Can Phyllanthus niruri Affect the Efficacy of Extracorporeal Shock Wave Lithotripsy for Renal Stones? A Randomized, Prospective, Long-Term Study

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Purpose: Phyllanthus niruri is a plant used in Brazilian folk medicine for the treatment of urolithiasis. We assessed the efficacy of P. niruri after extracorporeal shock wave lithotripsy for renal stones.

Materials and Methods: We prospectively evaluated 150 patients with renal stones that were as large as 25 mm and composed of calcium oxalate. All patients received 1 to 3 extracorporeal shock wave lithotripsy sessions by Dornier Lithotriptor S. After treatment 78 of 150 patients (52%) underwent therapy with Uriston®, a P. niruri extract (2 gm daily) for at least 3 months (group 1). Otherwise 72 of 150 patients (48%) were used as a control group (group 2). No significant difference in stone size between the 2 groups was found. Stone clearance was assessed after 30, 60, 90 and 180 days by abdominal x-ray and ultrasound scan.

Results: Stone-free rate (stone-free defined as the absence of any stone or residual fragments less than 3 mm) was 93.5% in group 1 and 83.3% in group 2 ($p = 0.48$) at the end point of the followup (180 days). For lower caliceal stones (56 patients) the stone-free rate was 93.7% in the treatment group and 70.8% in the control group ($p = 0.01$). Re-treatment need for group 1 was 39.7% and for group 2 it was 43.3% ($p = 0.2$). No side effects were recorded with extracorporeal shock wave lithotripsy or P. niruri therapy.

Conclusions: Regular self-administration of P. niruri after extracorporeal shock wave lithotripsy for renal stones results in an increased stone-free rate that appears statistically significant for lower caliceal location. Its efficacy and the absolute lack of side effects make this therapy suitable to improve overall outcomes after extracorporeal shock wave lithotripsy for lower pole stones.

Key Words: kidney calculi, lithotripsy

Extracorporeal shock wave lithotripsy represents a minimally invasive treatment for renal stones. The efficacy and safety of this procedure are well proven and demonstrated. Stone-free rates after ESWL® may vary according to stone size,[1] location[1–3] and the type of lithotriptor used.[4,5] Medical therapies may be used to avoid stone relapse, and these consist traditionally of citrate, potassium and magnesium, which act to correct the imbalance between the promoter and inhibitors of lithogenesis. Other therapies are used to dissolve stones. For many years litholytic agents such as Herniaria hirsuta, kampou extracts and other plants were a common way to treat urinary stones, especially in semi-arid zones and in countries with unreliable water sources.[6–8]

Phyllanthus niruri is a plant traditionally used in Brazilian folk medicine for the treatment of several pathological conditions, including urolithiasis. The plant may act as an inhibitor of crystal growth, because of a higher incorporation of glycosaminoglycans into the stone.[9] Uriston® consists of an extract from P. niruri labeled with specifics tannins. We assessed the efficacy of chronic therapy with Uriston® after ESWL® for renal stones composed of calcium oxalate.

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MATERIALS AND METHODS

From January 2003 to February 2005 we prospectively evaluated 150 patients with renal stones thought to be composed of calcium oxalate. Subjects with urinary tract infections, pregnant women or patients who already underwent renal surgery were excluded from the study. Stones were investigated through abdominal x-ray, ultrasound and excretory urogram. Patients were submitted to 1 to 3 session of ESWL® with the use of Dornier Lithotriptor S.

After ESWL® patients were randomly divided in 2 groups. Group 1 consisted of 78 patients who received an adjunctive treatment with oral medical therapy, and group 2 consisted of 72 patients who did not receive any therapy and served as a control group. The medical therapy of group 1 consisted of 2 gm per day of Uriston®, an extract from P. niruri self-administered once a day for a minimum of 90 days. Both groups were allowed to use symptomatic therapy with ketoprofen on demand and were asked to drink a minimum of 2 liters of water daily. Stone clearance was assessed after 30, 60, 90 and 180 days by abdominal x-ray and ultrasound scan. A stone-free condition was defined as the complete absence of any stone or the presence of residual fragments smaller than 3 mm.

Sampled data were inserted in a database and statistically analyzed with the help of SPSS® 8.0 version for Windows. A complete descriptive analysis of all available vari-

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TABLE 1. *Patient and stone characteristics*

	Group 1	Group 2	p Value
Mean pt age (range)	50 (25–78)	48 (24–73)	
Mean mm stone size (range)	12.2 (5–25)	11.5 (5–20)	
No. stone location:			
Upper caliceal	9	14	0.14
Middle caliceal	16	10	0.22
Lower caliceal	32	24	0.10
Pelvis	21	24	0.68

ables was performed. Statistical analysis was performed with student's t test, the Mann-Whitney U test, the chi-square test and 2-tailed Fisher's exact test. A significance level of 0.05 was chosen for all the tests.

RESULTS

All patients completed the study. Group 1 consisted of 42 men and 36 women (average age 50 years, range 25 to 78), and group 2 consisted of 38 men and 34 women (average age 48 years, range 24 to 73). The average stone size was 12.2 mm (range 5 to 25) for group 1 and 11.5 mm (range 5 to 20) for group 2, with no statistically significant difference between the 2 groups. Stone location in the kidney is reported in table 1. A Double-J® stent was placed before ESWL® in each case in which the stone size was larger than 20 mm. The average number of shock waves per session was 3,000 for both groups (range 2,400 to 3,500). Ultrasound and x-ray were used for focusing on the stone.

Stone-free condition with residual fragments less than 3 mm occurred in 73 (93.5%) of 78 patients in group 1 and in 60 (83.3%) of 72 patients in group 2 at the end point ($p = 0.48$). Stone-free condition without residual fragments occurred in 69 (88.5%) of 78 patients in group 1 and in 55 (76.4%) of 72 patients in group 2 ($p = 0.08$).

Table 2 presents the stone-free rates for different stone locations. Outcomes stratified by stone size and by different steps of followup (30, 60, 90 and 180 days after ESWL®) are reported in table 3. Regarding the stone-free patients, 29 of 73 in group 1 (39.7%) and 26 of 60 in group 2 (43.3%) underwent ESWL® re-treatment ($p = 0.2$). All the collected stones turned out to have a predominantly calcium oxalate composition (greater than 70%).

Medical therapy with Uriston® for group 1 lasted from 95 to 200 days (mean 134). No side effects were noticed during the treatment, neither with ESWL® nor with P. niruri intake. Patients who were not stone-free after 180 days (5 in group 1 and 12 in group 2) were successfully treated with percutaneous lithotripsy.

TABLE 2. *Outcomes stratified by stone location*

	% Group 1 Stone-Free	% Group 2 Stone-Free	p Value
With residual fragments less than 3 mm:			
Overall	93.5	83.3	0.10
Upper caliceal	100	92.8	0.06
Middle caliceal	93.7	90	0.54
Lower caliceal	93.7	70.8	<0.001
Pelvis	90.4	87.5	0.75
Without residual fragments:			
Overall	88.5	76.4	0.08
Upper caliceal	88.8	85.7	0.63
Middle caliceal	87.5	80.0	0.86
Lower caliceal	90.6	62.5	0.03
Pelvis	85.7	83.3	0.85

TABLE 3. *Outcomes stratified by stone size and followup*

	% Group 1 Stone-Free	% Group 2 Stone-Free	p Value
Stone size (mm):			
Less than 10	97.2	84.6	0.02
Greater than 11	90.4	82.6	0.24
Days followup:			
30	54	18.8	0.02
60	69.3	35.2	0.03
90	74.3	64.2	0.38
180	93.5	83.3	0.48

DISCUSSION

ESWL® represents a minimally invasive treatment for renal stones, and its efficacy and safety have improved accordingly with technological progress.[4,5,10] Nevertheless, outcomes of ESWL® may be affected by a number of features connected to both stone and patient characteristics. It is well known that stone size,[1] location[1–3] and composition[11] influence the clearance of residual fragments while a high body mass index compromises the results of stone focusing.[12]

As the technology has improved, some authors have reported outcomes of ESWL® with regard to the type of lithotriptor used. Matin et al found a comparable efficiency quotient between electrohydraulic and electromagnetic units.[4] Sheir et al, with a prospective, randomized comparative study, recently reported an overall stone-free rate of 88.5% and 82.4% for Dornier Lithotriptor S and Dornier MFL 5000, respectively.[5] Other studies investigated ESWL® results based on the location of the stones. Obek et al described an overall stone-free rate of 66% with a Lithostar® lithotriptor with 63%, 73% and 71% stone clearance for lower, middle and upper isolated caliceal stones, respectively.[13]

Lower pole stones still represent a difficult problem due to the reduced discharge of the fragments and their consequent recrystallization. The cause may be based on morphological features of the kidney. Elbahnasy et al described the 3 major radiographic characteristics of the lower pole that influence ESWL® outcomes as infundibulopelvic angle, infundibular length and width.[3] Other clinical studies of 10 to 20 mm lower caliceal stones found stone-free rates varying from 37% to 79.2%.[14,15]

Supportive medical therapy to improve ESWL® results has been attempted in the past by using potassium or magnesium citrates. Cicerello et al suggested that citrate reduces growth or agglomeration, increasing the clearance rate of calcium oxalate.[16] Soygur et al investigated the effect of potassium citrate therapy on the stone recurrence rate and the percentage of residual fragments after ESWL®. In the residual fragment group treated patients had a significantly greater remission rate compared to untreated patients (44.5 vs 12.5%), and no recurrences were noticed at 12 months in the stone-free group following potassium citrate therapy.[17]

In this study we evaluated the efficacy of Uriston®, an extract from P. niruri, after shock wave lithotripsy for renal stones. P. niruri is a plant belonging to the Euphorbiaceae family with a worldwide distribution. It is traditionally used in Brazilian folk medicine in the treatment of urolithiasis. Several authors have investigated its mechanism of action. In

1998 Campos and Schor described the powerful inhibitory effect of P. niruri on CaOx crystal adhesion and suggested that P. niruri intake may reduce urinary calcium in patients with hypercalciuria.[18,19] Barros et al confirmed the inhibition on CaOx crystal growth and aggregation with an in vitro aqueous extract from P. niruri.[20]

Freitas et al suggested that this effect was related to a higher incorporation of glycosaminoglycans into the stone, independently from urinary excretion of citrate and magnesium.[9] In fact, the calculi from a P. niruri treated group had a higher content of GAGs, suggesting that P. niruri reduces the deposition of crystalline particles.

The actual role of GAGs in urolithiasis has been widely evaluated and discussed. GAGs and especially chondroitin sulfate bind to the growth sites of crystals and therefore stop their aggregation. The outcomes of our experience may support all these premises in that residual fragments due to ESWL® seem to have a lower aggregation and crystallization potential.

Complete stone clearance occurred in 93.5% of patients in the treated group but only in 83.3% of patients in the control group. Taking into consideration lower caliceal stones, 93.7% of Uriston® patients were stone-free at 180 days compared to 70.8% of patients in the nontreated group. Stone size ($p = 0.02$) and medical therapy ($p = 0.03$) were the main predictors of stone clearance.

P. niruri reduces the relative risk of ESWL® failure 10.3% overall and 33% for stones located in the inferior calix. Further studies are required to fully understand the role of P. niruri. Nevertheless, clinical outcomes with the use of P. niruri after ESWL® are remarkable as they show a statistically significant increase in ESWL® effectiveness.

CONCLUSIONS

Regular intake of P. niruri after ESWL® results in an increased overall stone-free rate, in a lower re-treatment percentage and in a faster stone clearance. Its efficacy is only evident for stones in the lower caliceal location, where it may act to prevent recrystallization of stone fragments and thus increase their clearance. The effectiveness of P. niruri together with the absolute lack of side effects make this therapy suitable for improving overall outcomes of shock wave lithotripsy for lower pole renal stones.

Abbreviations and Acronyms

CaOx	=	calcium oxalate
ESWL®	=	extracorporeal shock wave lithotripsy
GAG	=	glycosaminoglycans

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