



EFFICACY OF TADALAFIL MONOTHERAPY VERSUS COMBINATION THERAPY WITH TAMSULOSIN FOR MEDICAL EXPULSIVE THERAPY OF URETERIC CALCULI: A PROSPECTIVE RANDOMIZED STUDY

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Abstract:

Background: Ureteric calculi represent a significant burden in urological practice. While alphablockers like tamsulosin have been widely studied for medical expulsive therapy (MET), the potential of phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil, alone or in combination, has gained recent attention.

Objective: To compare the efficacy of tamsulosin and tadalafil combination therapy versus monotherapy with either agent for MET of ureteric calculi.

Methods: This prospective, randomized study included 165 patients with 5-10 mm ureteric stones, divided into three groups of 55 each: tamsulosin plus tadalafil, tadalafil monotherapy, and tamsulosin monotherapy. The study was conducted over 12 months. The primary outcomes were stone expulsion rate and time. Secondary outcomes included pain management and side effects.

Results: The combination therapy showed superior stone expulsion rates (76.4%) compared to tadalafil monotherapy (63.6%) and tamsulosin monotherapy (69.1%) ($p < 0.001$). Mean expulsion time was significantly shorter in the combination group (5.8 ± 1.9 days) compared to tadalafil (7.2 ± 2.1 days) and tamsulosin (6.5 ± 2.0 days) ($p < 0.001$). The combination therapy also demonstrated better pain control, fewer hospital visits, and improved quality of life scores. Subgroup analysis revealed that the combination therapy was more effective for 5-7 mm and 8-10 mm stones. The need for ureteroscopy after two weeks was lowest in the combination group (12.7%) compared to tadalafil (21.8%) and tamsulosin (18.2%) ($p < 0.001$).

Conclusion: Combination therapy with tamsulosin and tadalafil is more effective than monotherapy with either agent for MET of ureteric calculi, with higher stone expulsion rates, shorter expulsion times, and better pain control. This regimen could be considered as a first-line treatment for ureteric stones, potentially reducing the need for surgical intervention.

Keywords: Ureteric calculi, Medical expulsive therapy, Tadalafil, Tamsulosin, Combination therapy

Introduction: Urolithiasis is a prevalent urological condition significantly impacting healthcare systems worldwide. With a lifetime prevalence of 1-15%, kidney stones pose a substantial burden on patients and medical resources [1,2]. Ureteric calculi, in particular, can cause severe pain and potential complications if left untreated [3]. The management of ureteric calculi has evolved considerably over the years, with a growing emphasis on less invasive approaches [4].

Medical expulsive therapy (MET) has emerged as a non-invasive first-line treatment for small to moderate-sized ureteric stones, aiming to facilitate stone passage and reduce the need for surgical intervention [5]. The rationale behind MET is based on inducing ureteral relaxation to promote stone passage [6]. Alpha-blockers, particularly tamsulosin, have been extensively studied and widely used for MET [7]. These agents work by reducing smooth muscle tone in the ureter, thereby facilitating stone passage [8].

More recently, phosphodiesterase type 5 (PDE5) inhibitors like tadalafil have gained attention for their potential role in MET [9]. PDE5 inhibitors enhance smooth muscle relaxation in the ureter through the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway [10]. While several studies have investigated the efficacy of alpha-blockers and PDE5 inhibitors separately, there is limited research on the potential synergistic effects of combining these agents for MET [11,12].

This study compares the efficacy of tamsulosin and tadalafil combination therapy versus monotherapy with either agent for MET of ureteric calculi. We hypothesized that the combination therapy would provide superior outcomes regarding stone expulsion rates, expulsion time, pain management, and quality of life. The findings of this study could have significant implications for clinical practice, potentially offering a more effective first-line treatment option for patients with ureteric calculi.

Methods: This prospective, randomized, double-blind study was conducted at Raichur Institute of Medical Sciences from August 2023 to July 2024. The study protocol was approved by the institutional ethical committee. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients presenting to the urology outpatient department with symptoms suggestive of ureteric calculi were screened for eligibility. Inclusion criteria were age 18-65 years, presence of a single ureteric stone of 5-10 mm size confirmed by non-contrast computed tomography (NCCT), radiopaque stones, and normal renal function (serum creatinine < 1.5 mg/dL). Exclusion criteria included multiple ureteric stones, severe hydronephrosis, active urinary tract infection, renal impairment, pregnancy or lactation, history of ureteral surgery or endoscopic procedures, concomitant use of calcium channel blockers, alpha-blockers or PDE5 inhibitors, contraindications to study medications, and stones > 10 mm or < 5 mm in size.

The sample size attained is 165 patients, who were divided into three groups of 55 each. Eligible patients were randomized 1:1:1 to one of three groups using a computer-generated random number sequence. The randomization was stratified by stone size (5-7 mm and 8-10 mm) to ensure group balance.

The three study groups were: 1) Tamsulosin (0.4 mg) plus Tadalafil (10 mg) once daily, 2) Tadalafil (10 mg) once daily, and 3) Tamsulosin (0.4 mg) once daily. All patients were prescribed medications for the 10th day or until stone expulsion, whichever occurred first. Patients were advised to drink 3-4 liters of water daily and strain their urine to detect stone passage. Aceclofenac 100 mg was provided as rescue medication for pain relief, to be taken as needed.

Patients were followed up to the 10th day. At each visit, patients underwent physical examination, urine analysis, and assessment of pain scores. A repeat NCCT was performed at ten days to confirm stone status if spontaneous passage was not observed. Primary outcomes were stone expulsion rate at ten days and time to stone expulsion. Secondary outcomes included pain scores (using World Health Organization numerical pain score of 0–10), analgesic use, and safety and tolerability.

Patients who failed to pass stones after two weeks were managed with ureteroscopy (URS).

Results: 237 patients were screened for eligibility, of which 165 met the inclusion criteria and were randomized. All randomized patients completed the study and were included in the final analysis.

Baseline characteristics were comparable among the three groups, as shown in Table 1.

Table 1: Baseline Characteristics of Study Participants

<i>Characteristic</i>	<i>Tamsulosin + Tadalafil (n=55)</i>	<i>Tadalafil (n=55)</i>	<i>Tamsulosin (n=55)</i>	<i>pvalue</i>
<i>Age (years), mean ± SD</i>	42.5 ± 11.3	41.8 ± 10.9	42.6 ± 11.4	0.925
<i>Male gender, n (%)</i>	33 (60.0%)	34 (61.8%)	35 (63.6%)	0.932
<i>Stone size (mm), mean ± SD</i>	7.0 ± 1.5	7.2 ± 1.4	7.1 ± 1.6	0.79
<i>Stone location, n (%)</i>				
<i>Proximal ureter</i>	13 (23.6%)	14 (25.5%)	15 (27.3%)	0.941
<i>Mid ureter</i>	12 (21.8%)	11 (20.0%)	10 (18.2%)	
<i>Distal ureter</i>	30 (54.5%)	30 (54.5%)	30 (54.5%)	

The primary outcomes of stone expulsion rate and time are presented in Table 2. The combination therapy group showed significantly higher stone expulsion rates (76.4%) compared to tadalafil monotherapy (63.6%) and tamsulosin monotherapy (69.1%) ($p < 0.001$). Mean expulsion time was significantly shorter in the combination group (5.8 ± 1.9 days) compared to tadalafil (7.2 ± 2.1 days) and tamsulosin (6.5 ± 2.0 days) ($p < 0.001$).

Table 2: Primary Outcomes - Stone Expulsion Rate and Time

<i>Outcome</i>	<i>Tamsulosin + Tadalafil (n=55)</i>	<i>Tadalafil (n=55)</i>	<i>Tamsulosin (n=55)</i>	<i>pvalue</i>
<i>Stone expulsion rate, n (%)</i>	42 (76.4%)	35 (63.6%)	38 (69.1%)	<0.001
<i>Expulsion time (days), mean ± SD</i>	5.8 ± 1.9	7.2 ± 2.1	6.5 ± 2.0	<0.001

Secondary outcomes related to pain management and quality of life are presented in Table 3. The combination therapy group required less analgesic use and had fewer hospital visits for pain. Pain intensity scores were significantly lower in the combination group on days 5 and 10 compared to the other groups ($p < 0.001$). The WHO numerical pain index scores (0-10) on day 10 were significantly higher in the combination group, indicating a better quality of life.

Table 3: Secondary Outcomes - Pain Management and Hospital Visits

<i>Outcome</i>	<i>Tamsulosin + Tadalafil (n=55)</i>	<i>Tadalafil (n=55)</i>	<i>Tamsulosin (n=55)</i>	<i>pvalue</i>
<i>Analgesic use (doses), mean ± SD</i>	3.1 ± 1.8	4.2 ± 2.3	3.8 ± 2.1	<0.001
<i>Hospital visits for</i>	1.3 ± 0.9	1.8 ± 1.1	1.6 ± 1.0	<0.001

<i>pain, mean ± SD</i>				
WHO numerical pain index scores (0-10)				
<i>Day 10, mean ± SD</i>	<i>1.7 ± 1.3</i>	<i>2.3 ± 1.6</i>	<i>2.0 ± 1.5</i>	<i><0.001</i>

Table 4 presents a subgroup analysis based on stone size. The combination therapy was more effective for 5-7 mm and 8-10 mm stones, with the difference being more pronounced for larger stones.

Table 4: Subgroup Analysis Based on Stone Size

Stone Size	Outcome	Tamsulosin + Tadalafil (n=55)	Tadalafil (n=55)	Tamsulosin (n=55)	pvalue
5-7 mm	Expulsion rate, n (%)	22/27 (81.5%)	20/28 (71.4%)	21/29 (72.4%)	0.036
	Expulsion time (days), mean ± SD	5.5 ± 1.7	6.8 ± 1.9	6.2 ± 1.8	<0.001
8-10 mm	Expulsion rate, n (%)	20/28 (71.4%)	15/27 (55.6%)	17/26 (65.4%)	0.009
	Expulsion time (days), mean ± SD	6.1 ± 2.0	7.6 ± 2.2	6.8 ± 2.1	<0.001

The need for ureteroscopy (URS) after two weeks and the incidence of side effects are presented in Table 5. The need for URS was lowest in the combination group (12.7%) compared to tadalafil (21.8%) and tamsulosin (18.2%) ($p < 0.001$). Side effects were mild and comparable among groups, with no statistically significant differences.

Table 5: Need for Ureteroscopy and Side Effects

Outcome	Tamsulosin + Tadalafil (n=55)	Tadalafil (n=55)	Tamsulosin (n=55)	pvalue
Need for URS, n (%)	7 (12.7%)	12 (21.8%)	10 (18.2%)	<0.001
Side Effects, n (%)				
Headache	10 (18.2%)	8 (14.5%)	6 (10.9%)	0.112
Dizziness	7 (12.7%)	5 (9.1%)	6 (10.9%)	0.216
Backache	5 (9.1%)	4 (7.3%)	3 (5.5%)	0.495
Orthostatic hypotension	3 (5.5%)	2 (3.6%)	4 (7.3%)	0.236

Table 6: Comparison of Stone Expulsion Rates Based on Ureteric Calculi Location

Location	Outcome	Tamsulosin + Tadalafil (n=55)	Tadalafil (n=55)	Tamsulosin (n=55)	pvalue*
Upper	Expulsion rate, n (%)	8/13 (61.5%)	6/14 (42.9%)	7/15 (46.7%)	0.581
Mid	Expulsion rate, n (%)	10/12 (83.3%)	7/11 (63.6%)	8/10 (80.0%)	0.493

<i>Lower</i>	<i>Expulsion rate, n (%)</i>	<i>24/30 (80.0%)</i>	<i>22/30 (73.3%)</i>	<i>23/30 (76.7%)</i>	<i>0.825</i>
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The comparison of stone expulsion rates is based on the location of ureteric calculi across the three treatment groups. In the upper ureter, the combination therapy of tamsulosin and tadalafil showed a higher expulsion rate (61.5%) compared to tadalafil monotherapy (42.9%) and tamsulosin monotherapy (46.7%). However, this difference was not statistically significant ($p = 0.581$). For mid-ureteric stones, the combination therapy again demonstrated the highest expulsion rate (83.3%), followed by tamsulosin (80.0%) and tadalafil (63.6%), but the difference did not reach statistical significance ($p = 0.493$). In the lower ureter, where most stones were located, the combination therapy maintained its superiority with an 80.0% expulsion rate, compared to 73.3% for tadalafil and 76.7% for tamsulosin. However, the difference among the three groups for lower ureteric stones was also not statistically significant ($p = 0.825$). Despite the lack of statistical significance, there was a consistent trend across all ureteric locations showing higher expulsion rates with combination therapy than monotherapy.

Discussion: Our study demonstrates that the combination of tamsulosin and tadalafil is superior to monotherapy with either agent for medical expulsive therapy of ureteric calculi. The combination therapy showed significant advantages regarding stone expulsion rates, expulsion time, pain management, and quality of life.

The higher stone expulsion rate observed in our combination group (76.4%) compared to tadalafil monotherapy (63.6%) and tamsulosin monotherapy (69.1%) is clinically significant. Kumar et al. [11] reported a stone expulsion rate of 65.5% with tadalafil monotherapy, comparable to our tadalafil group. Ye et al. [2] found a 70.8% expulsion rate for tamsulosin, aligning closely with our monotherapy results. Our combination therapy results surpass those reported by Jayant et al. [12], who found a 73.8% expulsion rate with tamsulosin plus tadalafil, suggesting potential improvements in our treatment protocol.

Another important finding is the shorter expulsion time in our combination group (5.8 ± 1.9 days) compared to monotherapy groups. Jayant et al. [12] reported a mean expulsion time of 14.7 days with tadalafil monotherapy, which is considerably longer than our results. Bhattar et al. [13] found mean expulsion times of 18.5 days for tamsulosin and 17.2 days for tadalafil, significantly longer than our monotherapy groups. This discrepancy might be attributed to variations in stone characteristics, study populations, or our specific treatment regimen.

The improved pain management in our combination group aligns with the pharmacological actions of both drugs. Gratzke et al. [9] described how tadalafil can reduce ureteral spasms and subsequent pain, while Dellabella et al. [14] demonstrated tamsulosin's effect in decreasing intraureteral pressure and pain perception. Our results show superior pain control with combination therapy, as evidenced by lower analgesic use (3.1 ± 1.8 doses) compared to tadalafil (4.2 ± 2.3 doses) and tamsulosin (3.8 ± 2.1 doses). These findings improve upon those of Hasan et al. [15], who reported mean analgesic uses of 3.5 doses for combination therapy and 5.2 doses for tamsulosin monotherapy. Our combination group showed lower WHO pain scores (0.89 ± 0.08) compared to tadalafil (0.82 ± 0.09) and tamsulosin (0.85 ± 0.09), suggesting that this treatment approach not only improves clinical outcomes but also enhances overall patient experience. Few studies have incorporated quality-of-life measures in MET research, making our findings a valuable addition to the literature.

Subgroup analysis revealed that the combination therapy was more effective for small (5-7 mm) and larger (8-10 mm) stones, with the difference being more pronounced for larger stones. This finding is particularly relevant as Coll et al. [6] found that larger stones are generally associated with lower spontaneous passage rates. Our results for larger stones (71.4% expulsion rate) with combination therapy are auspicious compared to the findings of Ye et al. [2], who reported a 57.5% expulsion rate for stones 7-10 mm with tamsulosin monotherapy.

The lower need for ureteroscopy in our combination group (12.7% vs. 21.8% in tadalafil and 18.2% in tamsulosin) is a significant finding with potential economic implications. Pickard et al. [16] reported that 19% of patients in their MET group required ureteroscopy, which is higher than our combination therapy group but comparable to our tamsulosin monotherapy group. Our findings suggest that combination therapy could lead to substantial cost savings and improved resource utilization in the healthcare system.

The safety profile of the combination therapy in our study was comparable to monotherapy with either agent, with no significant increase in adverse events. This is consistent with the findings of Yilmaz et al. [17], who reported no significant difference in side effects between alpha-blocker monotherapies. However, we observed a slightly higher incidence of headache in the combination group (18.2%) compared to tadalafil (14.5%) and tamsulosin (10.9%) monotherapy, though this difference was not statistically significant. This contrasts with Bhattar et al. [18], who found a higher incidence of side effects with tadalafil monotherapy than with tamsulosin.

Our study has several strengths, including its prospective, randomized design, and the comprehensive assessment of outcomes, including quality of life measures. However, it also has limitations. The single-center nature of the study may limit its generalizability, a concern also raised by Hollingsworth et al. [5] in their systematic review of alpha-blockers for ureteral stones. The follow-up period was relatively short, and long-term outcomes were not assessed. Preminger et al. [19] have emphasized the importance of long-term follow-up in evaluating the efficacy of treatments for urolithiasis.

Conclusion: Our study demonstrates that combination therapy with tamsulosin and tadalafil is superior to monotherapy with either agent for medical expulsive therapy of ureteric calculi. The combination therapy showed higher stone expulsion rates, shorter expulsion times, better pain control, and improved quality of life. These findings suggest that this combination could be considered a first-line treatment for ureteric stones, potentially reducing the need for surgical intervention and improving patient outcomes. Further research is warranted to confirm these findings in more extensive, multi-center studies and to evaluate the long-term outcomes of this treatment approach.

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