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# Prognostic factors of spontaneous expulsion in ureteral lithiasis

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Medical treatment, extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy are therapeutic options for ureteral stones. EWSL and endoscopic treatment of ureteral stones have a high success rate. However it has surgical as well as anaesthetic risks. For many patients, a medicinal treatment without invasive procedures is an option. Watchful waiting does not always result in stone clearance and may be associated with recurrent renal colic. The study of the prognostic factors for expulsion and the medical therapy will help us to select candidates for medical expulsive treatment.

*Objectives:* To evaluate the characteristics of the stones and the medication administered (alpha blockers, NSAIDs or a combination of both) as predictors of spontaneous passage of the stone.

*Material and methods:* A retrospective observational study of 260 patients with 278 ureteral stones was conducted. Primary endpoint was stone expulsion. Univariate and multivariate analysis were conducted testing the effect of stone location, size and composition, and medication (alpha-blockers, NSAIDs, or combination) on stone clearance.

*Results:* 34.2% of the stones studied were spontaneously eliminated. Stone location (pelvic ureter, OR= 1.823, p=0.013), size (<5mm, OR=3.37, p<0.02), and medication (combination of alpha blockers and NSAIDs, OR= 8.70, p<0.001) were predictors of spontaneous clearance. Multivariate analysis confirmed size (p=0.006) and medication (p<0.001) as independent predictive factors. The use of the combination of NSAIDs and alpha-blockers versus observation multiplied times 8.21 (95% CI 3.37–20.01) the possibilities of spontaneous expulsion.

*Conclusions:* Size of stone and medication were confirmed as independent factors for spontaneous expulsion of ureteral stones.



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## Factores predictivos para la expulsión de la litiasis ureteral

*Palabras clave:*
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RESUMEN

El tratamiento médico, la litotricia y la ureteroscopia son opciones terapéuticas para el tratamiento de la litiasis ureteral. La ureteroscopia y la litotricia son altamente resolutivas, si bien no están exentas de riesgos quirúrgicos y anestésicos. El tratamiento médico expulsivo es menos efectivo pero carece de esos riesgos. La selección de enfermos para el tratamiento médico debe ser cuidadosa, atendiendo a factores como el tamaño, la composición y la localización de la litiasis.

*Objetivos:* Analizar retrospectivamente el papel de las características litiásicas y de la medicación (alfabloqueantes, antiinflamatorios no esteroideos [AINE] o la combinación de ambos) como factores predictivos de la expulsión de cálculos ureterales.

*Material y métodos:* Para el estudio se encontraron disponibles 278 litiasis ureterales correspondientes a 260 enfermos. La variable principal del estudio fue el «resultado clínico» (expulsión o persistencia de la litiasis). Se analizaron la influencia de la localización, el tamaño, la composición y la medicación administrada (alfabloqueantes, AINE o la combinación de ambos) con el test de la chi cuadrado. A continuación, se llevó a cabo un análisis multivariante con un modelo de regresión logística para estudiar la influencia de cada una de las variables en presencia del resto de las covariables.

*Resultados:* Se produjo la expulsión del 34,2% de las litiasis. La localización (uréter pelviano, *odds ratio* [OR] = 1,823; p = 0,02), el tamaño (< 5 mm, OR = 3,37; p < 0,001) y la medicación administrada (combinación de alfabloqueantes y AINE, OR = 8,70; p < 0,001) resultaron factores predictivos para la expulsión. El análisis multivariante confirmó al tamaño (p = 0,006) y a la medicación (p < 0,001) como factores predictivos independientes. El tratamiento con una combinación de AINE y alfabloqueantes multiplica por 8,21 (intervalo de confianza del 95%: 3,37–20,01) las posibilidades de expulsión en comparación con la mera actitud expectante.

*Conclusiones:* El tamaño del cálculo y la medicación son factores predictivos independientes para la expulsión de la litiasis ureteral.



## Introduction

*In situ* extracorporeal lithotripsy and ureteroscopy (URS) are the two most commonly used therapeutic options for the treatment of ureteral stones. Depending on stone location or size, lithotripsy and URS resolve 63%-86% and 57%-92% of stones respectively. None of them is free from complications, and the complication rate is less than 1% for both.[1]

The effect of many drugs to facilitate ureteral stone passage has been studied. Since α receptors were found in smooth muscle of distal ureter, many studies have been conducted to assess alpha-blockers alone and combined with other drugs. Medical expulsive therapy (MET) with alpha-blockers has been shown to improve passage rate by 29%.[2] However, the possibility of renoureteral crises and complications derived from long-term ureteral obstruction are factors to be considered.[3-5]

An adequate stone selection together with the effect of MET may be a valid alternative for the treatment of ureteral stones avoiding anesthetic and surgical complications, and minimizing the risks of long-term ureteral obstruction.

The objective of this study was to retrospectively analyze stone characteristics and medication administered (alpha-blockers, non-steroidal anti-inflammatory drugs [NSAIDs], or the combination of both) as predictors of ureteral stone passage.

## Materials and methods

A retrospective study was conducted from May 2004 to November 2009. All ureteral stones seen at this hospital and documented by abdominal plain X-rays or CT and referred to the urinary stones clinic were reviewed.

The main variable was stone passage within 45 days of diagnosis. Morphological characteristics of stones (size, composition, and location) and medical treatment started at diagnosis were also collected, and patients were distributed into four management groups: observation, NSAIDs (any drug from this class), tamsulosin (0.4 mg/day), and combination of tamsulosin (0.4 mg/day) plus NSAIDs.

Follow-up was based on urinary sediment, ultrasound, abdominal X-rays and/or CT when there was doubt about stone location. “Passage” was defined as disappearance from the radiographic image or stone passage and recovery, both associated to clinical and laboratory normalization.

Patients who had fever, uncontrolled pain, or acute renal failure during follow-up were managed using the relevant therapeutic maneuvers and were included in the "no passage" group. Patients who did not pass the stone after 45 days of follow-up were included in this group and managed by observation or URS.

Data were collected using a relational database developed in Microsoft Access®[6] and were analyzed using SPSS® statistical software. For the univariate analysis, a Chi-square test was used to compare proportions and a Student's t test for means comparison. A value of $p<0.05$ was considered statistically significant.

The multivariate analysis was performed using a logistic regression model, including all model parameters and using the Wald method to calculate statistical significance. A backward stepwise approach with a likelihood ratio test was then used for determining a final adjusted model, assuming a 10% uncertainty.

## Results

From May 2004 to October 30, 2009, 274 patients with ureteral stones were included in the stone database.[6] Fourteen patients were excluded from analysis because of incomplete or erroneous data. Finally, 260 patients (278 stones) were available. Table 1 shows the demographic characteristics of patients enrolled, as well as the morphological features of stones. There were no significant differences in any of the demographic or morphological characteristics studied between the treatment groups.

Stone passage rate was 34.2% (95% confidence interval [CI]: 28.6–0.1%). Univariate analysis confirmed location ($p=0.013$), size ($p=0.02$), and medication administered ($p<0.01$) as prognostic factors. Table 2 details the passage rate in the different categories of study groups. Stone passage rate was significantly higher in the distal ureter as compared to higher segments. Similarly, passage rate was inversely proportional to stone size. The effect of medication also influenced stone passage rate, which was significantly higher in the group given the combination of alpha-blockers and NSAIDs (table 2).

A multivariate analysis (table 3) confirmed size ($p=0.006$) and medication to be independent predictors for ureteral stone passage ($p<0.01$). As compared to simple watchful waiting, NSAID therapy caused a 3.2-fold increase (95% CI: 1.68–6.04) in the chance of stone passage, while the combination of NSAIDs plus alpha-blockers caused an 8.2-fold increase (95% CI:.3.37–20.01). The variable "chemical composition" could be ruled out from the final predictive model (table 4).

## Discussion

Ureteral stones affect 15% of the population and are commonly diagnosed at emergency rooms.[7] Many of these stones are small and are located in the distal ureter, and are often passed spontaneously. It is estimated that up to 68% (95% CI, 46%–5%) of stones less than 5 mm in size are passed spontaneously, while the proportion decreases to 47% (95% CI: 36%-9%) for stones greater than 5 mm.[2,8]

**Table 1 – Demographic characteristics of patients and morphological features of stones (Chi-square test and analysis of variance)**

| | No drugs n=142 | NSAIDs n=65 | Alpha-blockers n=21 | Combination n=32 | P |
|---|---|---|---|---|---|
| Male, n (%) | 87 (61.3) | 38 (58.5) | 16 (76.2) | 19 (59.4 ) | |
| Mean age* | 46.5 (44.3–48.8) | 47.6 (44.1–51.2) | 49.4 (43.9–54.8) | 42.8 (38.1–47.6) | ANOVA=0.57 |
| Location (n=278) | | | | | 0.11 |
| Lumbar ureter, n (%) | 66 (43.1) | 25 (35.7) | 4 (18.2) | 8 (24.2) | |
| Sacral ureter, n (%) | 8 (5.2) | 2 (2.8) | 2 (9.1) | 0 (0) | |
| Pelvic ureter, n (%) | 79 (51.63) | 43 (61.4) | 16 (72.7) | 25 (75.8) | |
| Size | | | | | 0.39 |
| <5 mm, n (%) | 56 (36.6) | 31 (44.3) | 13 (59.1) | 17 (51.5) | |
| 5–7 mm, n (%) | 41 (26.8) | 21 (30) | 5 (22.7) | 4 (12.1) | |
| 7–10 mm, n (%) | 38 (24.8) | 13 (18.6) | 4 (18.2) | 11 (33.3) | |
| >10 mm, n (%) | 18 (11.8) | 5 (7.1) | 0 (0) | 1 (3) | |
| Composition | | | | | 0.06 |
| Unknown, n (%) | 125 (81.7) | 50 (71.4) | 17 (77.3) | 25 (75.8) | |
| Calcium oxalate, n (%) | 22 (14.4) | 18 (25.7) | 5 (22.7) | 7 (21.2) | |
| Calcium phosphate, n (%) | 3 (2) | 1 (1.4) | 0 (0) | 0 (0) | |
| Uric acid, n (%) | 3 (2) | 1 (1.4) | 0 (0) | 1 (4) | |

NSAIDs: nonsteroidal anti-inflammatory drugs; ANOVA: analysis of variance; CI: confidence interval.
*Data shown are the mean and 95% CI.

**Table 2 – Univariate analysis to assess the influence of different prognostic factors on stone passage**

| | Passage, % | No passage, % | OR (95% CI) | p |
|---|---|---|---|---|
| *Location* | 95 (34.2) | 183 (65.8) | | 0.013 |
| Lumbar ureter* | 28 (27.2) | 75 (72.8) | 1 | |
| Sacral ureter | 1 (8.3) | 11 (91.7) | 0.244 (0.030–1.974) | |
| Pelvic ureter | 66 (40.5) | 97 (59.5) | 1.823 (1.067–3.112) | |
| *Size* | 95 (34.2) | 183 (65.8) | | 0.02 |
| >10 mm* | 5 (20.8) | 19 (79.2) | 1 | |
| <5 mm | 55 (47) | 62 (53) | 3.371 (1.18–9.63) | |
| 5–7 mm | 19 (26.8) | 52 (73.2) | 1.39 (0.455–4.24) | |
| 7–10 mm | 16 (24.2) | 50 (75.8) | 1.22 (0.39–3.78) | |
| *Composition* | 95 (34.2) | 183 (65.8) | | ns |
| Calcium oxalate* | 21 (40.4) | 31 (59.6) | 1 | |
| Calcium phosphate | 2 (50) | 2 (50) | 1.47 (0.19–11.3) | |
| Uric acid | 2 (40) | 3 (60) | 0.98 (0.15–6.40) | |
| Unknown | 70 (32.3) | 147 (67.7) | 0.70 (0.38–1.31) | |
| *Medication* | 95 (34.2) | 183 (65.8) | | <0.01 |
| No drugs* | 32 (20.9) | 121 (79.1) | 1 | |
| NSAIDs | 33 (47.1) | 37 (52.9) | 3.37 (1.83–6.20) | |
| Alpha-blockers | 7 (31.8) | 15 (68.2) | 1.77 (0.66–4.69) | |
| Alpha-blockers+NSAIDs | 23 (69.7) | 10 (30.3) | 8.70 (3.76–20.11) | |

NSAIDs: nonsteroidal anti-inflammatory drugs; CI: confidence interval; ns: nonsignificant; OR: odds ratio.
ns=p>0.05.
* Marked categories acted as reference categories.

**Table 3 – Multivariate analysis to assess the influence of different prognostic factors on stone passage**

| | P | OR | 95% CI |
|---|---|---|---|
| *Location* | 0.095 (LR) | | |
| Lumbar ureter | 0.173 | | |
| Sacral ureter | 0.196 | 0.240 | (0.03–2.09) |
| Pelvic ureter | 0.280 | 1.392 | (0.76–2.54) |
| *Size* | 0.006 (LR) | | |
| >10 mm | 0.006 | | |
| <5 mm | 0.122 | 2.465 | (0.79–7.74) |
| 5–7 mm | 0.949 | 1.040 | (0.31–3.48) |
| 7–10 mm | 0.674 | 0.764 | (0.22–2.67) |
| *Composition* | 0.657 (LR) | | |
| Calcium oxalate | 0.648 | | |
| Calcium phosphate | 0.390 | 2.557 | (0.30–21.79) |
| Uric acid | 0.997 | .997 | (0.13–7.73) |
| Unknown | 0.490 | 0.781 | (0.38–1.58) |
| *Medication* | 0.000 (LR) | | |
| No drugs | 0.000 | | |
| NSAIDs | 0.000 | 3.190 | (1.68–6.04) |
| Alpha-blockers | 0.429 | 1.512 | (0.54–4.21) |
| Alpha-blockers+NSAIDs | 0.000 | 8.206 | (3.37–20.01) |

NSAIDs: nonsteroidal anti-inflammatory drugs; CI: confidence interval; LR: likelihood ratio; OR: odds ratio.

Location has also been shown to have an influence on the chance of stone passage; 71% of stones located in the distal ureter are passed spontaneously, as compared to 22% of those located in the proximal ureter.[9]

It has recently been demonstrated that alpha-blockers and calcium channel blockers are able to cause smooth muscle relaxation, thus facilitating stone passage through the ureter by blocking $\alpha$ receptors and calcium channels located in smooth muscle cells of the distal ureter. Several meta-analyses assessing the efficacy of MET have been reported. Such meta-analyses showed the superiority of tamsulosin over watchful waiting, as it improved passage rate by up to 29%.[8] Conflicting results have been reported for nifedipine. While the meta-analysis conducted by Preminger et al found no significant differences (9%; 95% CI: -7–25%).[8] Singh et al[2] showed that treatment with calcium channel blockers of stones of a moderate size in the distal ureter resulted in a 1.5-fold improvement in passage (95% CI: 1.34–1.68). Hollingsworth et al[10] showed a 1.9-fold higher passage rate (95% CI: 1.51-2.40) in patients treated with nifedipine and steroids.

Similarly, two studies have been conducted to assess the efficacy of NSAIDs for stone passage, one with celecoxib at 400 mg doses[11] and the other with diclofenac at 50 mg doses.[12] Stone passage rate was not improved in any of these studies. However, NSAIDs have been shown to be effective for pain treatment, and are recommended in this condition with a level of evidence 1b.[8]

As in most studies conducted to date, this study confirmed location and size to be prognostic factors for passage in the univariate analysis. Passage rates slightly lower than reported in other studies[2,8,9] were consistently found in all tested categories. This was due to study design, which required retrospective classification of patients, including in the spontaneous passage group only those patients with documented passage. The prospective cohort design used in the above studies allows for closer follow-up and more accurate patient classification. However, this fact did not appear to represent a bias, as shown by maintenance of the

**Table 4 – Backward stepwise method to assess the final model predicting stone passage**

| | | Backward stepwise method | | |
|---|---|---|---|---|
| Variable | | Change in LR | df | Sig. of change |
| Step 1 | Location | 4.555 | 2 | 0.103 |
| | Composition | 1.611 | 3 | 0.657 |
| | Medication | 29.728 | 3 | 0.000 |
| | Size | 12.924 | 3 | 0.005 |
| Step 2 | Location | 4.780 | 2 | 0.092 |
| | Medication | 29.803 | 3 | 0.000 |
| | Size | 12.325 | 3 | 0.006 |

LR: likelihood ratio.

relative results obtained when categories were compared to each other.

There are several models for predicting stone passage. Stone location and size are the most common predictors, but there are others such as symptoms of hydronephrosis.[13,14] No relationship has been reported to date between stone passage and composition. Our results agree with those reported in literature; stone location and size were maintained in the final predictive model, while composition was ruled out.

NSAIDs are indicated for treatment of renal colic. They inhibit prostaglandin synthesis, relax smooth muscle, and decrease vasodilation and, secondarily, urine output.[15] In contrast to previously discussed studies,[11,12] a greater stone passage rate was shown in this study in patients treated with NSAIDs. The longer follow-up in our study may be a difference accounting for this finding. The Phillips et al[11] study suggested a potential inadequate follow-up (30 days) based on studies showing that stone passage through the ureter may take up to 40 days.[3] On the other hand, the fact that the different NSAIDs and their doses were not recorded in detail reduces the validity of our study.

No studies assessing the combination of alpha-blockers and NSAIDs for stone passage during the renoureteral crisis have been found. The relaxing effect of smooth muscle shown by alpha-blockers,[2,10] enhanced by the anti-inflammatory effect of NSAIDs on the ureteral wall, may explain the superiority of the combination of drugs as compared to monotherapy with alpha-blockers (37.9%; 95% CI: 12.9–2,9) and NSAIDs (22.5%; 95% CI: 2.9–2.1).

## Conclusions

The combination of alpha-blockers and NSAIDs was shown to be the most effective therapeutic approach, leading to an 8.2-fold increase in the chance of passage as compared to watchful waiting.

## Conflict of interest

The authors declare no conflict of interest.

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