Evaluating the Effectiveness of Adding Magnesium Chloride to Conventional Protocol of Citrate Alkali Therapy in Children with Urolithiasis

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ABSTRACT

Background: Potassium citrate (K-Cit) is one of the medications widely used in patients with urolithiasis. However, in some cases with calcium oxalate (CaOx) urolithiasis, the significant response to alkaline therapy with K-Cit alone does not occur. There is scarce published data on the effect of magnesium chloride (Mg-Cl2) on urolithiasis in pediatric patients. This study aimed to evaluate the effect of a combination of K-Cit - MgCl2 as oral supplements on urinary parameters in children with CaOx urolithiasis.

Methods: This study was conducted on 24 children with CaOx urolithiasis supplements included potassium citrate (K-Cit) and magnesium chloride (Mg-Cl2). The serum and urinary electrolytes were measured before (phase 0) and after prescribing K-Cit alone (phase 1) and a combination of K-Cit and Mg-Cl2 (phase 2). Each phase of therapy lasted for 4 weeks.

Results: The mean age of patients was 6.46 ± 2.7 years. Hyperoxaluria and hypercalciuria were seen in 66% and 41% of patients, respectively. Serum magnesium increased significantly during phase 2 comparing with phase 0. Urinary citrate level was significantly higher in phase 1 and 2 in comparison with phase 0, P < 0.05. In addition, urinary oxalate excretion was significantly diminished in phase 2 comparing with phase 0 and 1, P < 0.05. Soft stool was reported by 4 patients, but not severe enough to discontinue medications.

Conclusions: These results suggested that a combination of K-Cit and Mg-Cl2 chloride is more effective on decreasing urinary oxalate excretion than K-Cit alone. The Iranian Clinical Trial registration number IRCT138707091282N1.

Key words: Children, magnesium chloride, nephrolithiasis, potassium citrate, urinary parameters

INTRODUCTION

The true incidence of nephrolithiasis in children is not clear. However, the incidence of pediatric urolithiasis has been estimated 0.13-0.94 per 1000 hospital admission.[1] Because of
high prevalence of kidney stone in adults, most of the related studies have been carried on this age group. Iran is one of the countries in the Middle East placed on the stone belt. Although, urinary stone is less prevalent in children than in adults, it may cause more serious problems. The smaller size of urinary tract and the higher risk of extracorporeal wave lithotripsy make urolithiasis management more difficult. Stone formation is a multi-factorial process, which comprises from imbalance between saturation of urine and inhibitor factors results in crystal nucleation and accumulation of insoluble compounds. More than 60% of stones contain calcium, oxalate or a combination of both. The importance of calcium oxalate stone is not only due to high prevalence but also its complications and the poorer response to medical management. Therefore, the prevention of stone formation is easier than to treatment. In stone-forming children and adults citrate supplementation is a successful preventive therapy. The preventive effects of different medications containing potassium, magnesium and citrate have been evaluated in many interventional studies conducted on patients with urinary stones.

Potassium citrate solution has been currently used as a therapeutic choice. Since calcium oxalate stones do not respond to alkalization of urine, more complementary medications are needed. Magnesium ion competes with calcium to combine with oxalate. Furthermore, magnesium oxalate has more solubility than calcium oxalate. Different medications containing magnesium salts (oxide, citrate and acetate) have been used in treatment protocols for urinary stones. The role of magnesium supplements in rising urinary magnesium has been debated. There are scarce published data evaluating the effect of magnesium and potassium salts on urinary parameters in stone-former children. Therefore, we conducted this study on children with calcium oxalate stones to investigate whether the urinary parameter changes after consumption of potassium citrate and magnesium salt solutions. As the administration of two medications containing citrate (magnesium citrate and potassium citrate) may increase citrate level beyond therapeutic index in children, we used magnesium chloride in its permitted level in combination with potassium citrate[8-10] [Table 1].

Both potassium citrate and magnesium chloride solution are not commercially available in Iran, two different solutions containing potassium citrate and magnesium chloride were prepared.

METHODS

This study was carried on children with renal 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 parents of children under 6 years and from both children older than 6 years and their parents before prescribing medications.

Subjects

Twenty-four patients (12 male and 12 female) aged 2 to 12 years (mean age 6.46 ± 2.7 year) with a history of urolithiasis 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 finding:

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

Inclusion criteria

- Children aged 2-12 years with possibility of calcium oxalate kidney stone
- No past history of peptic ulcer, chronic diarrhea, cardiac disease, primary hyperparathyroidism, consumption of anticonvulsant drugs
- No proven history of disorders affecting tubular ion excretion such as: recent

| Table 1: Recommended dietary allowance (RDA) 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            |

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pyelonephritis, distal renal tubular acidosis, chronic pyelonephritis, renal dysfunction and obstructive uropathy.

**Exclusion criteria**
- Patients who did not complete three phases of the study
- Patients who showed side effects of any solution during treatment

**Supplements**
The supplements included potassium citrate (K-Citrate) and magnesium chloride (MgCl\(_2\)); purchased from MERCK Company, Germany. The specific code for K-Citrate and magnesium chloride was 1.04956.9029 and 1.05832.5000, respectively. To provide potassium citrate solution, 220 gram of potassium citrate (C\(_6\)H\(_5\)K\(_3\)O\(_7\).H\(_2\)O) and 66 gram citric-acid (C\(_6\)H\(_8\)O\(_7\).H\(_2\)O) were solved in 1000 ml distilled water. Each one milliliter of potassium citrate solution contained 2 milliequivalent potassium ion. The prescribed dose of K-Cit was 1meq potassium ion/kg/d. Magnesium chloride solution with the concentration of 16meq/10cc was prepared by adding 162.64 gm of MgCl\(_2\).6H\(_2\)O solved in 1000 ml distilled water. Each milliliter of magnesium chloride contained 19.2 milligram magnesium element. Magnesium chloride was administered in divided doses equivalent to 3mg/kg/day for children less than 10 kg up to 10mg/kg/day in adolescents weighted 40 kg (RDA table). The maximum administered dose of magnesium was not beyond the recommended daily allowance, Table 1.

**Patient study**
The study was carried on in 3 phases. At the beginning of each phase, urine culture was sent and patients were examined for any possible gastrointestinal or urinary tract infections.

**Phase 0 (Initial phase)**
At first, serum and urinary sodium, potassium, magnesium, calcium and creatinine in addition to venous blood gas, urinary oxalate and citrate were measured. Then all patients received potassium citrate (poly-citrate potassium) in 3 divided doses (preferably after meal).

**Phase 1 (Potassium citrate phase)**
After 4 weeks, while patients had been receiving poly-citrate potassium, all mentioned parameters except for VBG, urinary and blood magnesium were determined.

**Phase 2 (combination phase)**
In the last phase, magnesium chloride solution in 3 divided doses (after meal) was added to the previous dose of poly-citrate potassium. This combination was continued for a 4-week course. At last, all mentioned parameters at the phase 0 were measured.

During 3 phases, patients were asked to continue their normal dietary habits.

**Sample collection**
Blood sampling was collected in fasting state for magnesium, sodium, potassium, chloride, calcium and creatinine.

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

**Sample analysis**
Serum and urine electrolytes were measured by the following methods:
- Serum sodium and potassium: electrolyte analyzer machine.
- Serum chloride: Chloride Reagent Chem Enzyme kit.
- Serum calcium: Calcium–Arsenazo method, BioSystems S.A; Spain.
- Serum and urine Magnesium: XyliGyl Blue, Colorimetric; ZiestChem Diagnostics, Iran.
- Serum Creatinine: Jaffe method
- Serum Phosphorus: Photometric method, Pars Azmoon kit.
- 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-Crolphthalein
- 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 as 0.038 ± 0.044; 0.042 ± 0.015; 0.318 ± 0.124, respectively.\(^1\) The value of 0.076 mol/mol equivalents to 0.06 was
considered as the upper limit for urinary Oxalate/Creatinine ratio.[12]

Statistical analysis
The data were analyzed using SPSS, version 17, for Windows. Values is presented as the mean ± the standard error. Repeated measured analysis of variance models was utilized to compare values in different phases. P value <0.05 was considered statistically significant.

RESULTS

Patient study
Twenty four patients participated in phase 0 and 1. Six children out of 24 did not attend the combination phase (phase 2), because of no stone in ultrasound reports. Mean age of patients was 6.46 ± 2.70 year. The mean age of male and female participants was 5.42 ± 2.23 years and 7.50 ± 2.81 years, respectively. Urinary tract infection was ruled out before commencing the study by midstream urine culture. Mean of pH was significantly higher in phase 2 comparing with phase 0 (7.02 ± 0.12 versus 5.37 ± 0.74), P < 0.05. Hyperoxaluria was reported in 66% of children. Regarding upper limits of normal urinary Calcium/Creatinine ratio based on age, hypercalciuria was seen in 41% of patients. In combination phase, 4 patients experienced loose stool, but not sufficient enough to withhold medications.

Serum sodium, chloride, potassium and calcium did not change significantly during three phases. Serum magnesium increased significantly during phase 2 comparing with phase 0 (1.99 ± 0.43 vs. 1.66 ± 0.24 mg/dl, P < 0.05), Table 2. However, the increment in serum magnesium was not beyond the upper limit of normal range.

Mean of urinary sodium, calcium, potassium, magnesium and chloride were not significantly different in 3 phases. Urinary phosphate and citrate were higher in phase 1 and 2 comparing with phase 0, P < 0.05. Urinary oxalate and oxalate/creatinine ratio were significantly lower in phase 1 and 2 compared with phase 0. Nevertheless, oxalate/creatinine ratio was not different in phase 1 and 2. Although, urine oxalate was lower in phase 2 comparing with phase 1, a significant difference was not achieved. 1Citrate/creatinine ratio increased significantly in phase 2 comparing with phase 1, (0.043 ± 0.01 versus 0.032 ± 0.004). Although, magnesium/creatinine ratio and magnesium/calcium tended to rise in phase 2 comparing with phase 0, the increments were not significant. The urinary parameters of each phase are summarized in Table 3. No serious adverse effect leading to drug discontinuation was reported during the study.

DISCUSSION
The formation of calcium-oxalate stone depends on the imbalances between supersaturating and inhibitory factors. Therefore, treatment protocols focus on both increasing inhibitory and decreasing promoting factors.

In this study, we evaluated urinary parameters after consuming potassium citrate and magnesium chloride in children with calcium-oxalate stone. The correction of metabolic abnormalities has been thought as the main modality to prevent or reduce stone formation. Potassium citrate solution has been used to increase urinary pH and citrate in calcium-oxalate stone. Pak et al. reported the effectiveness of potassium citrate therapy in increasing urinary pH, potassium and citrate but not in uric acid, oxalate, sodium and phosphorus.[13] Many studies discussed and even proved the inhibitory role of citrate and alkali urine in preventing urinary stone formation.[5,6,13-19] Citrate alkali therapy may reduce recurrence of stone formation regardless of stone composition and urinary metabolic abnormality.[20] Citrate prevents calcium oxalate stones formation by creating soluble combinations with urine calcium.

Table 2: Comparing serum parameters during initial and combination phases

<table>
<thead>
<tr>
<th>Serum parameter</th>
<th>Phase 0</th>
<th>Phase 2</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (meq/l)</td>
<td>4.16±0.47</td>
<td>5.32±3.81</td>
<td>Not significant</td>
</tr>
<tr>
<td>Chloride (meq/l)</td>
<td>103.52±6.72</td>
<td>102.02±12.05</td>
<td>Not significant</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>1.66±0.24</td>
<td>1.98±0.43</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.30±0.45</td>
<td>8.48±1.7</td>
<td>Not significant</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.57±0.19</td>
<td>0.71±0.35</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
and as a result reducing the degree of urine calcium oxalate saturation. In addition, citrate prevents the nucleation, growth and concentration of calcium oxalate crystals.[21]

In addition to citrate, magnesium ion has been reported to have an inhibitory effect on calcium oxalate stone formation by the following mechanisms:

- Preventing the growth of calcium oxalate and calcium phosphate crystals.[22]
- Inhibiting the nucleation rate at all oxalate concentration (in vitro).[23]
- Combining with oxalate in gastrointestinal tract and therefore reducing oxalate absorption from intestine.[9,24]
- Increasing urine pH and as a result increasing citrate secreting.[21]
- Potentiating the citrate-induced prolongation of CaOx crystal agglomeration time and inhibiting CaOx crystallization through the action of citrate.[6]
- Reducing recurrence rate of idiopathic calcium stones during the long administration.[25]

Evaluating the urinary parameters, both in healthy volunteers and adult patient volunteers 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 each alone.[21] It has been suggested that formation a soluble complex with urinary citrate and calcium was responsible for reducing calcium excretion.

Brundig et al. demonstrated that the administration of high doses of magnesium chloride reduced the urinary level of oxalic acid while increasing urine magnesium.[19]

Furthermore, the oral administration of magnesium citrate has been shown to have more bioavailability than magnesium oxide and magnesium hydroxide.[26]

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

While potassium citrate solution might lower the recurrence rate of calcium oxalate stones the same effects was not seen with magnesium salts.[15,28] Therefore, administering magnesium salts alone has not been recommended.[29]

Tiselius et al. revealed an increased amount of urine calcium and no changes in urinary excretion of magnesium and oxalate during 12 months

### Table 3: Values of urinary parameters during three phases

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Phase 0</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>85.5±10.6</td>
<td>84.7±7.7</td>
<td>81.4±7.9</td>
</tr>
<tr>
<td>Sodium (meq/l)</td>
<td>105.3±18.4</td>
<td>127.4±10.8</td>
<td>128.8±16.1</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>51.6±6.5</td>
<td>49.7±6.6</td>
<td>52.0±8.8</td>
</tr>
<tr>
<td>Chloride (mEq/l)</td>
<td>152.3±9.8</td>
<td>136.4±17.2</td>
<td>137.3±11.5</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>6.6±0.7</td>
<td>6.7±0.8</td>
<td>7.5±1.0</td>
</tr>
<tr>
<td>Phosphorous (mg/dl)</td>
<td>47.8±5.9</td>
<td>67.7±6.3*</td>
<td>79.7±12.3*</td>
</tr>
<tr>
<td>Urine Uric acid. Serum Cr/Urine Cr</td>
<td>0.23±0.04</td>
<td>Not measured</td>
<td>0.31±0.007</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>5.7±0.5</td>
<td>6.4±0.7</td>
<td>6.6±0.5</td>
</tr>
<tr>
<td>Citrate (U/L)</td>
<td>1.74±0.76</td>
<td>2.5±1.50*</td>
<td>2.6±1.45*</td>
</tr>
<tr>
<td>Oxalate (mg/dl)</td>
<td>3.20±5.81</td>
<td>0.31±0.15*</td>
<td>0.29±0.10*</td>
</tr>
<tr>
<td>Phosphate/Creatinine</td>
<td>0.64±0.24</td>
<td>1.05±0.91</td>
<td>0.88±0.36</td>
</tr>
<tr>
<td>Magnesium/Creatinin</td>
<td>0.81±0.07</td>
<td>1.1±0.1</td>
<td>0.87±0.1</td>
</tr>
<tr>
<td>Magnesium/Creatinine</td>
<td>0.033±0.012</td>
<td>Not measured</td>
<td>0.11±0.07</td>
</tr>
<tr>
<td>Oxalate/Creatinine</td>
<td>0.013±0.004</td>
<td>0.004±0.0005*</td>
<td>0.003±0.0006*</td>
</tr>
<tr>
<td>Calcium/Creatinine</td>
<td>0.105±0.77</td>
<td>0.147±0.151</td>
<td>0.149±0.11</td>
</tr>
<tr>
<td>Citrate/Creatinine</td>
<td>0.025±0.05</td>
<td>0.032±0.004*</td>
<td>0.043±0.014†</td>
</tr>
<tr>
<td>Potassium/Creatinine</td>
<td>0.65±0.42</td>
<td>0.80±0.43*</td>
<td>0.64±0.4</td>
</tr>
<tr>
<td>FE† Sodium</td>
<td>0.64±0.43</td>
<td>Not measured</td>
<td>0.76±0.08</td>
</tr>
<tr>
<td>FE Magnesium</td>
<td>3.02±0.3</td>
<td>Not measured</td>
<td>3.28±0.3</td>
</tr>
</tbody>
</table>

*P< 0.05 compared with control (phase 0) values. †P< 0.05 compared with K Cit (phase 1) values. ‡ Fraction Excretion
consumption of magnesium oxide.[25]

We demonstrated the increment of urinary phosphorus excretion in phase 2 and 1 comparing with phase 0, whereas the same results were not achieved by Kato et al.[21]

The rise in urinary citrate excretion after consuming citrate solution was reported in many studies. Here, we reported increased level of citrate excretion in phases 1 and 2 compared with phase 0. Furthermore, the citrate to creatinine level was higher in phase 2 compared with phase 1 and 0. Lowering level of urinary oxalate in addition to rising level of citrate and phosphate in combination phase might be helpful in treating Ca-Ox stone in children. However, Citrate/ Creatinine ratio was the only stone inhibitor parameter that had greater amount in phase 2 compared with phase 1. In addition, measurable urine oxalate was significantly lower in phase 2 comparing with phase 0. Administering higher doses of magnesium salts may result in changes in urinary parameters that tended to increase in phase 2 comparing with phase 1. However, prescribing high doses of many therapeutic agents has many limitations in pediatric setting.

Although, we administered magnesium in low amounts irrespective of Brundig’s study, the increased urinary levels of stone inhibitors (citrate and phosphate) and decreased level of stone promoter (Oxalate) were achieved.

CONCLUSION

Evaluating the effectiveness of adding magnesium salts such as magnesium chloride to conventional protocol of citrate alkali therapy in decreasing stone sizes should be considered. To achieve significant decrease in urine oxalate, higher doses of magnesium but not beyond the RDA might be considered.

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