

Efficacy of Conservative Therapy versus Tamsulosin Added Therapy in Patients with Lower Ureteral Calculi and their Health Related Quality of Life

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KEYWORDS

Calculi; Conservative therapy; Quality of life; stone expulsion; Tamsulosin; Ureteral colic.

ABSTRACT

Background: Alpha-1 blockers reduce smooth muscle tension and alleviate spasms, thereby decreasing obstructions and relieving irritative symptoms in the lower urinary tract. This study aimed to assess the effectiveness of Tamsulosin and its impact on health-related quality of life in patients with distal ureteral calculi. **Methods:** A total of 120 patients with distal ureteral calculi were enrolled in this study and randomly assigned into two groups. Group 1 (n=60) received conservative therapy, while Group 2 (n=60) received Tamsulosin (0.4 mg daily) in addition to conservative therapy. All patients were monitored for pain, intensity of ureteric colic, and spontaneous stone expulsion. Health-related quality of life (HRQoL) was assessed for each patient using the RAND SF-36 Health Survey 1.0. **Results:** Spontaneous stone passage occurred in 52 patients (85%) in Group 1 and in all 60 patients (100%) in Group 2, with a statistically significant difference between the groups ($P < 0.001$). Analysis by stone diameter further indicated significant differences favoring Tamsulosin treatment for stones ≤ 6 mm ($P = 0.04$) and > 6 mm ($P = 0.003$). Health-related quality of life scores were significantly higher in the Tamsulosin group compared to the conservative therapy group. **Conclusion:** Tamsulosin, an alpha-1 blocker, is recommended for treating distal ureteral calculi, as it facilitates faster stone expulsion, increases expulsion rates, and enhances quality of life by reducing the frequency and severity of ureteric colic.

1. Introduction

Ureteric calculi or the ureteral stones are those that lie within the ureter, between pelvico-ureteric junction and vesico-ureteric junction mainly towards the distal region. They are the major cause for ureteric colic, which is defined by episodic severe abdominal pain resulting from contraction of ureteric smooth muscles [1,2]. Ureteric calculi may obstruct urine outflow, thereby leading to an emergency health care condition in these patients [1,2]. As per literature, distal ureteric calculi can be managed with conservative approaches [3]. Although this conservative approach suffers few disadvantages such as urinary tract infection, hematuria, severe pain, nausea and vomiting; this thereby complicates the choice of interventional therapeutic approach like shock wave lithotripsy [4].⁴ Moreover these types of hypothetical complications arise within the patients with smaller sized ureteral stones [5].

The stone passage normally occurs within a period of 4 weeks based on the size of the stone and its location. Distal ureteral stones are easy to be managed with conservative medical approach when compared to proximal renal stones [6]. It has been recently demonstrated that the receptors to specific alpha 1 blockers (drugs that are commonly being used in the treatment of benign prostatic hyperplasia-Tamsulosin) are more prevalent in the distal part of ureter [4]. Making it an evidence for the treatment of distal ureteral calculi by relaxing the smooth muscles and further facilitating the ureteral stone clearance. In addition to passage of stone, tamsulosin drug therapy is reported to be beneficial in these patients by alleviating the ureteral colic and reducing the need of interventional therapy [7]. When compared to other drugs used in the management of ureteral calculi, adverse

events associated with tamsulosin therapy is less and the health related quality of life is also good creating perfect outline in the medical therapy of urology [8]. The aim of the present study was to comparatively study the efficacy of tamsulosin in combination with conservative therapy against ureteral calculi patients managed with conservative therapy only and also to assess and compare the health related quality of life in between these two groups.

2. Methods

This survey took place in India between August 2016 and April 2017 at a tertiary care hospital. In this one year period we came across 120 patients in the division of surgery. The study protocol was approved by the Institutional ethics committee, Vels University (Institutional Ethics Committee: IEC/DOPI/2016/03). Patients diagnosed with ureteral calculi were explained about the study protocol and written informed consent was obtained from all the study participants. The Patients diagnosed with Urinary Tract Infection, Solitaire kidney, severe refractory pain, multiple stones, severe hydronephrosis by obstruction were excluded from the study. About 120 patients were enrolled in to the study. Around 79 patients had left lower ureteral calculi and 41 had right lower ureteral calculi. The study was carried out by the collection and documentation of general information from the patient including personal history, family background, and medical illness associates with the ureteral calculi. The subjects were randomized in to two groups of each 60 patients, where group 1 was receiving conservative therapy such as hydration and NSAID's and group 2 was receiving α_1 blocker (tamsulosin) in addition to conservative therapy. Both the groups were followed up to 4 weeks since the spontaneous passage of stone will be higher during this period after the medical expulsive treatment. At the end of 4 weeks period all the patients will be questioned regarding if there was any experience of acute episodes of ureteral colic; and its score will be measured using Visual Analogue Scale (VAS). The patients were also enquired about spontaneous passage of stone and documented the same. VAS is used to express the patient's perception on the intensity of pain. Patients were requested to define the colicky pain experienced by them on a number scale between minor score of pain 0 to severe score of pain 10. The adverse effects associated with tamsulosin therapy were monitored and evaluated.

Statistical analysis

All statistical analysis was performed using SPSS 17.0 and graph pad prism 7.0. Unpaired students t test was used to compare two groups and p value less 0.05 was considered statistically significant throughout the study (95% confidence Interval).

QOL Valuation

Health related quality of life in both the groups was assessed using a structured and validated questionnaire (RAND SF-36). The RAND-SF36 is a general questionnaire for measuring the influence of health related Qol (physical, psychological and social aspects). The RAND-36 health survey contains 36 questions in 8 domains, which includes physical functioning (5 items), Physical health (4 items), Emotional problems (3 items), Energy/Fatigue (4 items), Emotional well being (5 items), Social functioning (2 items), Regarding Pain (2 items), General health (6 items). For each domain there is a minimum score of 0 and a maximum score of 100.

3. Results

Overall 120 patients were enrolled in to the study based on the inclusion and exclusion criteria. All 120 patients were randomized into 2 groups depending on the treatment they received; Group 1(G1)-conservative therapy and Group 2(G2) - Tamsulosin added therapy. The main outcome measures were spontaneous passage of stones, colicky (using VAS) and health related quality of life (using RAND SF36 health survey 1.0). A majority of the study participants were male in both the groups (G1 -85% and G2-80%). The mean (\pm SD) age of the patients was 39.6 ± 8.1 years (range 21-57) and 44.3 ± 8.2 (range 21-59) years in group 1 and group 2 respectively. A majority of the patients were in the age range 39-48 years (G1-60% and G2-52%) followed by 29-38 (22%) in group and 49-58 (28%) in group 2. Age wise distribution is illustrated in table 1. Statistically significant difference in age ($P=0.0013$) was observed between the groups. About 54% of the study participants suffered from hypertension in group 1, whereas surprisingly none had hypertension as a co-morbidity in group 2. Most of the patients in group 2 (61%) had diabetes mellitus whereas only 25% had DM in group 1.

Table 1: Comparison of mean±SD values of age, diameter of stone (mm) and spontaneous passage of stone between group1 and group 2.

DISTRIBUTIONS	Group 1 (n=60)	Group 2 (n=60)	P-VALUE
AGE (years)	39.6±8.1	44.3± 8.2	0.0013**
Spontaneous stone expulsion (days)	18.25±8.30	15.06±6.7	0.20
Diameter of the stone (mm)	7.9±3.2	7.9±3.2	<0.001***
VAS Score	8.7±1.8	7.4±1.3	<0.0001

The diameter of the stone ranged from 5-11mm in either group. The mean ± SD duration for stone expulsion time was 18.25±8.30, 15.06±6.7 and 16.65±7.75 days in group 1, group 2 and overall study participants respectively. Overall a majority of the patients spontaneously passed the stones in 3 weeks (47%) followed by 4 weeks (27%). This outcome was observed to be more in a shorter duration of time, post tamsulosin therapy among the group 2 patients. About 23% and 22% of the study participants in group 2 passed the stone spontaneously in the first week and second week respectively, where as in group 1 none and 4% of the patients had stone expulsion in the first and second week of the follow up. No Statistically significant difference (P=0.20) in spontaneous stone expulsion time was observed between the control and tamsulosin group figure 1.

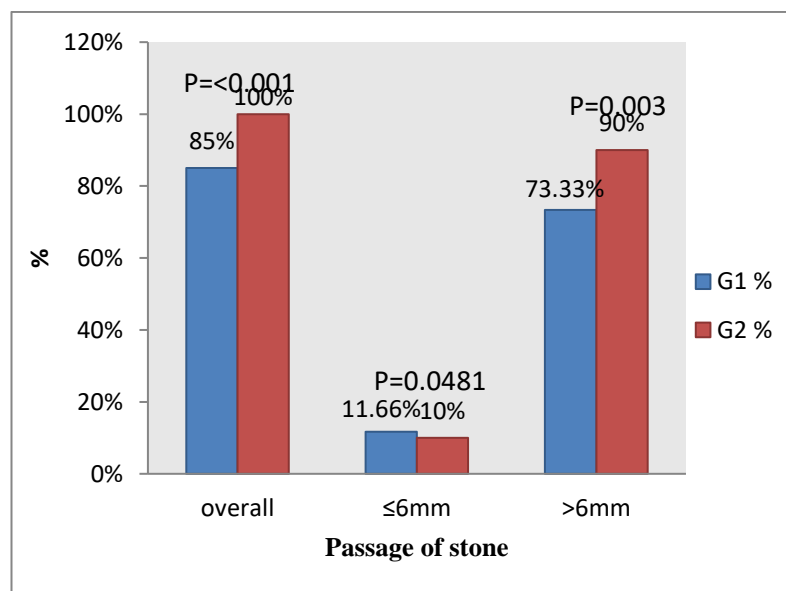


Figure 1. Distribution based on stone passage

When the groups were divided into two sub groups based on the diameter of the stone as being either 6mm or more than 6mm, the same results were obtained. Statistically significant difference in spontaneous passage of stone was observed in patients of both the groups with stone diameter measuring <6mm (P=0.0481) and >6mm (P=0.003). The intensity of pain was measured administrating the VAS score to each patient in both the group. It was observed that the VAS score was lesser in the patients receiving alpha 1 blocker (group 2) than the group receiving conservative therapy. The mean score of VAS score was found to be 8.7±1.8 and 7.4±1.3 in group 1 and group 2 respectively. A statistically significant difference in VAS score (P<0.0001) was observed between the groups figure 2. This shows that the intensity of pain was less in group 2 when compared to group 1 participants. Adverse Drug Reaction such as headache, dizziness, nausea and vomiting was observed in both the groups. However no major adverse reactions were reported. Drug Dechallenge or the medical intervention was not done as most of the ADR's were self limiting (figure 3).

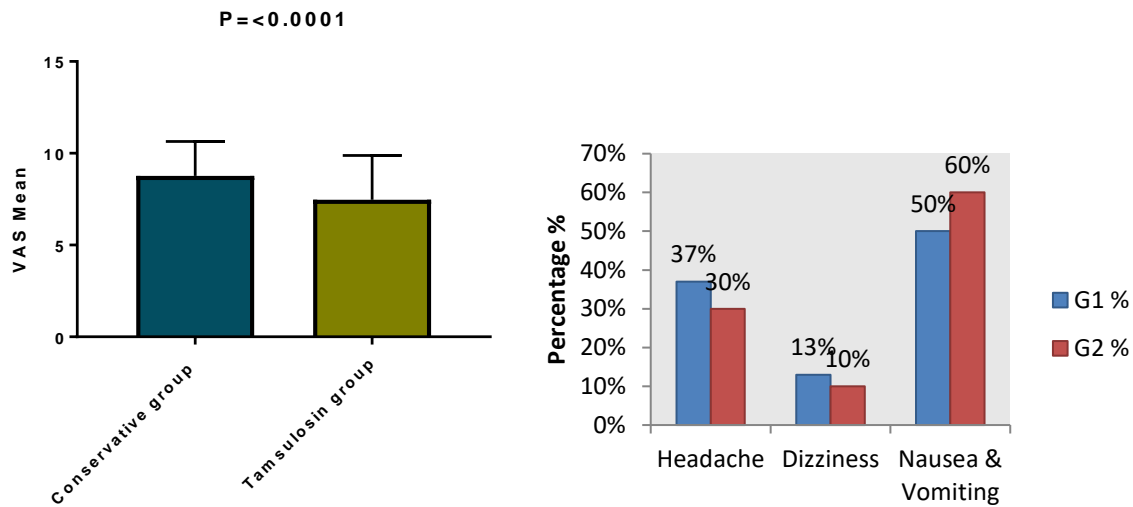


Figure 2. Distribution based on VAS Pain scale Figure 3. Distribution based on ADR

The health related quality of life was assessed in both tamsulosin and conservative group where tamsulosin group showed an improved quality of life in all the domains Physical Functioning (group1- 31.25%, group 2- 23.85%), Role of limitations due physical health (group1- 2.08% and group 2-56.25%), Role of limitations due to emotional problems(group1-0.55% and group 2-11.66%), Emotional Functioning (group1-15.52% group 2- 16.31%), Emotional well being (group 1-19% and 20.4%), Social functioning (group 1-26.04% and group 2- 28.3%), Pain(group 1-6.5% and group 2-9.6%), General health (group 1-15.91% and group 2-21.16%);(Figure 4).

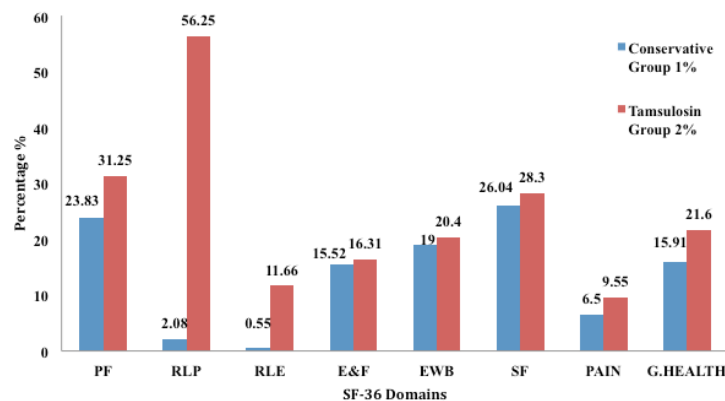


Figure 4. Overall domain scores

Note: PF-Physical Functioning, RLP- Role of limitations due to Physical Functioning, RLE- Role of limitations due to emotional functioning, EWB- Emotional Well Being, E&F-Energy & Fatigue, SF- Social Functioning, G.H-General Health

The Quality of life based on physical health showed a significance difference of ($P=0.003$) between the groups. The role of limitations due to physical health, The Role of limitation due to emotional problems and pain showed a significance difference of ($p<0.0001$) between the groups. However, social functioning and emotional well being showed a non-significant difference of ($p=0.40$) between the groups. On further analysis of the scores of general health and energy level between the groups showed a significant difference of ($p=0.0001$) and ($p=0.004$). These results provided the advantage of tamsulosin on the ureter probably by decreasing the peristaltic contraction table 2.

Table 2 : SF-36 domain score comparison

Domain	PF	RLP	RLE	EWB	E&F	SF	Pain	G.H
Group1 %	23.83	2.08	0.55	19	15.52	26.04	6.5	15.91
Group 2 %	31.25	56.25	11.66	20.4	16.31	28.3	9.55	21.6
P-VALUE	<0.003**	<0.0001***	<0.0001***	0.221	0.310	0.425	<0.001**	<0.0001***

Note: PF-Physical Functioning, RLP- Role of limitations due to Physical Functioning, RLE- Role of limitations due to emotional functioning, EWB- Emotional Well Being, E&F-Energy & Fatigue, SF- Social Functioning, G.H-General Health

4. Discussion

The recent advances like shock wave lithotripsy and its advances have hugely distracted the way of treating ureteral stones[1]. Widely, open surgeries and ureteroscopy are performed. However majority of the stones can pass spontaneously where these above mentioned invasive interventions are not usually obligatory. There are several literatures supporting the spontaneous passage of calculi for that measuring less than 4 mm in diameter, which can be managed with conservative therapy [2]. Ureteral stones placed in the proximal part of the ureter measuring more than 6mm have 5 % or lesser possibility for the spontaneous passage [4]. Although the calculi situated in the distal region has a 50% of possibility for its spontaneous passage and will be expelled within 10-15 days [9].

The uncontrollable colic is usually due to strain on muscular nerve endings, which leads to increased intra-luminal pressure creating an inability in ureteral peristalsis to move the urine distal, to the stone obstruction [8]. Several studies state that alpha-1 receptors are more prevalent in the ureteral smooth muscles. Hence it has been proposed that the blockade of the alpha-1 receptor will reduce the ureteral peristalsis with an ultimate lowering of intra-luminal pressure and its rise in ability of urinal flushing [10–12]. Therefore the use of alpha 1 receptor blocker is considered to be safe in stone expulsion Ukhal et al were the first to report the use alpha 1 receptor blocker with a positive approach in treating distal ureteral stones [13]. Cervenakov & colleagues[14] in their randomized study registered a significant advantage in tamsulosin added stone expulsion rate.

Dellabella et al [15] found a major efficacy of tamsulosin when compared to phloroglucan a spasmolytic drug used in Italy. These authors remarkably came out with an advantage of tamsulosin therapy with increased intraureteral pressure around the stone and further inducing the expulsion. Fascinatingly Dellabella et al [15] explained the advantage of tamsulosin therapy as a treatment with lesser pain. They reported that tamsulosin has a double action controlling the pain associated with ureteral colic, prevents the spasm and it also has an effect on sympathetic postganglionic neurons which blocks the pain conduction in central nervous system. Yilmaz et al[16] performed a randomized comparison of three alpha 1 blockers in treating distal ureteral stones, where 114 patients were enrolled in receiving Tamsulosin, Terazosin or Doxazosin for equally one month duration, surprisingly all the three agents were equally efficacious.

The current study investigated efficacy of tamsulosin as an alpha-blocker drug that provoke the relaxation of smooth muscles and which increase the spontaneous passage of stone. As reported earlier[14] in one of the randomized study spontaneous passage of stone was observed in 80.4% of patients who received alpha 1 blocker when compared to the group of patients 62.8% without the alpha 1 blocker. They reported the statistical significant difference in stone expulsion between the groups. In this study we found that 51(85%) out of 60 patients in group 1 and whole 60 (100%) in group 2 spontaneously passed the stones in first four weeks. The results obtained demonstrated a statistically significant difference of $P<0.001$ between the conservative group and Tamsulosin added group.

The aim of treating ureteral stones or renal stones is to ease out pain and relieve ureteral obstruction with the help of non-steroidal anti inflammatory drugs which are mostly being used today [17]. Several clinical studies state that the use of spasmotic drugs is useful in removing the ureteral spasm and further promoting the urinal out flow [18].¹⁷ From this study we observed that the Tamsulosin therapy and conservative therapy are effective when considering VAS score and mean ureteral colic among the study population. The mean frequency score was significantly lower in tamsulosin group than in conservative group. The efficacy of tamsulosin in reducing ureteral colic, decreasing the intra-ureteral pressure and increasing the stone expulsion rate is evident from the study observations. Dellabella et al [15] revealed that the tamsulosin therapy provides relief in ureteral colic pain, with significantly lesser use of analgesic.

Finally the health related quality of life was compared between the groups which provided a significant difference proving the advantage of tamsulosin added therapy to the conservative therapy with lesser adverse effect and good health related quality of life creating a positive profile in beneficial of the use of alpha 1 blocker in the distal ureteral calculi.

5. Conclusion

A conservative approach can be considered as an option in the treatment of uncomplicated distal ureteral stones. From this study we observed that the tamsulosin therapy is proved to be safe as conservative therapy and effective as demonstrated by the stone expulsion in the treatment group. Tamsulosin treatment benefits by shorter stone expulsion time, increased expulsion rate and improved quality of life by means of ureteral colic. Tamsulosin therapy was not superior over conservative therapy, but the efficacy in spontaneous stone expulsion was observed to be more with tamsulosin treatment. The use of specific alpha 1 blocker (tamsulosin) can be recommended for its higher efficacy and minimal side effects in the management of uncomplicated distal ureteral calculi when compared to advanced techniques like lithotripsy and ureteroscopy.

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