0022-5347/05/1741-0167/0
THE JOURNAL OF UROLOGY®

Vol. 174, 167–172, July 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000161600.54732.86

Urolithiasis/Endourology

RANDOMIZED TRIAL OF THE EFFICACY OF TAMSULOSIN, NIFEDIPINE AND PHLOROGLUCINOL IN MEDICAL EXPULSIVE THERAPY FOR DISTAL URETERAL CALCULI

MARCO DELLABELLA,* GIULIO MILANESE AND GIOVANNI MUZZONIGRO

From the Department of Urology and Division of Urology, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I.-G. M. Lancisi-G. Salesi, Polytechnic University of the Marche Region, School of Medicine, Ancona, Italy

ABSTRACT

Purpose: Recent studies show the interesting efficacy of different drug combinations for the spontaneous expulsion of distal ureteral stones. We performed a randomized, prospective study to assess and compare the efficacy of 3 drugs as medical expulsive therapy for distal ureteral calculi.

Materials and Methods: A total of 210 symptomatic patients with distal ureteral calculi greater than 4 mm were randomly allocated to home treatment with phloroglucinol, tamsulosin or nifedipine (groups 1 to 3, respectively). Each group was given a corticosteroid drug and antibiotic prophylaxis with an injectable nonsteroidal anti-inflammatory drug was also used on demand. The primary end point was the expulsion rate and the secondary end points were expulsion time, analgesic use, need for hospitalization and endoscopic treatment as well as the number of workdays lost, quality of life and drug side effects

Results: The expulsion rate was significantly higher in group 2 (97.1%) than in groups 1 (64.3%, $p < 0.0001$) or 3 (77.1%, $p < 0.0001$). Group 2 significantly achieved stone passage in a shorter time than the other 2 groups and showed a significantly decreased number of hospitalizations as well as a better decrease in endoscopic procedures performed to remove the stone. The control of renal colic pain was significantly superior in group 2 compared with the other groups, resulting in fewer workdays lost. Group 3 showed lower analgesic use and decreased workdays lost compared with group 1. No difference in side effects was observed among the groups.

Conclusions: Medical expulsive therapy should be considered for distal ureterolithiasis without complications before ureteroscopy or extracorporeal lithotripsy. The use of tamsulosin in this treatment regimen produced stone expulsion in almost all cases in a short time, allowing complete home patient treatment.

KEY WORDS: ureter, ureteral calculi, tamsulosin, nifedipine, phloroglucinol

About 8% to 15% of European and North American individuals have urolithiasis in their lifetimes. Renal colic is one of the most painful conditions that may occur and it is often caused by stone in the distal portion of the ureter. A watchful waiting approach may be expected to produce spontaneous stone expulsion in up to 50% of cases but some complications, such as urinary infection, hydronephrosis and repeat colic events, may occur.[1–4] Endoscopic treatment with ureteroscopy (URS) and extracorporeal shock wave lithotripsy allow distal ureterolithiasis to resolve in almost all cases.[2] However, these procedures are not risk-free and they require some experience and imply high costs.[5,6] On the contrary, the role of medical expulsive therapy (MET) in the treatment of this pathological condition is still unclear. In particular to our knowledge the most effective treatment regimen for spontaneous stone expulsion and the control of algesic symptoms has not been yet determined despite the widespread need in clinical practice.

In the literature several studies in animal models have tested the effects of different groups of drugs, such as antihistamines, prostaglandins, parasympatholytic agents, etc, on ureteral function. However, the clinical use of many drugs that may be potentially beneficial in patients with ureteral diseases has been limited by serious side effects.[7]

Few randomized studies have been done to verify the efficacy of different drug combinations for the spontaneous expulsion of distal ureteral stones. These trials have produced interesting results, achieving elimination rates of up to more than 80% and excellent pain control.[8,9] We recently reported that tamsulosin, a selective α1A-α1D antagonist, combined with a corticosteroid and appropriate antibiotic treatment allows the expulsion of juxtavesical ureteral stones in a decreased time and, in addition, it unexpectedly induces an almost complete decrease in painful symptoms until expulsion.[10] The current study was performed to assess and compare the expulsive effects of orally administered phloroglucinol, tamsulosin and nifedipine as MET for distal ureteral

Submitted for publication October 5, 2004.
Study received local ethics committee approval.
* Correspondence: Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I.-G. M. Lancisi-G. Salesi, Polytechnic University of the Marche Region, School of Medicine, Ancona, Italy (e-mail: d.urologia@ao-umbertoprimo.marche.it).

calculi greater than 4 mm in diameter when administered up to 28 days after the first painful manifestation.

MATERIALS AND METHODS

Participants. Between May 2002 and July 2003 we screened individuals who were referred because of acute renal colic to the emergency room at our department of urology for inclusion in this prospective, randomized, parallel group study. All patients were evaluated by physical examination, serum creatinine measurement, plain abdominal radiography and abdominal ultrasonography. All patients received first line treatment for painful manifestations with 1 intramuscular vial of diclofenac.

Men and women older than 18 years were eligible for study inclusion if they presented with ultrasonographically and/or radiologically visible distal ureteral stones 4 mm or larger below the common iliac vessels, and if renal colic resolution was achieved within the first hour after diclofenac administration. Exclusion criteria were lithiasis of the proximal-lumbar or intramural ureteral tract, marked hydronephrosis, acute renal failure, fever, multiple ureteral stones, painful symptoms more than 1 day in duration, a history of surgery or endoscopic procedures in the urinary tract, chronic renal failure, diabetes, peptic ulcer, concomitant treatment with alphalytic drugs, β-blockers, calcium antagonists or nitrates, pregnancy, lactation or patient desire for immediate stone removal. Patients provided written informed consent at the time of enrolment.

The trial was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee and a letter of information was addressed to the family physician. We held and analyzed all data.

Interventions. During their emergency room shifts 4 urologists used a random number table to assign patients to 3 treatment groups. Group 1 was treated with 80 mg phloroglucinol (3 tablets daily for a maximum of 28 days), group 2 received 0.4 mg tamsulosin (1 capsule daily for a maximum of 28 days) and group 3 was treated with slow release, 30 mg nifedipine (1 tablet daily for a maximum of 28 days). Cotrimoxazole (2 tablets daily for 8 days) and 30 mg deflazacort (1 tablet daily for 10 days) completed MET in each group. Diclofenac (75 mg vials as intramuscular injection) was prescribed in all cases in case of need. All patients were treated on an outpatient basis. In addition, all subjects were instructed to drink 2 l water daily and perform their usual everyday activities. The home treatment period lasted 28 days or until stone expulsion in all 3 groups.

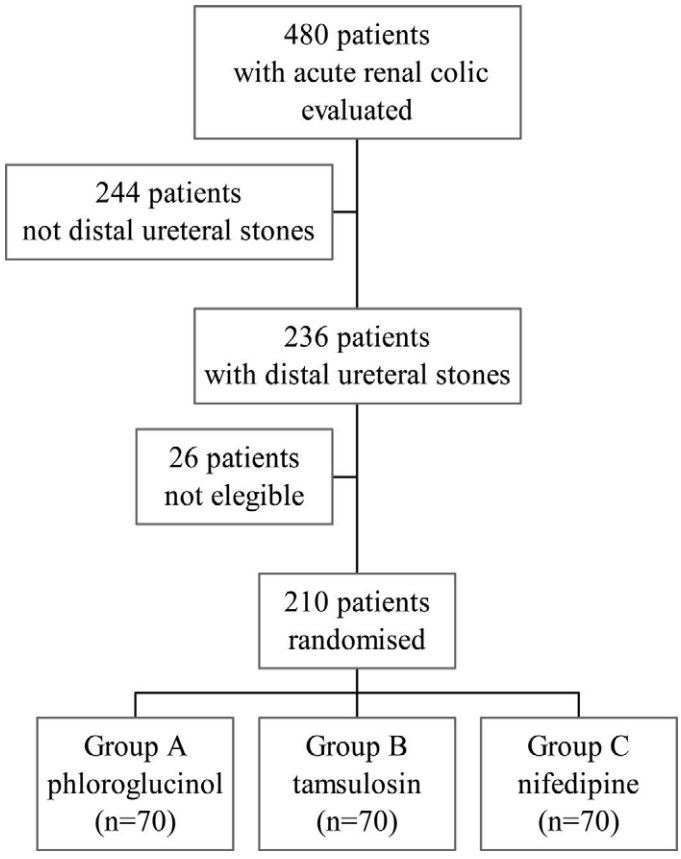

FIG. 1. Trial profile. All randomized patients completed trial

At our outpatient clinic all subjects were evaluated every 7 days by physical examination, abdominal ultrasonography and serum creatinine measurement. Plain abdominal radiography was performed on days 10 and 28. At the beginning of enrolment and at every followup visit each patient received the therapy for the next 7 days. All drugs supplied to patients were free samples. Only diclofenac vials were prescribed. Certain data were recorded on every patient, including age and sex, largest radiographic or ultrasonographic stone size, stone lateral location, day and time of stone expulsion, number of analgesic vials used, need for hospitalization and urgent or scheduled endoscopic procedures, number of workdays lost and therapy side effects. To evaluate quality of life during the assigned therapy all patients were invited to compile the EuroQoL questionnaire (EQ-5D) at the first followup visit after stone expulsion or at day 28.[11]

Unsuccessful stone expulsion within 28 days was considered therapy failure and ureteroscopy was scheduled for the patient. Patient hospitalization because of uncontrollable pain or an increase in creatinine of greater than 2 mg/dl during the study period was considered therapy failure. Loss to followup or study withdrawal after recruitment was considered treatment failure.

Outcomes. The primary efficacy end point of this study was stone expulsion, as confirmed by plain abdominal radiography and/or abdominal ultrasound at followup. Expulsion time, defined as the number of hours from the beginning of assigned oral therapy to stone expulsion, the quantity of analgesics used, defined as the number of analgesic vials used up to expulsion or to day 28, the need for hospitalization and/or endoscopic procedures, the number of workdays lost, defined as days of real inability to perform the usual daily activities, quality of life and side effects during therapy were also assessed as secondary end points.

Statistical analysis. End points were predefined and analyzed on an intent to treat basis. Discrete variables are shown as counts (percents) and continuous variables are shown as the mean $\pm$ SD or median (IQR). Sample size was calculated to achieve a statistical power of 80% at 5% type I error. Based on the results of a previous pilot study in which the difference in expulsion rates between phloroglucinol and tamsulosin was 30%[10] a sample size of 59 patients per group was required for this study. After allowing 20% for dropouts 70 subjects were enrolled per group.

Statistical analysis used for making comparison among groups was performed using ANOVA and the Bonferroni or Kruskal-Wallis and Mann-Whitney U tests, as appropriate. Comparisons between proportions were assessed using the chi-square or Fisher exact test, when appropriate. Correlation analysis was performed using Spearman's rank test. Time to expulsion in patients in each group was analyzed by plotting Kaplan-Meier curves and it was compared using log rank analysis. The Cox proportional hazards regression model was used to determine factors predictive of expulsion. The 2-tailed test was used for all comparisons with $p < 0.05$ considered statistically significant. SPSS 11.0 software (SPSS, Chicago, Illinois) was used for all calculations.