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ORIGINAL PAPER

Efficacy of expulsive therapy using nifedipine or tamsulosin, both associated with ketoprofene, after shock wave lithotripsy of ureteral stones

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Abstract Extracorporeal shock wave lithotripsy (ESWL) is currently considered one of the main treatments for ureteral stones. Some studies have reported the effectiveness of pharmacologic therapies (calcium antagonists or alpha-blockers) in facilitating ureteral stone expulsion after ESWL. We prospectively evaluated the efficacy, after ESWL, of nifedipine on upper-middle ureteral stones, and tamsulosin on lower ureteral stones, both associated to ketoprofene as anti-edema agent. From January 2003 to March 2005 we prospectively evaluated 113 patients affected by radiopaque or radiolucent ureteral stones. Average stone size was 10.16 ± 2.00 mm (range 6–14 mm). Thirty-seven stones were located in the upper ureter, 27 in the middle ureter, and 49 in the lower ureter. All patients received a single session of ESWL (mean number of shock waves: 3,500) by means of a Dornier Lithotripter S (mean energy power for each treatment: 84%). Both ultrasound and X-ray were used for stone scanning. After treatment, 63 of 113 patients were submitted to medical therapy to aid stone expulsion: nifedipine 30 mg/day for 14 days administered to 35 patients with upper-middle ureteral stones (group A1) and tamsulosin 0.4 mg/day for 14 days administered to 28 patients with stones located in the distal ureter (group A2). The remaining 50 patients were used as a control group (29 upper–middle ureteral stones—B1—and 21 lower ureteral stones—B2—), receiving only pain-relieving therapy. No significant difference in stone size between the groups defined was observed. Stone clearance was assessed 1 and 2 months after ESWL by means of KUB, ultrasound scan and/or excretory urography. A stone-free condition was defined as complete stone clearance or the presence of residual fragments smaller than 3 mm in diameter. The stone-free rates in the expulsive medical therapy group were 85.7 and 82.1% for the nifedipine (A1) and tamsulosin (A2) groups respectively; stone-free rates in the control groups were 51.7 and 57.1% (B1 and B2, respectively). Five patients (14.3%) in group A1, 5 (17.8%) in group A2, 14 (48.3%) in group B1 and 9 (42.8%) in group B2 were not stone-free after a single ESWL session and required ESWL re-treatment or an endoscopic treatment. Medical therapy following ESWL to facilitate ureteral stone expulsion results in increased 1- and 2-month stone-free rates and in a lower percentage of those needing re-treatment. The efficacy of nifedipine for the upper-mid ureteral tract associated with ketoprofene makes expulsive medical therapy suitable for improving overall outcomes of ESWL treatment for ureteral stones.

Keywords Urolithiasis · ESWL · Expulsive therapy

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Introduction

Urolithiasis has an incidence in the world of about 5% and the probability of a recurrence within 5–7 years is 50% [1]. The treatment of this pathology was revolutionized with the introduction, in the late 1980s, of extracorporeal shock wave lithotripsy (ESWL), a non-invasive technology that has become one of the primary treatments for urinary stones. Its success rates vary depending on stone size and location and by the type of lithotripter employed.

Today, ESWL has many advantages: a low morbidity rate, high patient compliance, ability to treat on an outpatient

basis, and no requirement for anaesthesia—except in children, in whom it still remains a first-line treatment [2].

However, ESWL can have some limits: it seems that in the last decade the effectiveness of newer lithotripters has reduced, with perhaps a higher percentage of side effects [3]; in addition, ESWL can be quite expensive and it often requires multiple treatments [4, 5]. Meanwhile, the minimally invasive procedure of ureteroscopy (URS), thanks to improvements in its technology, can represent a concrete alternative to ESWL, especially for distal ureteral stones [6].

In the debate between URS and ESWL, medical therapy can play a key role in support of ESWL: specifically, expulsive therapy for urinary stone disease using calcium antagonists, anti-edema agents, and alpha-blockers. A few studies have reported their effectiveness [7–10].

Our purpose is to evaluate the efficacy of nifedipine for the upper-mid ureteral tract, and of tamsulosin for the lower ureteral tract, both associated with an NSAID (ketoprofene), after an ESWL treatment.

Materials and methods

Between January 2003 and March 2005 a total of 113 patients with radiopaque or radiolucent ureteral lithiasis were selected for an ESWL treatment; before the procedure we evaluated patients with urinalysis, urine culture, coagulation profile, serum creatinine level, plain radiography of the urinary tract, ultrasonography, and/or excretory urography when a more accurate study of urinary tract was necessary. In our study, exclusion criteria were signs and symptoms of urinary tract infection, pregnancy, multiple stones, severe hydronephrosis, hypotension, gastric ulcer disease, obesity, a medical history of spontaneous stone expulsion, and previous ureteral surgery.

All patients underwent a single session of ESWL using Dornier Lithotripter S, an electromagnetic, third-generation unit that permits us to use ultrasound or X-ray for stone focusing. After ESWL treatment, the patients were divided into four groups: groups A1 and A2 received adjunctive medical expulsive therapy while group B1 and B2 served as controls. All the groups were allowed to use pain therapy with diclofenac (75 mg i.m.) on demand and were asked to drink 1.5–2 L per day of water.

The adjuvant medical therapy of group A1 and A2 were represented by nifedipine (30 mg per day orally for 14 days) and tamsulosin (0.4 mg/day orally for 14 days), respectively. Patients with upper-mid ureteral stones (group A1) received nifedipine, while patients with lower ureteral stones (group A2) received tamsulosin; in both cases, ketoprofene (50 mg twice a day orally for 7 days) was taken as an anti-edema agent. The patients were asked to report any side effects that occurred during the therapy. Stone clearance was assessed at 30 and 60 days after ESWL by means of KUB X-ray, ultrasound scan and/or excretory urography when it was required. A stone-free condition was defined as the complete absence of any stone or the presence of residual fragments smaller than 3 mm in diameter.

Sampled data were inserted in an apposite database and analysed with the help of the SPSS statistical package version 8.0. A complete descriptive analysis of all available variables was performed. Statistical analysis was carried out by means of Student's t test, Mann–Whitney U-test, Pearson test, and two-tailed Fischer's exact test. A significance level of 0.05 was chosen for all tests.

Results

All the patients completed the study. Group A1 consisted of 23 men and 12 women (average age 47 years, range 26–74), and group A2 consisted of 16 men and 12 women (average age 45 years, range 27–71). Group B1 consisted of 17 men and 12 women (average age 48 years, range 24–69), while group B2 consisted of 11 men and 10 women (average age 46 years, range 25–72).

The average stone size was 10.4 ± 2.27 mm (range 7–14) for group A1 and 10.00 ± 2.59 mm (range 6–13) for group A2 while 10.25 ± 1.35 (range 8–13) for group B1 and 9.9 ± 1.37 (range 7–12) for group B2; no statistically significant difference between the four groups was observed.

The expulsive medical therapy was performed in 63 patients: nifedipine (group A1) was administered to 35 patients (18 for upper ureteral and 17 for mid ureteral lithiasis), while tamsulosin was used in 28 patients for lower ureteral lithiasis (group A2). In group B1 and B2 (control cases), 29 patients with upper-mid ureteral stones and 21 patients with lower ureteral stones, respectively, did not receive adjuvant medical expulsive therapy (Table 1). The characteristics of SWL treatment were reported in Table 2. No side effects occurred that required withdrawal from treatment, either related to shock wave lithotripsy or to the expulsive therapy.

Table 1 Stone location

	Expulsive medical therapy		Control group	
	Group A1 (nifedipine)	Group A2 (tamsulosin)	Group B1	Group B2
Upper ureter	18		19	
Mid ureter	17		10	
Low ureter		28		21
Overall	35	28	29	21

Table 2 Characteristics of SWL treatment in all the groups

	Group A1	Group A2	Group B1	Group B2
SW number	3,100 ± 230	3,390 ± 90	3,150 ± 280	3,350 ± 120
Intendity (%)	70.9 ± 8.4	85.4 ± 13.4	72.3 ± 6.9	82.9 ± 14.5

An objective degree of fragmentation during or immediately after the treatment (US or X-rays detected) was evident in 40 out of the 63 patients receiving an adjunctive medical therapy (63.4%) and in 31 out of the 50 patients used as a control group (62%), without statistically significant differences among these two groups.

Complete stone expulsion occurred in 30 of 35 (85.7%; $P = 0.005$) patients in group A1 and in 23 of 28 (82.1%; $P = 0.05$) patients in group A2 by the study endpoint; in control groups we reported stone expulsion rates of 51.7% (15/29 patients—group B1) and 57.1% (12/21 patients). Tables 3 and 4 report the stone-free rate at the two stages of follow-up (30 and 60 days after ESWL treatment) and for different locations of stones. About 5 patients (14.3%) in group A1, 5 (17.8%) in group A2, 14 (48.3%) in group B1 and 9 (42.8%) in group B2 were not stone-free after a single ESWL session: five of 35 in group A1 (14.3%), three of 28 in group A2 (10.7%), ten of 29 in group B1 (34.5%) and seven of 21 in group B2 (33.3%) underwent ESWL re-treatment, while one of 35 (2.8%) in group A1, one of 28 in group A2 (3.6%), two of 29 (6.9%) in group B1 and four of 21 in group B2 (19.0%) required URS.

Discussion

ESWL is still considered front-line therapy for the treatment of ureteral stones, but it seems that in the last decade URS has progressively established itself as a valid alternative to ESWL [11]. Since the introduction, about 20 years ago, of ESWL with the Dornier HM3, lithotripters of second and third generations have been developed, improving ESWL technology and giving some advantages such as the elimination of the size and the incovenience of waterbaths as coupling devices and the advent of anaesthesia-free lithotripsy, which can be performed on an outpatient basis. However, the lithotripter's evolution has been limited because of an inadequate understanding of how and why shock waves produce effects on stone and tissue. This issue may explain why newer lithotripters are not so effective and may convey a higher risk of side effects [3].

On the other hand, URS is a promising technique that is growing with the advent of small, 7.5-French, semirigid ureteroscopes, flexible ureteroscopes, and Ho:YAG laser lithotripsy. An increasing number of endourologists choose URS as the preferred treatment for ureteric stones because it seems more cost-effective and often allows patients to achieve stone-free status earlier than with ESWL [4, 6].

In fact, ESWL can require multiple treatments, depending especially on stone size. Pace et al. [5] suggested that the stone-free percentage when re-treating ureteral stones with ESWL decreases significantly after the initial treatment. Thus in the management of ureteral stones, URS may be better than ESWL when initial shockwave lithotripsy fails.

The efficacy of ESWL could be increased with an associated medical therapy. Various drugs have an importance in urolithiasis treatment. We already know the effectiveness of dissolution agents like potassium citrate, which are used in order to correct the imbalance between the promoters and inhibitors of lithogenesis [12, 13]. Recently, an interesting role in litho-litic therapy has been demonstrated with an extract of *Phyllantus niruri* labelled with specific tannins [14]. A medical therapy can also facilitate stone expulsion with spasmolytic and anti-edema agents, as some studies have demonstrated [7–10].

Focusing our attention on spasmolytic agents, nifedipine has an influence on the contractile activity of the ureter: it seems to inhibit the stone-induced ureteral spasm and to maintain peristaltic rhythm. Some authors have proven its

Table 3 Stone-free rates at the two stages of follow-up

	Group A1	Group A2	Group B1	Group B2
1 month	51.4% (18/35)	50.0% (14/28)	24.1% (7/29)	28.6% (6/21)
2 months	85.7% (30/35)	82.1% (23/28)	51.7% (15/29)	57.1% (12/21)

Table 4 Stone-free rates for different locations of stones

	Group A1	Group A2	Group B1	Group B2	*P* value	*P* value
Upper ureter	77.7% (14/18)	–	47.3% (9/19)	–	0.05	0.005
Mid ureter	94.1% (16/17)	–	60.0% (6/10)	–	0.02	
Low ureter	–	82.1% (23/28)	–	57.1% (12/21)	0.05	
Overall	85.7% (30/35)	82.1% (23/28)	51.7% (15/29)	57.1% (12/21)		

safety and efficacy as a spasmolytic agent in ureteral stone treatment [7, 9]. Positive results have also been reported for tamsulosin, an alpha-1D blocker, which acts on the peristalsis of the juxtavesical ureteral tract [8, 10].

In our study we used nifedipine for the upper-mid ureteral tract and tamsulosin for the lower one. In addition, we associated an NSAID (ketoprofene) to nifedipine or tamsulosin in order to reduce edema induced by a stone's mechanical irritation. In the upper-mid ureteral tract, patients who received nifedipine + ketoprofene were stone-free in 85.7% of cases, while patients who did not receive medical therapy were stone-free in 51.7% of cases, with a significant evidence of efficacy of this expulsive therapy ($P = 0.003$). In the lower tract, the patients treated with tamsulosin + ketoprofene were stone-free in 82.1% of cases, versus 57.1% in the control group, resulting in non-significant data ($P = 0.055$). The combination of nifedipine with ketoprofene seems to be effective in the medical treatment of urolithiasis. However, further studies are needed to determine the efficacy of tamsulosin associated with ketoprofene and to evaluate which anti-edemic agent is best for this expulsive medical therapy, e.g., NSAIDs compared to corticosteroids.

By adding nifedipine and deflazacort after ESWL of ureteral stones, Porpiglia et al. [9] obtained a significant improvement in stone-free rates in comparison to a control group (75 vs. 44% in the upper-mid ureter, 75 vs. 50% overall). With similar stone sizes, using nifedipine associated with ketoprofene, we have registered better percentages (85.7 vs. 51.7% in the upper-mid ureter), confirming the effectiveness of this spasmolytic agent for the upper-mid ureteral stones.

Concerning lower ureteral stones, Kupeli et al. [15] showed positive results using tamsulosin after ESWL in 24 patients: a 70.8% stone-free rate. By associating tamsulosin with ketoprofene as expulsive therapy for lower ureteral stones, we have obtained a better stone-free rate (82.1%) compared to the control group (57.1%), not achieving yet a significant result ($P = 0.055$). Consequently, further studies are required to demonstrate an effectivity of this pharmacological association in urolithiasis medical treatment.

According to the literature, ESWL remains the treatment of choice for stones of 1 cm or smaller in the upper ureter, while URS has achieved excellent results as first-line therapy for upper ureteral calculi greater than 1 cm [16, 17]. In a recent study, Lam et al. [18] compared ESWL with Ho:YAG laser lithotripsy for upper-mid ureteric stones and obtained stone-free rates of 50 and 80% (stone sizes of <1.0 and >1.0 cm, respectively) for ESWL versus stone-free rates of 93 and 100% (stone sizes of <1.0 and >1.0 cm, respectively) for URS. In a review article, Anagnostou et al. [19] showed that ESWL success rates for lower ureteric calculi vary from 58 to 67%, requiring multiple treatments. URS has significantly better stone-free rates than ESWL for distal ureteral stones [6, 20, 21].

Using a medical expulsive therapy after ESWL, we have obtained encouraging stone-free rates (85.7% for upper ureteral stones and 82.1% for lower ureteral stones) that reduce the gap in success rates between ESWL and URS. It should be noted that in comparison to ESWL, URS is a more invasive procedure with a larger number of post-operative complications, a major frequency of auxiliary procedures, and, in most cases, the need for anaesthesia [22]. Furthermore, we must not forget that equipment, expertise, and experience are all required to achieve superior outcomes with this endoscopic treatment [19].

Conclusions

Expulsive medical therapy results in increased stone-free rates and in lower percentages of patients requiring re-treatment. Expulsive medical therapy can be self-administered and can play a key role in the choice between URS and ESWL for stone disease treatment. The efficacy of nifedipine for the upper-mid ureteral tract associated with ketoprofene makes expulsive medical therapy suitable for improving overall outcomes of ESWL treatment for ureteral stones.

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