ADJUVANT MEDICAL THERAPY AFTER SURGICAL STONE MANAGEMENT

Comprehensive Kidney Stone Center at Duke University Medical Center
Durham, North Carolina

Glenn M. Preminger, M.D.
Advent of minimally invasive procedures
SWL, PNL, URS

Further advances in medical stone management

Yet, some still disparage the need for prophylactic medical stone therapy
MEDICAL MANAGEMENT OF NEPHROLITHIASIS

PROGRESS

Improved diagnostic methods now uncover the underlying cause of stone disease in 97% of individuals.

Advances in selective medical therapy can reduce one’s risk of recurrent stone formation by 90 - 95%.

Can medical therapy be used to help clear the collecting system of residual fragments following stone removal (SWL-PNL-URS)?
IMPACT OF MEDICAL STONE MANAGEMENT

SPECIFIC QUESTIONS

Do residual stone fragments impact on recurrent stone formation?

Is medical therapy available to facilitate residual stone fragment passage following SWL, PNL, URS?

Is medical therapy effective in preventing new stone formation and/or growth of residual fragments?
<table>
<thead>
<tr>
<th></th>
<th>Growth / Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPACT OF RESIDUAL STONES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>STONE FRAGMENTS</strong></td>
<td></td>
</tr>
<tr>
<td>After Open Surgery</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5%</td>
</tr>
<tr>
<td>Yes</td>
<td>53%</td>
</tr>
<tr>
<td>After PNL</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9%</td>
</tr>
<tr>
<td>Yes</td>
<td>63%</td>
</tr>
</tbody>
</table>

Blandy & Singh, 1976
Segura, et al, 1987
<table>
<thead>
<tr>
<th>Author / Year</th>
<th># Pts</th>
<th>Months of F/U</th>
<th>If Stone Free</th>
<th>If Residual Fragments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingeman, ‘89</td>
<td>240</td>
<td>26</td>
<td>9%</td>
<td>63%</td>
</tr>
<tr>
<td>Nijman, ‘89</td>
<td>73</td>
<td>29</td>
<td>10%</td>
<td>33%</td>
</tr>
<tr>
<td>Beck, ‘91</td>
<td>38</td>
<td>27</td>
<td>13%</td>
<td>78%</td>
</tr>
<tr>
<td>Fuchs, ‘91</td>
<td>117</td>
<td>28</td>
<td>6%</td>
<td>55%</td>
</tr>
<tr>
<td>Zanetti, ‘91</td>
<td>254</td>
<td>40</td>
<td>14%</td>
<td>65%</td>
</tr>
<tr>
<td>Nakamoto, ‘93</td>
<td>167</td>
<td>45</td>
<td>17%</td>
<td>45%</td>
</tr>
</tbody>
</table>
160 patients with small (< 4mm) asymptomatic residual calculi in anatomically normal upper tracts

Followed for 1.6 to 88.8 (mean 23) months to time of stone-free status, observation or intervention

Indications for intervention:
- Increasing stone size
- Onset of symptoms
- Obstruction

Statistical analysis of possible outcomes

Streem, 1996
## RESIDUAL FRAGMENTS

### CLINICAL SIGNIFICANCE

<table>
<thead>
<tr>
<th>Probability</th>
<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone-free</td>
<td>22%</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>Becoming Symptomatic</td>
<td>12%</td>
<td>34%</td>
<td>48%</td>
</tr>
<tr>
<td>Requiring intervention</td>
<td>18%</td>
<td>47%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Streem, 1996
RESIDUAL FRAGMENTS

PROBABILITY OF INTERVENTION

 Months

 0 5 10 15 20 25 30 35 40 45 50 55 60

 %

 0 10 20 30 40 50 60 70 80

 Events

 Streem, 1996
Following SWL, a significant number of patients with small, non-infected residual calculi will require intervention or suffer symptomatic episodes within 2 years.

The term "clinically insignificant" residual stone fragments post-SWL is likely a misnomer.

Streem, 1996
MEDICAL MANAGEMENT OF NEPHROLITHIASIS

SPECIFIC QUESTION

Is medical therapy available to facilitate residual stone fragment passage following SWL?
Randomized, prospective trial

40 patients with calcium stone fragments
30 patients with struvite stone fragments

Received either non-specific sodium citrate therapy or conservative measures (fluids and diet control)

Cicerello, et al, 1994
FACILITATED CLEARANCE OF RESIDUAL STONES

EFFECT OF SODIUM CITRATE

Stone Fragment Clearance

Ca Ox 75% 86%
Infection 32% 40% 86%

Cicerello, et al, 1994
FACILITATED CLEARANCE OF RESIDUAL STONES

EFFECT OF SODIUM CITRATE

Stone Growth and / or Reaggregation

Cicerello, et al, 1994
Previous studies suggest that potassium alkali may work better than sodium citrate.

Prospective study of 44 patients with residual CaOx fragments after SWL, < 5 mm in diameter.

Patients randomized to receive potassium citrate versus conservative measures (diet & fluids).

Cicerello, et al, 2000
## FACILITATED CLEARANCE OF RESIDUAL STONES

### EFFECT OF POTASSIUM CITRATE

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Potassium Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual frag clearance</td>
<td>45%</td>
<td>81%</td>
</tr>
<tr>
<td>Fragment growth &amp; reaggregation</td>
<td>36%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Cicerello, et al, 2000
### FACILITATED CLEARANCE OF RESIDUAL STONES

#### EFFECT OF POTASSIUM CITRATE

<table>
<thead>
<tr>
<th></th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone Fragment Clearance (%)</td>
<td>65%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>81%</td>
</tr>
</tbody>
</table>

*Cicerello, et al, 2000*
FACILITATED CLEARANCE OF RESIDUAL STONES

EFFECT OF POTASSIUM CITRATE

110 patients undergoing SWL of lower pole calculi

4 weeks following SWL
Stone free: 56 pts 51%
Residual stone: 34 pts 49%

Divided into 2 groups, matched for gender, age and urinary values of calcium, citrate and UA

Potassium citrate (60 mEq / day) vs. controls

Soygur, et al, 2002
FACILITATED CLEARANCE OF RESIDUAL STONES

STONE ACTIVITY @ 12 MONTHS F/U

<table>
<thead>
<tr>
<th></th>
<th>Stone Free</th>
<th>Residual Frags</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>K-Cit</td>
</tr>
<tr>
<td>Stone remission</td>
<td>71%</td>
<td>12%</td>
</tr>
<tr>
<td>Stone size unchanged</td>
<td>100%</td>
<td>44%</td>
</tr>
<tr>
<td>Stone size increased</td>
<td>63%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Soygur, et al, 2002
Persistence and growth are common findings in natural history of residual fragments following shock wave lithotripsy.

Citrate therapy:
- Increases fragment clearance rate
- Reduces growth and agglomeration of residual stone fragments

Consider the routine use of potassium citrate following SWL.
## FACILITATED CLEARANCE OF URETERAL STONES MET AFTER SWL

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine/Deflazacort</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td><strong>Stone free</strong></td>
<td>75%*</td>
<td>50%</td>
</tr>
<tr>
<td>Diclofenac (mg/pt)</td>
<td>37.5*</td>
<td>86.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td><strong>Stone Free</strong></td>
<td>71%**</td>
<td>33%</td>
</tr>
</tbody>
</table>

*P = 0.02
*P = 0.019

Propiglia & Scarpa, 2002
Kupeli et al, 2004
All patients underwent flexible URS with a 365\(\mu\) holmium laser fiber and received codeine.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Flomax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean stone size (mm)</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Renal / ureteral calculi</td>
<td>22 / 16</td>
<td>22 / 18</td>
</tr>
<tr>
<td>Stone free</td>
<td>69%</td>
<td>87%*</td>
</tr>
<tr>
<td>Ureteral colic</td>
<td>22.2%</td>
<td>5.4%*</td>
</tr>
</tbody>
</table>

* = \(p < 0.01\)

PROSPECTIVE, RANDOMIZED TRIAL

John & Razdan, 2010
MEDICAL MANAGEMENT OF NEPHROLITHIASIS

SPECIFIC QUESTION

Can medical therapy reduce the risks of residual stone fragments?
MEDICAL RX OF RESIDUAL STONES

PATIENT POPULATIONS

141 patients referred for metabolic evaluation following SWL
92 patients re-contacted for personal interview and f/u radiographs
80 patients re-evaluated 43 months following SWL, with pre- and post-treatment radiographs

Fine, et al, 1995
MEDICAL RX OF RESIDUAL STONES

PATIENT POPULATION AFTER SWL

Stone Free

Med Rx
N=19

No Med Rx
N=12

Residual Fragments

Med Rx
N=36

No Med Rx
N=13

Fine, et al, 1995
MEDICAL RX OF RESIDUAL STONES

METHODS

All patients underwent personal interview to assess:

- Duration and compliance with recommended medical therapy
- Activity of stone disease pre- and post-SWL
- Pre-, post- and follow-up radiographs reviewed by two investigators

Fine, et al, 1995
MEDICAL RX OF RESIDUAL STONES

REDUCTION IN STONE FORMATION

% Reduction in Stone Formation

- Stone-Free
  - 91% with Med Rx
  - 35% without Med Rx

- Residual Frags
  - 81% with Med Rx
  - 17% without Med Rx

Fine, et al, 1995
MEDICAL TREATMENT OF RESIDUAL STONES

Cost of Residual Stones

- **Stone-Free**: $69, $879
- **Residual Frag**: $738, $1,959

*Fine, et al, 1995*
MEDICAL RX AFTER SWL IN CHILDREN

EFFECT OF POTASSIUM CITRATE

Children aged 4 to 14 years (mean 6.6 years) were evaluated for the effects of potassium citrate on residual fragments as well as true new stone formation during long-term follow-up.

Group I - K-citrate 1 mEq/kg daily for 12 months
Group II – Age and sex matched controls
Mean follow-up - 24.4 months

Sarica, et al, 2006
MEDICAL RX AFTER SWL IN CHILDREN

EFFECT OF POTASSIUM CITRATE

Remission Rate

<table>
<thead>
<tr>
<th>Condition</th>
<th>Med Rx</th>
<th>No Med Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone-Free</td>
<td>93%</td>
<td>65%</td>
</tr>
<tr>
<td>Residual Frags</td>
<td>82%</td>
<td>27%</td>
</tr>
</tbody>
</table>

* P < 0.05

Sarica, et al, 2006
MEDICAL RX OF RESIDUAL STONES

EFFECT OF MEDICAL RX AFTER PNL

Retrospective review of 185 patients who underwent PNL (247 procedures)

106 patients completed metabolic evaluations

36 patients excluded due to one of the following:

- Cystinuria
- Neurologic bladder dysfunction
- Incomplete follow-up
- Anatomic abnormalities
- Conservative treatment (Fluids or diet alone)

MEDICAL RX OF RESIDUAL STONES

EFFECT OF MEDICAL RX AFTER PNL


* P < 0.0001
MEDICAL RX OF RESIDUAL STONES

EFFECT OF MEDICAL RX AFTER PNL


* P < 0.0001
URETERAL CALCULI

ADJUVANT MEDICAL THERAPY

**Efficacy**
- Facilitated stone passage
- Improved stone free rates

**Morbidity**
- Pain
- Quality of life
IMPACT OF ALPHA-BLOCKERS ON STENT SYMPTOMS
META-ANALYSIS

Urinary Sx
P=0.005

Pain
P=0.0004

Gen Health
P=0.001

Yakoubi & Monga, 2011
MEDICAL MANAGEMENT OF NEPHROLITHIASIS

SPECIFIC ANSWERS

Do residual stone fragments impact on recurrent stone formation?  YES !

Is medical therapy available to facilitate residual stone fragment passage following SWL / PNL / URS ?  YES !

Is medical therapy effective in preventing new stone formation and/or growth of residual fragments?  YES !
MEDICAL RX OF RESIDUAL STONES

CONCLUSIONS

Residual stone fragments following SWL / PNL / URS appear to pose a significant risk for stone growth and recurrent stone formation.

Medical therapy may facilitate clearance of residual stone fragments.
Selective medical therapy can significantly reduce recurrent stone formation or growth of residual fragments following stone removal.

Appropriate medical management provides a cost-effective alternative to recurrent stone removal.
MEDICAL RX OF RESIDUAL STONES

RECOMMENDATIONS

All attempts should be made to render patients completely stone-free to avoid risks and complications of residual stone fragments.

Consider treatment with potassium citrate or medical expulsive therapy to facilitate spontaneous passage of residual fragments.

Appropriate metabolic evaluation and specific medical therapy should be initiated in most patients following any form of surgical stone removal.