

Medical Expulsive Therapy for Lower Ureteric Stones :A Comparative Study

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Abstract:

Background: lower ureteric stones and accompanying ureteric colics represent one of the most common medical problems faced by urologist, the treatment usually starts with conservative therapy, however, if the stone fails to pass within 4-6 weeks, a prompts action should be taken to save the kidney, this usually involves one of the minimally invasive therapy options like shock wave lithotripsy (ESWL), or ureteroscopy .However this is not free of risk, and cost, for these reasons, urologists now concentrate on what's called medical expulsive therapy, which means using drugs to enhance stone passage.

Objective : in this study we evaluated and compared three of the most commonly used drugs, nifedipine, tamsulosin, and sildenafil citrate, for their expulsive role in lower ureteric stones.

Methods: through out the period from Feb .2008 until Nov .2009, 98 patients with lower ureteric stones were enrolled in this study, they were thoroughly examined and investigated, then randomized into 4 groups, the first group patients received nifedipine, the second group patients received tamsulosin, the third group patients received sildenafil citrate, and the fourth group patients served as control .Patients followed up for one month and monitored for stone passage, time of stone passage and number of ureteric colics experienced while on treatment .Data collected and analyzed statistically.

Results: only patients on tamsulosin therapy showed a statistically significant improvement in stone passage rate (81.4%, compared to those on nifedipine)69.6%, sildenafil citrate (57.6%, and control (54.5 .%)Both nifedipine and tamsulosin significantly shortened the time needed for stone passage and reduced the number of ureteric colics, while sildenafil citrate failed to show any beneficial effect compared to control.

Conclusions: tamsulosin may have a significant role in enhancing lower ureteric stone passage within shorter time and with less pain, and it is superior to nifedipine, and sildenafil citrate in this regard.

Key words: nifedipine, tamsulosin, sildenafil citrate, expulsive therapy, ureteric stones.

Introduction:

Ureteric colics represent one of the common medical problems encountered by urologists in the emergency rooms, they are usually caused by ureteral stones, management of such condition is usually conservative at first, if the stone fail to pass a more prompt action is needed, which is usually by one of the minimally invasive procedures like extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, or percutaneous nephrolithotomy , depending on the stone size, location and the presence and degree of associated obstruction ^(1,2). However, these minimally invasive procedures are not risk free and expensive for patients, and require some experience for the managing doctor, for these reasons urologists are aiming at a new approach that lies in between the observational conservative therapy and the interventional therapy, what's called now "medical expulsion therapy of ureteral stones", which is the use of drugs to induce ureteric relaxation and enhance stone passage.

Spontaneous stone passage depends on many factors, including stone size, site, degree of impaction, and associated obstruction. American Urological Association (AUA) guidelines state that ureteral stones of less than 5 mm will pass in up to 98 %of patients, for those larger than 7 mm,

the passage rate is 25 %for proximal, 45 %for middle, and 75 %for distal ureteric stones^(1,3). Time to pass also depends on the stone size, stones up to 2mm taking 8 days to pass, stones 4-6 mm taking 22 days to pass⁽⁴⁾, however, most authors recommend that stone passage time should not exceed 4-6 weeks to avoid the risk of renal damage^(2,4).

Many pharmacological groups have been proposed for stone passage enhancement, some are clinically tried, and others are still experimental, the list includes the use of hormones, calcium channel blockers, corticosteroids, α blockers, cyclooxygenase inhibitors, phosphodiesterase (PDE) inhibitors, neurokinin receptor antagonists, potassium channel openers, and nitrous oxide donors^(5,6). However, most of the clinical trials concentrated on either calcium channel blockers, or α blockers, either alone or in combination with corticosteroids, only recently PDE inhibitors have been suggested for these clinical trials^(2,6).

Ureteral stones induce spasm of the ureteric smooth muscle which in turn arrests stone passage; this smooth muscle contraction is mediated by calcium, a decrease in calcium concentration causes relaxation that will decrease pain and facilitates stone passage, this rationalized the use of nifedipine) a Ca^{+2} channel blocker to promote stone passage⁽⁷⁾.

Although both α and β adrenergic receptors are present in the human ureter, studies showed a predominance of α receptors⁽⁸⁾, which are classified into $\alpha 1$ and $\alpha 2$, in turn, $\alpha 1$ receptors are further subclassified into $\alpha 1A$ (proximal urethra, prostate, bladder outlet), $\alpha 1B$ (vessels, smooth muscles), and $\alpha 1D$ (detrusor, lower ureter)⁽⁹⁾. Tamsulosin is uroselective for $\alpha 1A$ and $\alpha 1D$, causing improvement in the bladder outflow obstruction symptoms as well as relaxation of lower ureter smooth muscle facilitating stone passage, and pain relief⁽¹⁰⁾.

PDE enzymes are responsible for the breakdown of cAMP, thus their inhibition increases cAMP level causing smooth muscle relaxation. PDE I,II,IV, and V were identified in the human ureter with predominance of types IV, and V, and their inhibition caused ureteric relaxation in vitro⁽¹¹⁾. Kuhn et al demonstrated that rolipram (PDE IV inhibitor) and E 4021 (PDE V inhibitor) relaxed human ureteral strips and concluded that use of selective PDE inhibitors might be useful in the management of ureteral stones and ureteral colic⁽¹²⁾.

The current study was done to assess and compare the expulsive efficacy of 3 of the most commonly used drugs, Ca^{+2} channel blockers (nifedipine), α blockers (tamsulosin), and PDE inhibitors (sildenafil citrate).

Patients and Methods:

During the period between February 2008 till November 2009, 98 patients with lower ureteric stone were enrolled in the study, they were recruited from urology clinic in surgical specialties hospital, emergency unit and private clinic. All patients underwent full clinical examination, laboratory investigations (including urine analysis, and renal function testing), and imaging with abdominal ultrasound, and kidney, ureter, and bladder abdominal x-ray films (KUB).

Inclusion criteria were: adults (>18 years) with single unilateral lower ureteric stone of less than 10 mm in its largest diameter with no hydronephrosis at the stone side. All patients were having their first attack of stone disease. Patients with recurrent stones, bilateral disease, urinary tract infection, hydroureteronephrosis, previous surgical or endoscopic intervention on the same side, diabetics, hypertensives, peptic ulcer patients, pregnant women, and those with suspected allergy to any of the medications used, all are excluded from the study. A signed consent was taken from all patients.

Enrolled patients were randomized into 4 groups, in all the 4 groups patients received the following drugs :diclofenac sodium suppositories 100 mg daily, tramadol ampoules 100 mg on need, ciprofloxacin tablets 500 mg twice daily, uricole powder sachets three times daily.

Group (1): in addition to the fixed medication above, patients were given slow release nifedipine tablets 30 mg once daily.

Group (2): in addition to the fixed medications, they were given tamsulosin tablets 0.4 mg once daily.

Group(3): in addition to the fixed medications, they were given sildenafil citrate tablets 50 mg once daily.

Group (4): they only received the above mentioned fixed medications and served as control.

Patients were instructed to drink lot of oral fluids, and observe for stone passage during urination, and were followed on weekly basis for one month by urine analysis, renal function testing, abdominal US, and KUB when needed .The rate and time of stone passage, as well as the number of painful colicky attacks were recorded on the follow up sheets.

Patients who pass the stone were considered as responders, and those who failed to do so within one month were considered as non-responders and were referred for other management options, while those who failed to keep contact were omitted from the study.

Data were collected and statistically analyzed using SPSS software version 13 .P value <0.05 was regarded statistically significant.

Results:

Table 1 show the demographic features of patients in all groups regarding age, sex and stone side and size, there were no significant differences between groups for any of these variables.

Table 2 shows the response to different treatment options measured by rates of stone expulsion, time of stone expulsion, and number of ureteric colic experienced by the patients while on treatment, and table 3 shows the significance of these responses compared to control.

a) Rate of stone expulsion :only group 2 showed a significantly higher rate of stone expulsion compared to the control, (81.4%) versus (54.5%), [P<0.05], while groups 1 and 3 showed no significant difference in stone expulsion rate,(69.6%) and (57.6%) respectively.

b) Time on stone expulsion :groups 1 and 2 showed significantly shorter time of expulsion compared with the control (P<0.01), while the time taken by those on sildenafil treatment (group 3) was not significantly different from the control.

c) Number of ureteric colics : patients in groups 1 and 2 had significantly fewer attacks of ureteric colics compared to the control group, while those in group 3 showed no significant difference from the control.

d) No patient suffered from any significant side effect.

Discussion:

Management of small lower ureteric stones is a matter of controversy, although some prefer to observe with symptomatic treatment, others prefer early intervention to avoid risk of renal damage, while others choose to stand in between, using drugs to ease stone passage .Ueno et al . evaluated more than 500 patients with lower ureteric stones and reported a spontaneous passage rate of 57%⁽¹⁸⁾, furthermore, Kinder et al .reported a 94 %spontaneous expulsion rate for stones ≤5mm, and a 45 %rate for larger stones ⁽¹⁹⁾.

Over the last 2-3 decades, several trials have been made to assess the beneficial effect of various drugs in easing the passage of ureteric stone. Ca ++channel blockers specifically nifedipine were of the first drugs tested for their expulsive efficacy .Borghi et al .carried out a randomized, double blinded study, and found that nifedipine significantly improved the stone passage rate, shortened the time needed, and decreased the requirement for analgesia ⁽⁷⁾. A similar result was obtained by Porpiglia et al⁽¹³⁾, and Cooper et al⁽¹⁴⁾, while Sanita et al failed to find a statistically significant improvement in the stone passage rate in patients treated with nifedipine compared to the control group⁽¹⁵⁾ .In all the studies mentioned above, one of the corticosteroids was used with nifedipine, Borghi et al .used methylprednisolone, Porpiglia et al used deflazacort, while Cooper et al used prednisolone tablets; this may partly explain the high success rate reported in these studies. In our study, the stone passage rate was found to be higher in the nifedipine group

(69.6%) compared to the control group (54.5%), but this higher rate was not found to be statistically significant ($P>0.05$), a similar result was reported by Salem, who compared the effect of nifedipine and tamsulosin to placebo in the management of lower ureteric stones and found that patients who took nifedipine had not got any significant benefit over patients in the control group in terms of stone passage rate⁽¹⁰⁾. However, we found that nifedipine caused the stones to pass in a significantly shorter time with less pain attacks, which in turn means less requirement for analgesics, a similar result was reported by Borghi, Popiglia, and Cooper^(7,13,14).

Table 1 :the demographic distribution of patients in the four groups

<i>parameter</i>		<i>Group1</i> <i>nifedipine</i>	<i>Goup2</i> <i>tamsulosin</i>	<i>Group3</i> <i>sildenafil</i>	<i>Group4</i> <i>control</i>
SEX	<i>Male</i>	14	15	15	13
	<i>Female</i>	9	12	11	9
	<i>Total</i>	23	27	26	22
STONE SIDE	<i>Right</i>	13	14	16	11
	<i>Left</i>	10	13	10	11
	<i>Total</i>	23	27	26	22
AGE (year- old)	<i>Min.</i>	20	21	19	20
	<i>Max.</i>	55	55	54	51
	<i>Mean</i>	39.4	38.4	39.3	40.5
	<i>SE</i>	1.83	1.84	1.8	1.34
STONE SIZE (mm)	<i>Min.</i>	3.5	3.5	3.8	3.5
	<i>Max.</i>	9.6	9.6	9.8	10
	<i>Mean</i>	6.5	6.3	6.4	6.4
	<i>SE</i>	0.42	0.32	0.31	0.39

SE :standard error of mean

Table 2 :Results in the 4 groups measured as rate of stone passage, time of stone passage, and number of painful colics experienced by the patients.

<i>Parameter</i>		<i>Group1</i>	<i>Group2</i>	<i>Group3</i>	<i>Group4</i>
Stone passage	Passed	16)69.6(%)	22)81.4(%)	15)57.6(%)	12)54.5(%)
	Failed to pass	7)30.4(%)	5)18.5(%)	11)42.3(%)	10)45.4(%)
Time to pass the stone (days)	<i>Min.</i>	6	3	6	6
	<i>Max.</i>	20	16	23	22
	<i>Mean</i>	11.9	8.0	15.0	17.5
	<i>SE</i>	1.09	0.94	1.16	1.21
No .of painful attacks	<i>Min.</i>	3	2	5	6
	<i>Max.</i>	11	6	14	21
	<i>Mean</i>	5.65	3.4	8.7	10.6
	<i>SE</i>	0.41	0.17	0.46	0.8

Table 3: Comparison of response in each group to control in terms of expulsion time, and no .of ureteric colics.

	<i>df</i>	<i>Si. (2 tailed) for expulsion time P value</i>	<i>Sig.(2 tailed) for no .of colics P value</i>
tamsulosin - control	21	.002	.000
Nifedipine-control	21	.002	.000
Sildenafil-control	21	.537	.122

df :degree of freedom

Tamsulosin, a selective α 1D adrenoreceptor blocker, has been thoroughly investigated for its expulsive role in ureteric stone management, like many other selective and non-selective α blockers .In our study, we found tamsulosin to be the best of the three drugs studied, it significantly improved the stone expulsion rate, shortened the time needed, and decreased the analgesia required, when compared to control group .Cervenakov et al were the first to evaluate the efficacy of tamsulosin in the expulsion of distal ureteric stones, stone passage rate was higher in treatment group than control group⁽⁹⁾. Dellabella et al conducted a randomized trial to study the role of tamsulosin in treating juxtavesical ureteric stones sized 4-13 mm, and found a significant role of tamsulosin in improving expulsion rate, shortening the time and decreasing analgesic requirement ⁽⁸⁾. A longer trial to evaluate the impact of tamsulosin on stone expulsion was conducted by Sio and Autorino et al, patients were stratified prior randomization according to age, sex, and stone size, they found a significantly higher stone passage rate, within shorter time and with less hospitalization requirement in the group receiving tamsulosin compared to control ⁽¹⁶⁾. On the other hand, Resim et al .conducted a 42 days follow up study to evaluate the expulsive effect of tamsulosin versus symptomatic treatment and failed to identify a significant difference in distal ureteric stone passage in tamsulosin treated group compared to control group ⁽¹⁷⁾.

After the efficacy of both nifedipine and tamsulosin has been reported by many authors, Porpiglia et al .(2004), and Dellabella et al (2005) compared the efficacy of tamsulosin, nifedipine and control .While Porpiglia et al .found a similarly significant role for both drugs in expelling stones compared to control, Dellabella reported a significant role only for tamsulosin, with the nifedipine group expulsion rate was not different from the control.^(20,21)

We found that sildenafil citrate, a PDE V inhibitor, had no statistically significant role neither in enhancing stone passage, nor in shortening passage time, nor in decreasing ureteric colics when compared to control group. Romics and colleagues, in a randomized double blinded controlled trial, showed that drotaverine, a selective PDE IV inhibitor significantly reduced acute renal colics when compared to placebo ⁽²²⁾. Rolipram is the most commonly investigated PDE IV inhibitor, it was found to be the most potent PDE inhibitor to cause in vitro ureteric smooth muscle relaxation, however, it has notoriously high systemic side effects that limits its clinical use ^(23,24). In addition, it appears that PDE V isoform inhibition does cause ureteral relaxation, but to a lesser extent ⁽²⁵⁾. Steif and colleagues demonstrated a predominance of PDE IV over other isoforms in human ureter ⁽¹¹⁾. No clinical study that evaluated PDE inhibitors as agents to facilitate stone passage has been found in the literature to compare with⁽²⁶⁾.

Conclusions:

The results of this study revealed that tamsulosin) α 1D blocker (is superior to nifedipine)ca ++ channel blocker(, and sildenafil citrate)PDE V inhibitor (in enhancing lower ureteric stone

expulsion, shortening time of expulsion, and decreasing attacks of ureteric colics and analgesic requirement, this may be partly due to the high density of α receptors in the lower ureter . Nifedipine enhanced the stone passage but not to a significant level, yet shortened the time of passage and decreased pain attacks significantly, on the other hand, sildenafil citrate failed to show any favorable effect when used for lower ureteric stones.

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