

# Comparison of Therapeutic Efficacy and Safety of Combination Therapy of Antimuscarinic Drugs and Alpha Blockers Versus Mono Therapy in the Treatment of Urolithiasis in A Tertiary Care Hospital, Bangalore, India

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## Abstract

**Objective:** This study aimed to compare the efficacy of combination therapy of alpha blockers and anti-muscarinic versus mono therapy in treatment of urolithiasis. **Methodology:** The study on the comparison of the combination therapy of anti muscarinics and alpha blockers versus monotherapy in the treatment of urolithiasis was conducted in aster CMI hospital in Bangalore and was conducted in 150 patients. the study was conducted on inpatients admitted into the departments of medicine including nephrology, emergency medicine and general medicine. Patients receiving alpha blockers and anti muscarinics combination therapy and mono therapy in the treatment of urolithiasis. Structured data collection was used for collecting the details. **Result:** Among 150 patients 54 of them were prescribed with monotherapy with either alpha blockers or anti muscarinics that in the alpha blockers tamsulosin was prescribed 15 times, alfuzosin was prescribed 5 times and silodosin was prescribed 4 times. Also we were prescribed with mono therapy with either alpha blocker or anti muscarinics that in the anti muscarinics tolterodine was prescribed more which includes 24 times and oxybutynin was prescribed 6 times. **Conclusion:** the combination therapy of alpha blockers and anti muscarinics is significantly better than either drug alone in the treatment of urolithiasis, it was as well found that urolithiasis is more common among male patients which accounts for 72 % of the patients. In this study it was shown that the prescribed dose of tamsulosin is 0.4 mg and tolterodine is 4 or 2 mg depending on the size or type of stone present. It was shown that the maximum patients were prescribed with tolterodine in their monotherapy which is 50 % of total and tamsulosin was prescribed for 31% of the patients in monotherapy and according to previous studies, tolterodine reduced urinary symptoms and improved general health in patients but in general there was no significant difference between them.

**Keywords:** urolithiasis, combination therapy, mono therapy, alpha-blockers, anti-muscarinics

## Introduction

It is the process of forming stones in the kidney, bladder, and/or urethra (urinary tract). Kidney stones are a common cause of blood in the urine and pain in the abdomen, flank, or groin. Kidney stones occur in 1 in 20 people at some time in their life. The development of the stones is related to decreased urine volume or increased excretion of stone-forming components such as calcium, oxalate, urate, cysteine, xanthine, and phosphate. The stones form in the urine collecting area (the pelvis) of the kidney and they may range in size from tiny to staghorn stones the size of the renal pelvis itself. The majority of the stones pass spontaneously within 48 hours, however, some stones may not pass. There are several factors which influence the ability to pass a stone. These include the size of the person, prior stone passage, prostate enlargement, pregnancy, and the size of the stone (Shekarriz and Stoller, 2001).

The epidemiology of urolithiasis differs according to geographical area in term of prevalence and incidence, age and sex distribution, stone composition and stone location. Such differences have been explained in terms of race, diet and climate factors. Furthermore, changing socio-economic conditions have generated changes in the prevalence, incidence and distribution for age, sex and type of lithiasis in terms of both the site and the chemical-physical composition of the calculi. Epidemiological surveys have been previously reviewed showing that in economically developed countries the prevalence rate ranged between 4% and 20% (Trinchieri, A2008).

Renal stones are thought to be caused by abnormalities in urine environment, namely, an imbalance between promoters and inhibitors of stone formation. This in turn depends on abnormalities of the most relevant urine constituents. Therefore, the medical management is aimed at normalizing these derangements, to reduce the risk of forming new stone. This is accomplished by either reducing urine state of

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saturation with respect to a given salt or increasing urine inhibitor activity, or both (Lopes et al., 2001).

Many papers have recently been published supporting the efficacy of medical expulsion therapy with alpha-adrenoceptor antagonists or calcium channel antagonists. Among the former, tamsulosin was shown to increase the rate of spontaneous stone passage by approximately 50% for small distal stones. In a randomized perspective study in patients with distal ureteral stones, tamsulosin gave an expulsion rate of 97.1% vs 77.1% of nifedipine ( $p < 0.0001$ ). These patients achieved stone passage in a shorter time and showed a significantly decreased number of hospitalizations and endoscopic procedures. Alone or in association with NSAIDs, tamsulosin also appeared to decrease the severity of renal colic (Scales et al., 2012; Chew et al., 2004). This issue was addressed in a recent review of papers reporting expulsion facilitation of moderately sized, distal, ureteral stones. Treatments with alpha-antagonists or calcium-channel blockers were compared to a standard therapy group in studies that reported stone expulsion rates. A pooled analysis of 16 studies using an alpha-antagonist and 9 studies using a calcium-channel blocker suggested that the addition of each of these agents, compared to standard therapy, significantly improved spontaneous stone expulsion (relative risk 1.59 vs 1.50 and number needed to treat 3.3 vs 3.9, for alpha-antagonists and calcium channel blockers, respectively). Subgroup analysis of trials using concomitant medications such as low-dose steroids yielded a similar improvement in stone expulsion rate. Adverse effects were only minor and rare. It was concluded that expulsive therapy, using either alpha-antagonists or calcium channel blockers increased the stone expulsion rate (Singh, Alter and Littlepage, 2007; Cervenakov, 2002).

It has been reported that obstruction and infection, connected to invasive urological procedures, were the major causative factors of renal insufficiency in patients with recurrent stone disease. The occurrence of renal insufficiency has been likely abated with the use of modern non-invasive procedures, but attention should still be paid to the association between obstruction and infection, which represents a threat for the development of urosepsis. When a patient with renal colic is suspected to progress to this dangerous complication, he should urgently be referred to a urologist in order to remove the obstruction, either temporarily (ureteral stenting) or ultimately (ureteroscopic ESWL, ureterolitholapaxy) (Marangella et al., 1990; Daudon et al., 2003).

## Materials and Methods

Study was conducted at tertiary care hospital and was conducted in 150 patients. Eligible patients were enrolled based on inclusion and exclusion criteria. Structured data collection was used for collecting the details. This form mainly contains demographic details, social habits, current medication, past medical and medication history, laboratory investigations, and other relevant data needed for present study were collected from patient's progress records, treatment chart, and laboratory reports. The data collected are subjected for various drug-drug interaction and ADR by using, primary (Micromedex), secondary and tertiary resources which are available in clinical pharmacy department. The collected information was documented and subjected for assessment using suitable statistical method. Descriptive statistical analysis has been carried out in the present study. Simple percentage calculations were used and expressed using charts and graphs.

## Result and Discussion

The study on the comparison of the combination therapy of anti muscarinics and alpha blockers versus monotherapy in the treatment of urolithiasis was conducted in aster cmi hospital, the study was conducted on inpatients admitted into the departments of medicine including nephrology, emergency medicine and general medicine. In our study we included 150 number of patients of different age group who got admitted to the hospital due to various complaints. Among them 15% were of 13-23 years of age, 27% were of 24-34 years, 11% were of 35-45 years, 20% were of 46-56 years, 18% were of 57-67 years, 8% were of 68-78 years and 1% were of 79-89 years of age. From our study, we found that mostly male patients are admitted which includes 72% and the female patients includes 28% of the total. From the study we found that majority of the patients were prescribed by combination therapy which includes 65% and the rest of the patients were given monotherapy treatment which is 35% of the total. Most of the patients who presented to the hospital were associated with other diseases also, such situation is called as Co-morbidity.

Among the 150 patients which were admitted 127 of them were present with past medical history in which 43 of them were having history of diabetes mellitus, 12 patients were having UTI, 22 patients with history of HTN, 10 patients with history of dyslipidemia, 3 patients with history of anxiety, 2 patients with history of anemia, 4 patients with history of hepatitis B and 2 patients with history of thyroid dysfunction. Among the study, 54 of patients were prescribed with monotherapy with either alpha blockers or anti muscarinics that in the alpha blockers tamsulosin was prescribed 15 times, alfuzosin was prescribed 5 times and silodosin was prescribed 4 times. Among 150 patients 54 of them were prescribed with mono therapy with either alpha blocker or anti muscarinics that in the anti muscarinics tolterodine was prescribed more which includes 24 times and oxybutynin was prescribed 6 times.

Table 1: Investigation of patient

TYPE OF INVESTIGATION	NUMBER OF PATIENTS
Uteroscopy	3
cystoscopy	4
serology	8
PT INR	12
ECG	5
RP 2	4
CT scan KUB	62
USG KUB	38
CBC	5
ECHO	3
DTPA scan	6
TOTAL	150

Among 150 patients presented to the hospital majority of the were diagnosed with CT scan KUB which includes 62 of them and 38 patients were diagnosed by USG KUB, 12 of them were diagnosed with PT INR, 8 of them were diagnosed with serology, 6 of them were diagnosed by DTPA scan, 5 of them with CBC, 5 of them with ECG, 4 of them with cystoscopy, 3 of them with uteroscopy and 3 of them were diagnosed with ECHO. Table 1

Table 2: Most commonly prescribed discharge medication

NAME OF DRUG	NUMBER OF PATIENTS
Pantoprazole	82
Tramadol+Acetaminophen	80
Prulifloxacin	63
Pyridoxine+Mg citrate	7
Citric acid +Potassium citrate	33
Faropenem	11
Trypsin+Chymoripsin	4
Nitrofurantoin	7
Ofloxacin	3
Cefuroxime	9
Levofloxacin	3
Meropenem	5
Tamsulosin+Tolterodine	96
Alfuzosin	5
Tamsulosin	15
Silodosin	4
Tolterodine	17
Oxybutynin	4

Among 150 patients who were presented to the hospital , all of them were prescribed with discharge medications , the most common medications prescribed were pantoprazole which accounts for 82 of the patients , the combination tablet of tramadol and acetaminophen which is 80 of the patients , prulifloxacin was prescribed 63 times , the combination of citric acid and potassium citrate was prescribed 33 times , faropenem was prescribed 11 times , the combination of pyridoxine and mg citrate was given 7 times , nitrofurantoin was prescribed 7 times , cefuroxime was prescribed 9 times , oxybutynin was prescribed 4 times , tolterodine was prescribed 17 times ,

silodosin was prescribed 4 times , tamsulosin was prescribed 15 times , alfuzosin was prescribed 5 times , the combination of tolterodine and tamsulosin was prescribed 96 times , meropenem was prescribed 5 times , levofloxacin was prescribed 3 times , ofloxacin was prescribed 3 times and the combination of trypsin and chymoripsin was prescribed 4 times .Table2

In the combination therapy the dosage prescribed is either 4 mg or 2 mg which is tamsulosin 0.4 mg + tolterodine 4 mg and tamsulosin 0.4 mg + tolterodine 2 mg respectively. Table 3

Table 3: Dosage regimen in combination therapy

NAME OF DRUG	DOSAGE
<b>Tamsulosin + tolterodine</b>	0.4 mg + 2 mg
<b>Tamsulosin + tolterodine</b>	0.4 mg + 4 mg

in monotherapy the dosage prescribed is alfuzosin 10 mg is 10%, tamsulosin 0.4 mg is 31%, tolterodine 4 mg is 50% and silodosin 8 mg is 9%. table 4

Table 4: Dosage regimen in monotherapy

NAME OF DRUG	DOSAGE	NUMBER OF PATIENTS	PERCENTAGE
<b>Alfuzosin</b>	10 mg	5	10%
<b>Tamsulosin</b>	0.4 mg	15	31%
<b>Tolterodine</b>	4 mg	24	50%
<b>Silodosin</b>	8 mg	4	9%
<b>Total</b>		48	100%

It was shown that most of the patients were prescribed with combination therapy which was 65 % and 35 % were prescribed with monotherapy , and also according to the reviewed literatures preferably combination therapy is chosen over monotherapy due to improved ureteral stent related complications , QOL , reduced analgesic use and irrigative symptoms , reduced flank pain , voiding pain and improved sexual life , spontaneous stone passage through ureter was more and faster stone explosion time was seen in combination therapy patients than in patients with monotherapy.

## Conclusion

The present study revealed that the combination therapy of alpha blockers and anti muscarinics is significantly better than either drug alone in the treatment of urolithiasis, as observed in the study the majority of the patients were prescribed with the combination therapy which accounts for 65 % of the patients. It was as well found that urolithiasis is more common among male patients which accounts for 72 % of the patients. that most common prescribed discharge medication was pantoprazole which is 82 of the patients in order to reduce acidity produced by other concurrent medications administration and 80 of them were prescribed with combination of tramadol + acetaminophen as their pain killers due to unbearable pain of urolithiasis. In this study it was shown that the prescribed dose of tamsulosin is 0.4 mg and tolterodine is 4 or 2 mg depending on the size or type of stone present. It was shown that the maximum patients were prescribed with tolterodine in their monotherapy which is 50 % of total and tamsulosin was prescribed for 31% of the patients in monotherapy and according to previous studies, tolterodine reduced urinary symptoms and improved general health in patients but in general there was no significant difference between them.

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