4], but also has a general alkalinizing effect which is beneficial for patients with uric acid [4] as well as cystine stones [55]. Moreover, alkali citrate may even be beneficial for retarding the growth of infection stones [7]. Therefore, alkali citrate could be a sort of panacea for almost any kind of kidney stone disease. As obvious from the present review, a main limitation for more widespread use of alkali citrate preparations is the relatively low tolerability of available alkali citrate preparations. Overall, 17% of subjects on placebo, but almost one third on alkali citrate treatment for prevention of stone recurrences, prematurely left randomized trials. It is noteworthy that the highest ever reported drop-out rate, almost half of the patients, was observed on treatment with potassium magnesium citrate [41], which basically appears to be more efficient than potassium citrate in lowering the activity product of calcium oxalate [29]. Adverse effects that reduce treatment compliance have been noted mainly in the gastrointestinal tract and include eructation, bloating or gaseousness in 26% and frank diarrhea in 12% of potassium magnesium citrate treated patients [41]. Thus, the development of better tolerated alkali citrate preparations remains an important issue for the future.

The fact that any alkali would suffice to increase urinary pH and citrate [4] could offer interesting alternatives for stone patients who do not tolerate currently available alkali citrate preparations. As observed by Wabner and Pak [33], 1.2 l of orange juice per day cause increases in urine pH and citrate similar to a conventional dose of potassium citrate. More recently, Kessler and Hesse [56] studied 24 healthy male volunteers and observed that bicarbonate-rich mineral water, administered in equimolar concentrations with respect to the amount of delivered alkali, was equally effective to sodium potassium citrate in increasing urine pH and citrate as well as decreasing relative urinary supersaturations of calcium oxalate and uric acid. Finally, Premgamone et al. [46] reported equal stone size reductions over time in stone formers randomized to either sodium potassium citrate or a tea based on the herbal plant *O. grandiflorus* which is known to increase urinary citrate. Remarkably, alkali citrate induced adverse effects in 26% of patients, whereas stone formers treated with the herbal tea did not experience adverse effects at all [46]. In summary, many patients who do not tolerate alkali citrate medications might profit from such more "natural" sources of alkali.

In conclusion, our literature review confirms that alkali citrate has a significant effect not only on urine chemistries and supersaturation levels, but more importantly also reduces the incidence of stone recurrences. Furthermore, rates of clearance or dissolution of

preexisting stones or fragments are significantly improved, which may call for routine treatment with alkali citrate in all patients undergoing shock-wave lithotripsy. Finally, for those patients who do not tolerate alkali citrate preparations, sufficient amounts of bicarbonate-rich mineral water, orange juice or a herbal tea based on *O. grandiflorus* appear to be valuable alternatives.

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