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Efficacy of the combination of tadalafil and tamsulosin versus tadalafil alone as a medical expulsive therapy for stone L1/3 ureter 10 mm or less: A prospective comparative placebo-controlled study

Ahmed Reda*, Mostafa Kamel, Mohamed Loay, Yaser M. Abdelsalam, Mohamed A. Zarzour

Department of Urology, Assiut University Hospital, Assiut, Egypt

Abstract

Background: The lifetime occurrence of urinary stones is approximately 1%–15%, and the peak age of occurrence is 30 years. Approximately one fifths of urinary tract stones are found in the ureter, of which two thirds are in the distal ureter. Many drugs, including phosphodiesterase-5 inhibitors and α-blockers, are used to relax the smooth muscles in medical expulsive therapy. We aimed to compare the combination of tadalafil and tamsulosin versus tadalafil alone as medical expulsive therapy for stones in the L1/3 ureter of 10 mm or less.

Materials and methods: A total of 150 patients with L1/3 ureteric stones measuring 10 mm or less were enrolled in the study and randomly assigned to one of 3 equal groups using a computer-generated random number. Patients in group A prescribed tadalafil 10 mg/d. However, those in group B were prescribed tamsulosin 0.4 mg and tadalafil 10 mg/d, whereas those in group C received a placebo once daily. Stone expulsion rate and pain recurrence were evaluated after 14 days.

Results: The stone expulsion rate was significantly higher in the tadalafil and tamsulosin groups and the tamsulosin group than in the placebo group in the current study by 68% in the combination group, 64% in the tadalafil alone group, and 42% in the placebo group ($p = 0.019$). In the current study, a combination was associated with lower pain recurrence than tadalafil alone or placebo, with means of (1.9, 1, and 2.98, with a p value of 0.001). Stone size was not effective in any group.

Conclusions: The combination of phosphodiesterase-5 inhibitors and α-blockers effectively increases the expulsion of lower ureteric stones (5–10 mm), but with the same effect as phosphodiesterase-5 inhibitors alone, with the advantage of decreasing pain recurrence. Stone size did not affect the expulsion rate in patients who received medical expulsive therapy for stones less than 1 cm in size.

Keywords: Tadalafil; Tamsulosin; Ureteric stone

1. Introduction

Urolithiasis is one of the most common urinary tract diseases. The lifetime prevalence of urolithiasis is 1%–15%, with the highest incidence at age 30 years. Men are sick 2–3 times more frequently than women.[1] A significant proportion (approximately 1/5 of urolithiasis) is in the ureter, and two thirds are in the distal ureter.[2] The transport of stones from the kidneys through the ureters is accompanied by smooth muscle spasms, submucosal edema, and pain.[3]

The removal of stones from the ureter depends not only on their size and shape but also on the strength of contraction and stimulation of adrenergic receptors present in the smooth muscles of the ureter and detrusor. The distal portion of the ureter is usually the largest obstacle when carrying stones.[4]

Ureteral smooth muscle is treated with various drugs with different mechanisms. Blocking the α_1-adrenergic receptor, especially in the distal third, reduces basal smooth muscle contraction, and propulsive forward peristalsis is induced, which aids in stone expulsion.[5–7]

Another drug, tadalafil, is used as medical expulsion therapy because of its action on the smooth muscle circulating guanosine monophosphate nitric oxide signaling pathway to increase circulating guanosine monophosphate levels, thereby relaxing the smooth muscle of the ureter.[5,8,9]

Therefore, the combination of both drugs may affect the expulsion rate and duration of expulsion. We have clarified this point in the present study.

2. Materials and methods

The study was conducted in the Department of Urology at Assiut University over 7 months. All patients with lower ureteric stones ranging from 5 to 10 mm in size, diagnosed by computed tomography (CT) scan, were included in the study. The sample size was calculated at 80% power, and a significance level of 90% was used for the test. With a 10% dropout rate, the sample size was calculated as 150 patients (1:1:1).

*Corresponding Author: Ahmed Reda, Department of Urology, Assiut university Hospital, Assiut university street, AUN, Assiut, 71515, Egypt. E-mail address: ahmedreda_leo@yahoo.com (A. Reda).

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Table 1

Comparison between the 3 groups according to the anthropometric measures, comorbidities, previous surgeries, stone size, site, grade of obstruction, and grade of pain.

Characteristics		Tadalafil (n = 50)	Tamsulosin + tadalafil (n = 50)	Placebo (n = 50)	Test value	*p*	Significance
Sex	Female	19 (38%)	17 (34%)	16 (32%)	0.412*	0.814	NS
	Male	31 (62%)	33 (66%)	34 (68%)			
Age	Mean ± SD	42.86 ± 14.131	41.06 ± 14.548	45.24 ± 14.478	1.062†	0.348	NS
BMI	Mean ± SD	25.8 ± 3.67	26.29 ± 2.9	25.86 ± 3.63	0.300†	0.741	NS
DM	No	48 (96%)	47 (94.0%)	48 (96.0%)	0.300*	0.861	NS
	Yes	2 (4.0%)	3 (6.0%)	2 (4.0%)			
HTN	No	48 (96.0%)	47 (94.0%)	46 (92.0%)	0.709*	0.701	NS
	Yes	2 (4.0%)	3 (6.0%)	4 (8.0%)			
Cardiac	No	48 (96.0%)	46 (92.0%)	46 (92.0%)	0.857*	0.651	NS
	Yes	2 (4.0%)	4 (8.0%)	4 (8.0%)			
CKD	No	49 (98.0%)	48 (96.0%)	48 (96.0%)	0.414*	0.813	NS
	Yes	1 (2.0%)	2 (4.0%)	2 (4.0%)			
Previous URS	No	46 (92.0%)	46 (92.0%)	45 (90.0%)	0.168*	0.919	NS
	Yes	4 (8.0%)	4 (8.0%)	5 (10.0%)			
Previous ureterolithotomy	No	47 (94.0%)	46 (92.0%)	46 (92.0%)	0.196*	0.907	NS
	Yes	3 (6.0%)	4 (8.0%)	4 (8.0%)			
Stone side	Left	25 (50.0%)	24 (48.0%)	26 (52.0%)	0.160*	0.923	NS
	Right	25 (50.0%)	26 (52.0%)	24 (48.0%)			
Stone size	Mean ± SD	6.94 ± 1.867	6.92 ± 1.867	6.76 ± 1.768	0.146†	0.864	NS
Grade of obstruction	Mean ± SD	2.26 ± 0.443	2.22 ± 0.418	2.30 ± 0.463	0.410†	0.665	NS
Grade of pain at presentation	Mean ± SD	3.92 ± 1.736	3.66 ± 1.451	3.50 ± 1.403	0.951†	0.389	NS

$p > 0.05$: nonsignificant (NS); $p < 0.05$: significant (S); $p < 0.01$: highly significant (HS).
*χ^2 test.
†One-way analysis of variance.
BMI = body mass index; CKD = chronic kidney disease; DM = diabetes mellitus; HTN = hypertension; URS = ureteroscopy.

2.1. Inclusion criteria

Patients older than 18 years and those with a distal ureteric stone with a maximum dimension of 5–10 mm were eligible.

2.2. Exclusion criteria

Pregnant or lactating mothers were excluded as were patients with urinary tract infections. The patient had severe hydroureteronephrosis. The patient had multiple ureteric stones. The patient had solitary kidneys. The patient had acute or chronic renal failure. The patients had previous therapies for stones. The patient had ureteric strictures. The patients were concomitantly treated with calcium antagonists, β-blockers, corticosteroids, or nitrates.

Written informed consent was obtained from all the participants. The study methodology and protocol were approved by the institutional review board of the Assiut Faculty of Medicine. This trial was registered at ClinicalTrials.gov (NCT05150899). A detailed history and clinical examination, routine urine examination and/or urine culture, serum creatinine, digital x-ray kidney, ureter and bladder (KUB) and/or ultrasonography of the abdomen and pelvis, and/or CT-KUB were performed in all patients. Stone size was determined using the largest dimension in the CT scan.

The patients were randomized into 3 equal groups based on a computer-generated random number. Patients in group A prescribed 10 mg-tadalafil once daily, group B 0.4-mg tamsulosin, and 10-mg tadalafil once daily, whereas those in group C received a placebo once daily. All groups received 50-mg diclofenac on demand. The treatment was continued for 4 weeks.

All patients were evaluated by physical examination, serum creatinine levels, and the same imaging modality by which lower ureteric stones were previously diagnosed in those who either could not present a stone or presented a stone that did not match the original size and shape. In cases of doubt, CT-KUB was performed despite previous imaging modalities to confirm stone expulsion.

The primary outcome was the rate of expulsion and pain recurrence (in the form of analgesia or hospitalization). Side effects of the drugs were assessed.

3. Results

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS Corp, Armonk, NY) version 20.

Table 2

Comparison between the 3 groups based on the occurrence of pain during treatment and the rate of expulsions.

		Tadalafil (n = 50)	Tamsulosin + tadalafil (n = 50)	Placebo (n= 50)	Test value	*p*	Significance
No. pain recurrences during treatment	Mean ± SD	1.90 ± 0.995	1.06 ± 0.712	2.98 ± 1.286	44.129	<0.001*	HS
Expulsion	Yes	32 (64.0%)	34 (68.0%)	21 (42.0%)	7.882	0.018†	S
	No	18 (36.0%)	16 (32.0%)	29 (58.0%)			

TTT = $p > 0.05$: nonsignificant (NS); $p < 0.05$: significant (S); $p < 0.01$: highly significant (HS).
*One-way analysis of variance.
†χ^2 test.

Table 3

Comparison between the 3 groups based on the recurrence of pain during treatment using a post-hoc test.

Dependent variable: Recurrence number						
Tukey HSD						
					95% Confidence interval	
(I) treatment	**(J) treatment**	**Mean difference (I-J)**	**SE**	**Significance**	**Lower bound**	**Upper bound**
Tadalafil	Tadalafil + tamsulosin	0.840*	0.205	<0.001	0.35	1.33
	Placebo	–1.080*	0.205	<0.001	–1.57	–0.59
Tadalafil + tamsulosin	Tadalafil	–0.840*	0.205	<0.001	–1.33	–0.35
	Placebo	–1.920*	0.205	<0.001	–2.41	–1.43
Placebo	Tadalafil	1.080*	0.205	<0.001	0.59	1.57
	Tadalafil + tamsulosin	1.920*	0.205	<0.001	1.43	2.41

*The mean difference is significant at the 0.05 level.
HSD = honest significant difference.

Qualitative data were presented as numbers and percentages, whereas the quantitative data were presented as means, standard deviations, and ranges when their distribution was parametric. The χ^2 test was used to compare the 3 groups of qualitative data. One-way analysis variance was used to compare 3 independent groups with quantitative data and parametric distributions. A post hoc test compared the 3 groups according to pain recurrence during treatment. Table 1 shows the anthropometric measurements, history of the patients, stone character, and grade of obstruction which shows no significant difference between the groups.

4. Discussion

Urolithiasis is a chronic disease that affects both economic and public health because it affects young people and has a high recurrence rate of 50% at 5 years and 75% at 10 years.[10] Ureteric stones were the most symptomatic. Studies have shown that the spontaneous passage of distal ureteral stones is 71%–98% for stones smaller than 5 mm and 25%–51% for stones 5–10 mm in size.[11]

Medical expulsive therapy has become an alternative initial treatment for patients with distal ureteral stones.[11,12] The most common adrenergic receptors found in ureters are α_{1D} and α_{1A}, which, under the influence of α-blockers, relax the ureters, making it easier to drain stones.[13] Tadalafil, a PDE-5 inhibitor, acts on the nitric oxide/cGMP signaling pathway to increase cGMP levels, thereby relaxing the ureteric smooth muscle and facilitating stone passage.[14,15]

In the current study, the stone expulsion rate was significantly higher in the tadalafil and tamsulosin groups and in the tamsulosin group than in the placebo group (68% in the combination group and 64% in the tadalafil group, compared with 42% in the placebo group, $p = 0.018$). Furthermore, we found that the expulsion rates of both drugs were better than the expulsion rates in historical controls used in earlier studies.[16–19] However, in their studies, Kumar et al.[20] and Jayant et al.[6] compared the stone expulsion rate of tamsulosin with a combination of tamsulosin and tadalafil. The expulsion rates were 74.2% and 83.9% ($p = 0.349$) and 65.5% and 83.6% ($p = 0.031$), respectively. This result of high success may be caused by the use of prednisolone and the long duration of treatment (4 weeks), with a low sample size of only 62 patients.

In the current study, recurrence of pain was lower in the combination than in tadalafil alone and placebo by (1.9, 1, and 2.98 with a p value of 0.001), respectively, and the post hoc test confirmed a significant difference. The lower number of colic episodes and emergency department visits in group A also reflected better pain

Table 4

Effect of stone size on expulsion rate.

Stone size	Expulsion	Tadalafil (n = 50)	Tadalafil + tamsulosin (n = 50)	Placebo (n = 50)	*p*
3 mm	Yes	0	1	2	0.233
(n = 5)	No	1	1	0	
4 mm	Yes	3	1	0	0.231
(n = 11)	No	2	2	3	
5 mm	Yes	2	5	6	0.129
(n = 20)	No	4	2	1	
6 mm	Yes	4	3	8	0.076
(n = 25)	No	4	5	1	
7 mm	Yes	6	8	10	0.341
(n = 32)	No	4	1	3	
8 mm	Yes	5	8	4	0.562
(n = 28)	No	4	3	4	
9 mm	Yes	4	3	1	0.435
(n = 16)	No	2	3	3	
10 mm	Yes	3	4	2	0.263
(n = 13)	No	2	0	2	

$p > 0.05$: nonsignificant (NS); $p < 0.05$: significant (S); $p < 0.01$: highly significant (HS).
*χ^2 test.

control. These effects may be caused by decreased frequency and amplitude of phasic contractions accompanying ureteric obstruction and an improved antispasmodic impact of tamsulosin and tadalafil.[20] Hasan et al.[21] reported a significantly lower pain score of 3.9 versus 7.9 ($p < 0.0001$) and a significantly lower analgesic requirement in the tadalafil group than in the placebo group. Gnyawali et al. reported that better pain control was also reflected by the lower number of colic episodes and emergency department visits with the combination of (tadalafil and tamsulosin) table (Tables 2, 3).[22]

In a meta-analysis by Li et al.,[23] 5 studies (4 treatments) involving 771 patients were included in the analysis. In the pairwise meta-analysis, tamsulosin plus tadalafil was significantly better than tamsulosin alone concerning colic episodes (mean deviation [MD], 1.35, 95% confidence interval [CI], 1.10 to 1.59); $p = 0.000$) as in our study. In addition, 5 studies (4 treatments) including 771 patients were included in the analysis. In the pairwise meta-analysis, the time to expel stones in the tadalafil group was significantly shorter than in the tamsulosin group (MD, –0.33, 95% CI, –0.62 to –0.03, $p = 0.028$). Medium heterogeneity was observed, with an I^2 index of 58.3%. A more remarkable benefit was also found in the combination of tamsulosin and tadalafil compared with tamsulosin (MD, –0.42, 95% CI, –0.64 to –0.19) with a good consistency ($I^2 = 0$), but the included studies had no control placebo groups and a low sample size.[23]

Jendeberg et al.[24] (2017) reported that the spontaneous passage rate at 20 weeks was 312 of 392 stones, 98% in 0–2 mm, 98% in 3 mm, 81% in 4 mm, 65% in 5 mm, 33% in 6 mm, and 9% in ≥6.5 mm wide stones. Ordon et al.[25] (2015) reported a statistically significant improvement in the stone passage, whereas significantly more (29%; CI, 20% to 37%) patients passed their stones with α-blocker therapy than did patients receiving a placebo. In our study, there were no differences between groups according to the size of the stones; this result may be caused by nonadherence to treatment or a long-standing stone or bilharzial ureter (Table 4).[25]

Our study has a placebo with a good sample size that clarifies the debate regarding using both tadalafil and tamsulosin for distal ureteric stones. Choi et al.[26] (2015) described large stones with low expulsion rates. However, this study included all ureteric stone sites, and the patients received no treatment.

5. Conclusions

In this study, we can say that the combination of PD5I and an α-blocker effectively increases the expulsion of lower ureteric stones (5–10 mm) but with the same effect as PD5I alone, with the added benefit of decreasing pain recurrence. Stone size did not affect the expulsion rate in patients who underwent medical expulsive therapy for stones less than 1 cm.

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None.

Statement of ethics

The study methodology and protocol were approved by the institutional review board of the Assiut Faculty of Medicine. This trial was registered at ClinicalTrials.gov (NCT05150899). Written informed consent was obtained from all the participants. The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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None.

Author contributions

AR: Conceived and designed the analysis;
MK: Collected the data;
MI: Contributed data or analysis tools;
YMA: Performed the analysis;
MZ: Wrote the paper.

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