Original Article

Evaluating the effectiveness of adding magnesium chloride to conventional protocol of citrate alkali therapy on kidney stone size

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Abstract

Background: Potassium citrate (K-Cit) is one of the therapeutic solutions broadly used in patients with urolithiasis. However, recent studies have shown that it is not so effective. Therefore, the goal of our study was to evaluate the effect of a combination of K-Cit - $MgCl_2$ oral supplements, on urinary stone size.

Materials and Methods: This study was performed on 70 asymptomatic urolithiasis cases. The supplements included K-Cit and magnesium chloride ($MgCl_2$), purchased from (Merck Company, Germany). The patients were randomly divided into two groups. The urinary stone size was measured in the control group after prescribing K-Cit alone and the treated group with combination of K-Cit and $MgCl_2$ for 4 weeks by ultrasonography and also urinary parameter was measured in each groups.

Results: The mean age of patients was 16.26 ± 5.70 years. Hyperoxaluria and hypercalciuria were seen in 70% and 52% of patients, respectively. Initially, the mean urinary stone size was measured in each groups and there is not any significant different. However, we find a significant decrease in urinary stone size in group which is treated with combination of K-Cit and $MgCl_2$ for 4 weeks in comparison with control group treated with K-Cit alone in the same duration of therapeutic course (5.1 ± 0.8 vs. 2.5 ± 1.2, $P < 0.05$). All ultrasonography were performed by one radiologist and device.

Conclusion: Our results suggested that a combination of K-Cit and $MgCl_2$ chloride is more effective on decreasing urinary stone size than K-Cit alone.

Key Words: Magnesium chloride, potassium citrate, urolithiasis

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INTRODUCTION

Urolithiasis is a well-known and important disorder because of severe complications and different etiologic conditions.[1] Iran is one of the countries in the Middle-East placed on the stone belt. Stone formation is a multi-factorial process, which comes from excessive saturation of urine, and low concentration of inhibitor factors, which results in crystal nucleation and accumulation of insoluble compounds.[2,3] Most

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of stones contain calcium, oxalate, or a combination of both.[4,5] Calcium oxalate stones are so important because of the two main facts, firstly high prevalence of them, second, poorer response to current therapeutics approaches. Therefore, the prevention of stone formation is more effective than its treatment. In stone-forming patients with a recurrent episodes of kidney stone, citrate supplementation is a one of the routine preventive therapy, but it does not seem to be so effective in this situation. The importance of finding an efficient supplement therapy to this routine therapeutic and preventive approach is undeniable. The preventive effects of different solutions containing potassium, magnesium, and citrate have been evaluated in many interventional studies conducted on patients with kidney stones.

Potassium citrate (K-Cit) solution has been currently used as a therapeutic choice. Since calcium oxalate stones do not respond effectively to this alkalization of urine, more complementary solutions are needed. One of the best candidates in this regard is magnesium ion, magnesium ion might be compete with calcium to attach with oxalate. Interestingly, magnesium oxalate seems to be more soluble than calcium oxalate.[6] Different solutions containing magnesium salts (oxide, citrate, and acetate) have been evaluated in therapeutic approaches in patients with kidney stones.[6,7] The role of these kinds of magnesium supplements in effective increasing in urinary magnesium has been debated.[7] In our previous pilot research project,[8] we prove the positive and significant effect of magnesium chloride ($MgCl_2$) solution in combination with K-Cit in urinary parameter. Therefore, we conducted this study on patients with calcium oxalate stones to investigate whether the stone size change after the consumption of K-Cit and $MgCl_2$ solutions. Renal ultrasonography is commonly used to establish the diagnosis of kidney stone and for follow-up in those found to have stones. Advantages are its cost and lack of exposure to ionizing radiation. Current studies demonstrate that the acoustic shadow width in ultrasonography provides good sensitivity, specificity and accuracy in detection of kidney stone and also follow-up for changing in size.[9]

We used $MgCl_2$ in its permitted level in combination with K-Cit.[10] Both K-Cit and $MgCl_2$ solution are not commercially available in Iran, two different solutions containing K-Cit and $MgCl_2$ were prepared.

MATERIALS AND METHODS

This study was performed on children aged 6 months to 18 years with kidney stone with the approval of the Ethics Committee of the Research Department of Isfahan University of Medical Sciences and had the Iranian Clinical Trial Registration Number IRCT138707091282N1.

In addition, written consent was obtained from the parents of the children under 6 years and from both children older than 6 years and their parents before prescribing medications.

Seventy patients with a history of kidney stone proven by ultrasound have been enrolled in the study.

The composition of stones was considered to be calcium oxalate in these cases according to one of the following findings:

- The existence of hyperoxaluria, hypercalciuria or both in spot urine collection in the presence of kidney stone
- The history of passing calcium oxalate stone in urine.

Inclusion criteria

- Asymptomatic patients with possibility of calcium oxalate kidney stone
- The participant should not have a history of peptic ulcer, cardiac disease, primary chronic diarrhea and other background diseases and also consumption of anti-convulsant drugs.

Exclusion criteria

- Patients who did not complete 4 weeks treatment of the study
- Patients who showed side effects of any solution during treatment
- Patients who refused to consume either K-Cit or $MgCl_2$.

The supplements included K-Cit and $MgCl_2$; purchased from Merck Company, Germany. The specific codes for K-Cit and $MgCl_2$ were 1.04956.9029 and 1.05832.5000, respectively. To provide K-Cit solution; 220 g of K-Cit $C_6H_5K_3O_7.H_2O$ plus 66 g citric-acid $C_6H_8O_7.H_2O$ were dissolved in 1000 ml distilled water. Each 1 ml of K-Cit solution contained 2 milliequivalent potassium ion. The prescribed dose of K-Cit was 1 mEq potassium ion/kg/day $MgCl_2$ solution with the concentration of 16 mEq/10 cc was prepared by adding 162.64 g of $MgCl_2.6H_2O$ solved in 1000 ml distilled water. Each ml of $MgCl_2$ has 19.2 mg magnesium element. $MgCl_2$ was prescribed in doses equivalent to 10 mg/kg/day in adult to maximum 400 mg/day (recommended daily allowance [RDA] table). The maximum administered dose of magnesium was not beyond the RDA [Table 1].

The study was performed in two groups. At the beginning we performed ultrasonography to find out

Table 1: Recommended dietary allowance for magnesium

Life stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	30	30
Infants	7-12 months	75	75
Children	1-3 years	80	80
Children	4-8 years	130	130
Children	9-13 years	240	240
Adolescents	14-18 years	410	360

the primary size of stone and also the location of kidney stone, urine culture was performed, and patients were examined for any possible gastrointestinal or urinary tract infections.

In the beginning of the study, urinary sodium, magnesium, potassium, creatinin, and calcium in addition to venous blood gas (VBG), urinary citrate, and oxalate were measured. Then, all patients received K-Cit (poly-citrate potassium) in 3 separated doses during day (preferably after meal). After 4 weeks treatment, while patients had been receiving poly-citrate potassium, all mentioned parameters except for VBG and urinary magnesium were evaluate, and also the same radiologist and device performed ultrasonography.

$MgCl_2$ solution in 3 divided doses per day (after meal) was added to the previously mentioned dose of poly-citrate potassium. This combination was continued for a 4-week course. At last, all mentioned parameters at the beginning of the study were measured.

During the treatment period, patients were asked to continue their normal dietary habits.

Kidney ultrasound was performed by ultrasonography logic 7 general electric machine and by a fix radiologist blinded to the study.

The fasting spot urine was measured for oxalate, potassium, sodium, createnin, magnesium, and calcium.

Urine electrolytes were measured by the following methods

- Urinary citrate and oxalate: Enzymatic method and capillary electrophoresis, respectively (R-Biopharm GmbH, Germany)
- Urinary pH: pH meter 34 (Beckman Coulter)
- Urine creatinine: Alkaline picrate
- Urine calcium: 0-crsolphthalein
- Urine phosphorus: Molybdate blue
- Urine sodium, potassium and chloride: Ion-selective electrodes.

According to the study on healthy Iranian children by Safarinejad, the mean of normal range of Ca/Cr, magnesium/Cr and phosphate/creatinine were assumed to be 0.038 ± 0.044 mg/mg; 0.042 ± 0.015 mg/mg; 0.318 ± 0.124 mg/mg respectively.[11] The value of 0.076 mol/mol equivalents to 0.06 (mg/mg) was considered as the upper limit for urinary oxalate/creatinine ratio.[12]

The data were analyzed using SPSS, version 17, IBM (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). Values are presented as the mean ± the standard deviation. Repeated measured analysis of variance models was utilized to compare values in different phases. $P < 0.05$ was considered statistically significant.

RESULTS

Seventy asymptomatic kidney stone patients participated were divided randomly in two groups and also, each groups were matched based on sex and age and also location of stone in kidney (upper, middle and lower calyx). Fourteen participate did not attend the complete follow-up. The female/male ratio in each groups was approximately 3/4. The mean age of the patients was 16.26 ± 5.70 years. Urinary tract infection was ruled out before commencing the study by midstream urine culture.

Mean of pH was significantly higher in Group 2 which received combination of K-Cit + MgCL comparing with Group 1 which is received K-Cit alone (7.05 ± 0.14 vs. 6.27 ± 0.64), $P < 0.05$. Hyperoxaluria was reported in 70% of urolithiasis patient participants. Regarding upper limits of normal urinary calcium/creatinine ratio based on age, hypercalciuria was seen in 52% of patients. In the second group which is received combination of K-Cit + $MgCl_2$, 8 patients experienced loose stool, but not sufficient enough to withhold medications.

A total of 56 patients completed the study. At the commencement of the study, all patients performed ultrasound imaging as primary detection of stone size and also urine test. The duration of follow-up was 1 month.

At the end of the study, urinary oxalate and oxalate/creatinine ratio were significantly lower in group which is treated by combination of $MgCl_2$ + K-Cit in comparison with K-Cit alone. Citrate/creatinine ratio increased significantly in $MgCl_2$ + K-Cit group comparing with K-Cit one, (0.053 ± 0.01 vs. 0.031 ± 0.004) $P < 0.05$. Initially, the mean urinary stone size was measure in each groups and there isn't any significant different (5.6 ± 0.7 and 4.8 ± 0.6). But we could find a significant decrease in urinary stone size in group which is treated with combination of

K-Cit and $MgCl_2$ for 4 weeks in comparison with control group treated with K-Cit alone in the same duration of therapeutic course, 5.1 ± 0.8 versus 2.5 ± 1.2 $P < 0.05$. All sonographies were performed by one radiologist and device.

DISCUSSION

The formation of calcium-oxalate stone depends on imbalances between super saturating and inhibitory factors. Therefore, treatment protocols concentrate on both increasing inhibitory and decreasing promoting factors.

In this study, we evaluated stone size after consuming K-Cit and $MgCl_2$ in patients with calcium-oxalate kidney stones and also confirmed its positive effects on urinary parameters. K-Cit solution has been used to elevate urinary pH and citrate urinary concentration as inhibitory factor for stone formation. Pak *et al*. indicated the effectiveness of K-Cit therapy in increasing urinary pH, potassium and citrate but not in decreasing of urinary concentration of oxalate as a one of the major promoting factors in this kind of stones.[13] Many studies discussed the inhibitory role of urinary citrate concentration and alkali urine in preventing urinary stone formation.[5,6,13-19] Citrate alkali therapy might be reduced recurrence of stone formation but it is not so effective.[20] Citrate could prevent calcium oxalate stones formation by creating soluble complexes with urine calcium and as a result reducing the degree of urine calcium oxalate saturation. Furthermore, citrate prevents the nucleation, growth, and concentration of calcium oxalate crystals theoretically.[21]

On the other hand, magnesium ion also has been reported to have an effective inhibitory effect on calcium oxalate stone formation by the following theoretically mechanisms:

- Preventing the growth of calcium oxalate and calcium phosphate crystals[22]
- Inhibiting the nucleation rate in all oxalate concentrations (*in vitro*)[23]
- Combining with oxalate in gastrointestinal tract and as a result could reduce oxalate absorption from intestine[9,24]
- Increasing urine pH and consequently increasing citrate secretion[21]
- Prolonged CaOx crystal agglomeration time and inhibiting CaOx crystallization through the action of citrate[6]
- Reducing recurrence rate of idiopathic calcium stones during long-term administration.[25]

The study showed that the simultaneous administration of potassium-sodium citrate and magnesium oxide (MgO and K-Na-Cit) increased the urinary excretion of magnesium and citrate and decreased calcium excretion more than consumption of K-Na-Cit alone.[21]

Brundig *et al*. showed that the administration of high doses of $MgCl_2$ decreased the urinary level of oxalic acid while increasing magnesium concentration in urine.[19]

Producing MgO solution is so difficult and it sedimate rapidly. Furthermore, surprisingly, the oral administration of $MgCl_2$ has been proved to have more bioavailability than MgO and magnesium hydroxide.[26] Therefore, it seems that $MgCl_2$ could be a good choice for a complementary solution to routine K-Cit therapeutic approach.

In addition to magnesium, diethylaminoethanol cellulose had been also administered to correct oxalate hyper absorption.[27] However, this medication has not been used widely in pediatric cases.

While K-Cit solution might lower the recurrence rate of calcium oxalate stones, the same effects was not proved with magnesium salts alone.[28,29] Therefore, using magnesium salts alone without any combination solutions has not been effective.[30] Such as, Tiselius *et al*. study which is revealed an increased amount of urine calcium and no changes in urinary excretion of magnesium and oxalate during 12 months consumption of MgO and so it is not so effective.[25]

Here, we demonstrated significant decreased in kidney stone size in group which is treated with K-Cit and $MgCl_2$ in comparison with K-Cit alone. We also report increased level of citrate excretion in combination therapy. Lowering level of urinary oxalate in addition to rising level of citrate in combination phase might be helpful in treating and also prevention of progression of CaOx stone kidney stones.

The increased urinary levels of stone inhibitor (citrate) and decreased level of stone promoter (oxalate) in addition to significant decrease in kidney stone size in combination therapy of K-Cit, Mg-Cl_2 in comparison with routine K-Cit therapy in this study were achieved which is could be introduced combination therapy as effective substitution for routine K-Cit therapy alone.

The effectiveness of adding magnesium salts such as $MgCl_2$ to routine approach of citrate alkali therapy in reducing stone sizes should be considered. These findings will need to be confirmed with further studies with the large sample size, with special attention to the reproducibility of measuring these parameters.

CONCLUSION

Our results suggested that a combination of K-Cit and MgCl2 chloride is more effective on decreasing urinary stone size than K-Cit alone.

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Conflicts of interest

There are no conflicts of interest.

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