



COMPARISON OF TAMSULOSIN, NAFTOPIDIL AND TADALAFIL AS MEDICAL EXPULSIVE THERAPY FOR LOWER URETERIC CALCULUS: AN OBSERVATIONAL STUDY

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ABSTRACT

Background: Medical Expulsive Therapy is the most facile and trustable nonsurgical modality for patients having ureteral stones. Thus this study aims to investigate and compare the efficacy of three drugs used for Medical Expulsive Therapy, namely Tamsulosin, Tadalafil and Naftopidil for treating the distal ureteric calculus. **Materials and Methods:** This prospective observational study was carried out in the department of urology, over a period of 2 years. A total of 120 cases of ureteric calculus were included and each Tamsulosin, Tadalafil and Naftopidil group had forty cases. The data was first entered into an excel files and exported into SPSS 20.0 version. Descriptive statistical, ANOVA and Chi-square (X²) test was used to estimate and compare the variables between groups. P value of <0.05 was regarded as statistically significant advantage. **Results:** No statistical difference found among the tamsulosin, tadalafil and naftopidil group with respect to age, gender, size of calculus, time of stone expulsion, total analgesic use and number of pain episodes, endoscopic treatment. Statistically significant association was found between adverse effects and the drugs used. **Conclusion:** Tadalafil seems to be more efficient, followed by Naftopidil and then Tamsulosin, in terms of stone expulsion and adverse effects.

KEYWORDS : Tamsulosin, Tadalafil, Naftopidil, Medical Expulsive Therapy

INTRODUCTION:

In the current scenario, there are innumerable options for diagnosing and treating calculus associated with the urinary tract, particularly the kidney and ureter, which includes approaches such as conservative, wait and watch as well as active interventions. The treatment of ureteric calculus via endoscopy is highly reliable one and also bestows high success rate in removing the calculus immediately^[1]. On the contrary, this type of treatment entails the risk due to surgery and anaesthesia, which are not negligible and rarely involves serious complications^[2]. Therefore, an appealing and reliable option for most of the ureteric calculus patients is conservative treatment. However, the conservative approach does not always result in complete clearance of calculus and may also lead to recurrent renal or ureteric colic^[3].

The alpha (α) blockers have been investigated to be a potential drug for treating ureteric calculus disease, which is solely due to the adrenergic (α) receptors detected in smooth muscle cells of ureter^[4]. The first success with Medical Expulsive Therapy (MET) was demonstrated by using the nonselective α -blocker Doxazosin for patients having lower/distal ureteric calculus, reported in the late 1990's^[5]. From then on, many clinical trials have been conducted to analyse the efficiency of MET with the usage of α -1A/D selective blocker. Tamsulosin alone or in combination form with one or more drugs (namely antibiotics, corticosteroids, diclofenac etc.) have been studied.^[6]

Recently, Tadalafil, a newer type of phosphodiesterase-5 (PDE-5) inhibitor has emerged, which acts on nitric oxide/cyclic Guanosine Monophosphate (NO/cGMP) signaling pathway of smooth muscles that increases the cGMP level and

ultimately results in ureteric relaxation. This smooth muscle relaxation property of Tadalafil has led to its immediate approval by the Food and Drug Administration (FDA), for treating the lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED).^[7]

Another MET drug called Naftopidil is a α_1D - adrenergic receptor antagonist and is an effective drug for treating lower urinary tracts (LUTs) and its associated symptoms (such as BPH). Naftopidil is evidenced to have higher efficiency accompanied with fewer side effects and hence readily accepted as a medical expulsive agent.^[8]

AIMS AND OBJECTIVES

The main aim of this research work is to investigate and compare the efficacy of MET drugs such as Tamsulosin, Tadalafil and Naftopidil for treating the distal ureteric calculus.

METHODS

This prospective observational study was carried out in the department of urology, over a period of 2 years from July 2015 to June 2017.

The study population includes all patients between 18-65 years of age who presented to the urology outpatient and inpatient department with acute ureteric colic diagnosed to have single distal ureteric calculus of size ≤ 7 mm were selected as the study subjects.

Cases with Multiple calculi, calculus with moderate hydronephrosis, pregnancy and lactation, solitary kidney, history of previous ureteral surgery or endoscopic procedure,

calculus with Urinary tract infection, patients on corticosteroids or calcium channel blockers, renal insufficiency (serum creatinine > 1.5gms/dl), known cases of hypertension, Diabetes mellitus, Ischemic Heart Disease were excluded from the study.

A total of 120 cases of distal ureteric calculus were included in this study and they were divided into three groups with forty cases in each group. Group 1 were administered with tablet Tamsulosin 0.4mg for 21 days, one tablet daily at bedtime, Group 2 were administered with tablet Naftopidil 50mg for 21 days, one tablet orally in the morning and Group 3 were administered with tablet Tadalafil 10mg for 21 days, one tab in the night.

Detailed history and examination was done to all the patients by the principal investigator. Patients were assessed regarding stone expulsion rate, time to stone expulsion, total analgesic use, adverse effects of drugs and endoscopic treatment (Intervention rate). The maximum follow-up period was for 3 weeks after which patients were assessed using appropriate imaging studies like X-ray KUB and/or USG.

The data was first entered into an excel files and exported into SPSS 20.0 version. Descriptive statistical, ANOVA and Chi-square (χ^2) test was used to estimate and compare the variables between groups. P value of <0.05 was regarded as statistically significant advantage.

RESULTS

Most of our study cases (28.3%) were in the age group of 41-50 years, followed by 23.3% of the patients in 21-30 years age group, 22.5% of the patients between 31-40 years age group. About 11.7% of the patients were present in each of the age group between 51-60 years and above 60 years. Out of 120 cases studied, we found a male predominance (80%) while 20% of the patients were females. (TABLE 1)

In the present study, there were no statistical difference found among the tamsulosin, tadalafil and naftopidil group with respect to age, size of calculus, time of stone expulsion, total analgesic use and number of pain episodes. (TABLE 2)

With respect to adverse effects, it is observed that 95.8% of the patients did not have adverse effects. Further 87.5%, 100%, 100% of the patients treated with tamsulosin, naftopidil and tadalafil group, respectively did not have adverse effects respectively. From the observed chi-square value of 10.435 and p value of 0.034 which is less than 0.05, hence there is an association between the MET drugs and adverse effects (headache, giddiness).

In the present study, there were no statistical association found between the tamsulosin, tadalafil and naftopidil group with respect to gender, stone expulsion and endoscopic treatment. (TABLE 3)

DISCUSSION

Among all urinary tract stones, 20% present as ureteral stones, of which 70% are found in the lower third of the ureter.^[9] The factors influencing the spontaneous expulsion of ureteral stones are stone location, size, number, shape, spasm in the ureteral smooth muscles, mucosal edema or inflammation and ureteral anatomy.^[10] It would seem logical that medical therapy should be used to reduce edema, spasm and cause relaxation of smooth muscles.

Tamsulosin is the most common α_{1A} receptor blocker, that is used for assisting the ureteral stone passage^[11]. Tamsulosin is used for treating BPH and recently, its off-label use has been identified to be an efficient and a safe MET drug for initially managing the ureteral stones expulsion and pain^[12].

Tamsulosin's selectivity for α_{1A} is 3.3 times greater than for α_{1D} ^[13].

Naftopidil, an α_{1D} adrenergic receptor antagonist, which is described to have the highest recorded selectivity to α_{1D} receptor. The Naftopidil selectivity for α_{1D} is 3.1-times greater than that for α_{1A} ^[14]. Therefore, it can be seen that the effect of adrenergic receptor for the α_{1D} receptor seems to be higher for Naftopidil than that for the Tamsulosin, indicating that the Naftopidil may display greater efficiency as MET drug than the Tamsulosin^[15].

In recent times, phosphodiesterase-5 (PDE5) inhibitors have been found to relax the ureteric muscle and have also exhibited a few advantages in the expulsion of stone^[16]. Tadalafil is one such PDE5 inhibitor, that functions by a NO/cGMP signaling pathway of smooth muscles and results in production of high amount of cGMP and thereby leading to the ureteral muscle relaxation^[17]. Among the recently discovered PDE5 inhibitors, Tadalafil have been found to possess the longest duration of action (about 36 hours). Tadalafil has been most often used in treating ED and LUTS due to BPH. The use of this drug as MET for treating ureteral stone is comparatively less than that of Tamsulosin^[18].

In the present study, a total of 86.7% of the patients had stone expulsion 31 out of 40 (77.5%) for Tamsulosin, 35 out of 40 (87.5%) for Naftopidil and 38 out of 40 (95%) for Tadalafil allowed the passage of stone. The stone expulsion rate of Tadalafil (Group 3) in treating the lower ureteric calculi is higher when compared to group 1 and group 2. There was no statistically significant difference $p = 0.069 > 0.05$ observed between the stone expulsion rate and the MET drugs.

Tadalafil showed highest stone expulsion rate compared to tamsulosin and naftopidil. It is important to note that the drug given acts through PDE5 receptors, which are totally separate pathways in modulation of ureteric motility and thus opening the potential of combining these drugs to further aid the ureteric stone expulsion.

A combination of tamsulosin and tadalafil has already been successfully used by Jayant et al^[19]. Kumar et al. showed a stone expulsion rate of 66.7% with tadalafil in comparison to 64.4% with tamsulosin^[20].

In this research study, the mean time taken for the expulsion of stone after the commencing the treatment was obtained as an average of 6.6 days for Tamsulosin group, 6.9 days for Naftopidil group while 5.71 days for Tadalafil group. Therefore, the time to stone expulsion of Tadalafil was found to be shorter when compared to group 1 and group 2. The total P value was 0.084 (>0.05) for the three MET drugs, showing that there is no statistically significant difference in terms of time to stone expulsion.

Girish et al^[21], observed from their studies that the mean time to stone expulsion from the onset of treatment for group A (Tamsulosin) was an average of 4.15 days, for group B (Tadalafil) was 3.6 days and for group 3 (Tamsulosin with Tadalafil) was 4 days with the total P value was 0.545 > 0.05. The time to stone expulsion was shorter comparatively to Group A. Kumar et al^[22] investigated the mean time to stone expulsion in group A (Tamsulosin), group B (Silodosin) and group C (Tadalafil) to be 16.5 ± 4.6 days, 14.8 ± 3.3 days and 16.2 ± 4.2 days and they found that the time for stone expulsion was significantly less in group B when compared to group A and group C. According to Bahadur KH et al^[18], the mean time to stone expulsion was shorter with Tadalafil 8.08 ± 3.3 days than with tamsulosin with 9.64 ± 3.8 days. However, there was no statistically significant difference observed in terms of time to stone expulsion $p=0.094$. The

study performed by Sun et al^[8], similar to our study, exhibited no statistically significant difference in terms of time to stone expulsion between placebo (group 1) and Naftopidil (group 2).

The present research study focused to study and compare the adverse effects such as headache, giddiness in patients who received Tamsulosin, Naftopidil and Tadalafil. In this study, it can be witnessed that an overall 95.8% patients who consumed these MET drugs exhibited no adverse side effects, both in terms of headache and giddiness.

In group 1, 4 patients out of 40 had giddiness and 1 patient out of 40 had headache. In group 2 and 3, no patients were detected with any adverse side effect. This shows that Naftopidil and Tadalafil produced no adverse effect, when compared to Tamsulosin. A statistically significant difference was observed for these MET drugs in terms of adverse effects. But, the patients with these side effects were not significant enough to exclude from the study.

Kumar et al^[22] investigated the adverse effects pertaining to the drugs in terms of headache, orthostatic hypotension, backache and dizziness, and observed that the side effects were more prevalent in Tadalafil (group C) when compared to group A and B. However, the patients with these side effects were not significant enough to evade them off from the research study.

In another study, Sun et al^[8] detected the Naftopidil drug did not induce any serious side effects. There are several other literatures^[23, 24] which reported indicating that the use of MET mono drugs (such as Tamsulosin, Tadalafil, Naftopidil and so forth) did not produce any adverse side effects.

In this study, a total of 26.7% underwent follow endoscopic treatment due to failure of passage of calculus. There was no statistical significant difference between the three MET drugs in terms of follow up endoscopic treatment. There are many previous studies conducted by Sun et al^[8], Ahmad et al^[23] and Cao et al^[25] reported the similar findings with respect to endoscopic treatment.

CONCLUSION

All three MET drugs i.e. Tamsulosin, Naftopidil and Tadalafil, exhibited the same efficacy for treating patients in terms of physical factors such as age (18 to 65 years), sex and stone size. Tadalafil group revealed a better stone expulsion rate for lower ureteric calculus <7mm than Tamsulosin group and Naftopidil group. The statistical differences for these three drugs were not significant in terms of stone expulsion rate. Among the three drugs, Tadalafil group showed significantly lesser time to stone expulsion than the Tamsulosin and Naftopidil.

However, there was no overall statistically significant difference in terms of time to stone expulsion for the three drugs. The adverse effects such as giddiness and headache were observed. Naftopidil and Tadalafil drugs did not have adverse effects when compared to Tamsulosin. A statistically significant difference for these drugs with regards to adverse effect was observed. But, no patients displaying side effects were excluded from the study, since the symptoms were mild.

LIST OF ABBREVIATIONS:

- MET – MEDICAL EXPULSIVE THERAPY
- PDE 5 - PHOSPHODIESTERASE-5
- BPH – BENIGN PROSTATIC HYPERPLASIA
- NO – NITRIC OXIDE
- C GMP – CYCLIC GUANOSINE MONOPHOSPHATE

Table 1: Clinical presentation of study participants

Variables	Frequency (n)	Percentage (%)
Stone lateralization		
Left loin pain	62	51.7
Right loin pain	58	48.3
Size of calculus		
≤ 5 mm	31	25.8
> 5 mm	89	74.2
Stone Expulsion		
No	16	13.3
Yes	104	86.7
Time to stone expulsion (days)		
3 – 5 days	34	32.6
6 – 8 days	54	51.9
≥ 9 days	16	15.3
Number of Tablets Consumed		
1 – 2	44	36.7
3 – 5	76	63.3
Adverse effects		
No	115	95.8
Yes	5	4.2
Pain episodes		
≤ 2 episodes	44	36.7
≥ 3 episodes	76	63.3

Table 2: Difference between variables and different MET groups

Variables	MET groups			p value
	Tamsulosin	Tadalafil	Naftopidil	
Age in years	39.08 ± 13.49	41.08 ± 12.69	42.23 ± 13.99	0.570
Size of calculus (mm)	5.87 ± 1.04	6.25 ± 0.92	6.22 ± 0.87	0.141
Time to stone expulsion (days)	6.63 ± 2.32	5.71 ± 1.27	6.94 ± 3.10	0.084
Total analgesic use (number of tablets consumed)	2.70 ± 1.09	2.83 ± 0.71	2.78 ± 0.94	0.833
Number of pain episodes	2.68 ± 1.095	2.83 ± 0.712	2.80 ± 0.148	0.742

Table 3: Association between variables and different MET groups

Variables	MET groups			Total	p value
	Tamsulosin	Tadalafil	Naftopidil		
Gender					
Male	34(85.0)	30(75.0)	32(80.0)	96(80.0)	0.535
Female	6(15.0)	10(25.0)	8(20.0)	24(20.0)	
Stone expulsion					
No	9(22.5)	2(5.0)	5(12.5)	16(13.3)	0.069
Yes	31(77.5)	38(95.0)	35(87.5)	104(86.7)	
Adverse effects					
No	35 (87.5)	40 (100.0)	40 (100.0)	115 (95.8)	0.034 *
Giddiness	4 (10.0)	0 (0.00)	0 (0.00)	4 (3.3)	
Headache	1 (2.5)	0 (0.00)	0 (0.00)	1 (0.8)	

Endoscopic Treatment					
URS with DJ stenting	9 (22.5)	2 (5.0)	5 (12.5)	16(13.3)	0.069
No	31 (77.5)	38 (95.0)	35(86.7)	104 (86.7)	

*Significant

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