

## MEDICAL EXPULSIVE THERAPY- AN EFFECTIVE TREATMENT OPTION FOR LOWER URETERIC CALCULI

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### ABSTRACT

#### BACKGROUND

This is a prospective randomized trial to study the efficacy of medical expulsive therapy for lower ureteric calculi. Ureteral stones are a global health issue. Almost 20% of urinary tract stones are found in the ureter with majority (70%) being located in the lower third of the ureter.

#### MATERIALS AND METHODS

Patients diagnosed with lower ureteric calculi in the Department of Surgery, People's College of Medical Sciences and RC, Bhopal were included in this study. The study comprised of 180 patients which were randomly divided equally into three groups. Patients in the first group were subjected to conservative management; silodosin was added to those in the second group and patients in the third group were administered a combination of silodosin and deflazacort.

#### RESULTS

A statistically significant stone expulsion rate was seen in group 3 as compared to group 1 and 2.

#### CONCLUSION

Medical expulsive therapy with alpha-blockers (Silodosin) and corticosteroids (Deflazacort) is effective for management of lower ureteric calculi and avoids surgical intervention in many patients.

#### KEY WORDS

Lower Ureteric Calculi, Medical Expulsive Therapy.

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#### BACKGROUND

Ureteral stones are a global health issue. Almost 20% of urinary tract stones are found in the ureter with majority (70%) being located in the lower third of the ureter.

The normal ureter has three distinct sites of narrowing namely the ureteropelvic junction, crossing of the iliac vessels and the ureterovesical junction. There is no intrinsic change in the ureteral caliber at first two locations. However, the ureterovesical junction has true physical restriction of the ureter as it makes the intramural passage through the bladder wall to the ureteric orifice. These three sites of ureteral narrowing are clinically significant because they are common locations for urinary calculi to lodge during passage.

The ureter contains both  $\alpha$  and  $\beta$  adrenergic receptors. Three different subtypes of  $\alpha$  receptors have been pharmacologically identified:  $\alpha 1a$ ,  $\alpha 1b$ , and  $\alpha 1d$ . The highest density of  $\alpha 1a$  receptor binding sites was detected in the distal ureter. The distribution of  $\alpha$  receptors throughout the inner and outer smooth muscle of the ureter was highest for  $\alpha 1d$ , especially in the distal ureter, followed by  $\alpha 1a$  and  $\alpha 1b$ .<sup>[1,2,3,4]</sup>

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#### MATERIALS AND METHODS

A prospective and randomized control study of 180 consecutive patients visiting the Department of Surgery, PCMS & RC, Bhopal over a period of 1 year (Jan 2016 to Dec 2016) that fulfilled the study criteria. 180 patients were randomly divided equally in three groups by computer generated numbers. Patients in the first group were subjected to conservative management, silodosin was added to those in the second group and patients in the third group were administered a combination of silodosin and deflazacort.

#### Groups

1. Conservative supportive treatment (Control group).
2. Medical expulsive therapy, group 1 (Silodosin 8 mg).
3. Medical expulsive therapy, group 2 (Silodosin 8 mg with deflazacort 30 mg.)

#### Inclusion criteria

Age 15 to 65 years, stone size  $\leq 10$  mm in lower ureter.

#### Exclusion criteria

Presence of multiple stones, pregnancy, congestive cardiac failure, chronic renal failure grade III/IV/V, pyonephrosis, diabetes mellitus, any anatomical abnormalities (obstructive megaureter, vesico-ureteric reflux, ureterocele), previous history of steroid intake, previous history of surgery for urolithiasis, bilateral stones.

#### Source of Data

Clinical examination, laboratory/ radiology investigations, medical literature.

**Study Tools**

Detailed history, clinical examination, skiagram and ultra-sonogram of KUB region.

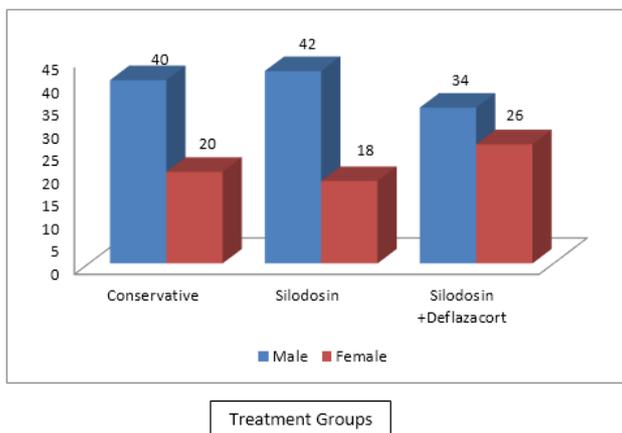
**Statistical Analysis**

The software used for statistical analysis is 22.0 and data was analysed using One-Way ANOVA test & Fisher’s exact between the groups and P < 0.001 was considered significant.

**RESULTS**

	Male	Female	Total	p-Value
Conservative	40 (66.6%)	20 (33.3%)	60 (33.3%)	< 0.001
Silodosin	42 (69.3%)	18 (30%)	60 (33.3%)	
Silodosin +Deflazacort	34 (56.1%)	26 (42.9%)	60 (33.3%)	
	116 (64.4%)	64 (35.5%)	180 (100%)	

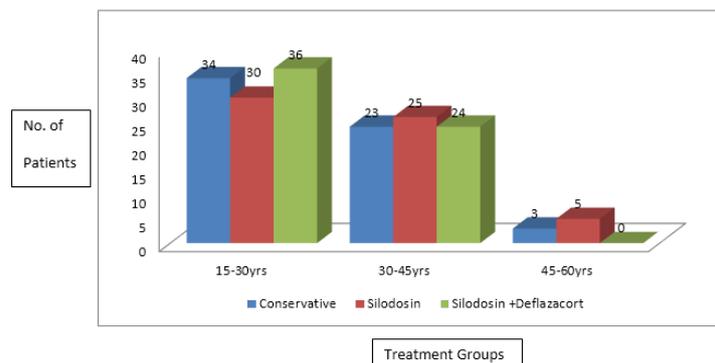
**Table 1. Distribution of Patients According to Gender in Different Treatment Groups**



Inference- Distribution of patients was done randomly. Number of male patients in conservative, silodosin, and silodosin + deflazacort group were 40, 42, and 34 respectively whereas number of female patients were 20, 18, and 26 in three respective groups.

	15-30 Yrs.	30-45 Yrs.	45-60 Yrs.	Total No. of Patients	p-Value
Conservative	34 (56.1%)	23 (38.3%)	3 (5%)	60 (33.3%)	< 0.001
Silodosin	30 (50%)	25 (41.6)	5 (8.3%)	60 (33.3%)	
Silodosin +Deflazacort	36 (60%)	24 (40%)	0	60 (33.3%)	
Total	100 (55.5%)	72 (40%)	8 (4.4%)	180 (100%)	

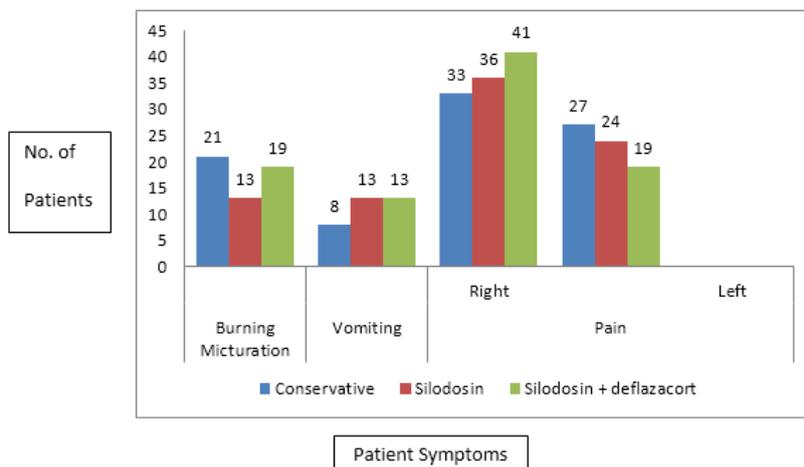
**Table 2. Age Distribution of Patients in Different Treatment Groups**



Inference- Out of 180 patients, maximum number of patients treated between 15-30 yrs. that is 100 patients in which conservative group had 34 patients in age group 15 -30 yrs., 23 patients in 30-45 yrs. age group, 3 patients in 45-60 yrs. age group. In age group 30-45 yrs; there were 72 patients out of which we had 23 patients in conservative group, 25 patients in silodosin group and 24 patients in silodosin + deflazacort group. In age group 45-60 yrs., there were total of 8 patients, 3 patients in conservative group and 5 patients in silodosin group respectively.

	Burning Micturition	Vomiting	Pain	
			Right	Left
Conservative	21	8	33	27
Silodosin	13	13	36	24
Silodosin + Deflazacort	19	13	41	19

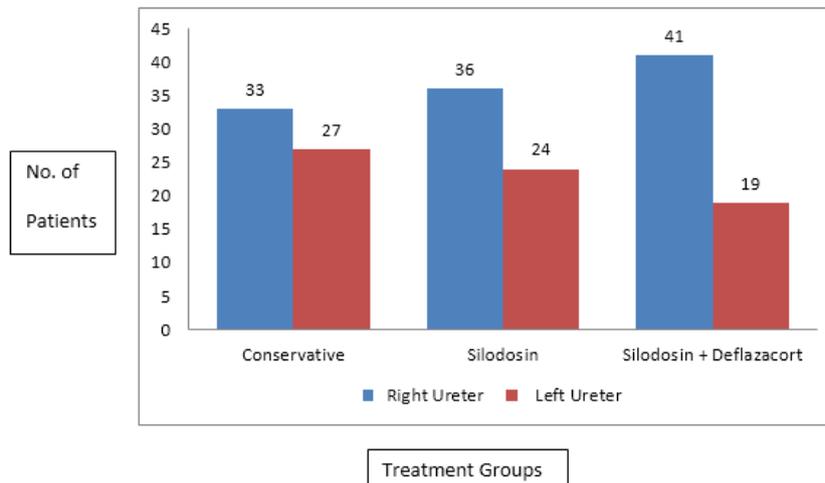
**Table 3. Distribution of Patient Symptoms in Different Treatment Groups**



Inference- Patients mainly presented with symptoms like burning micturition and vomiting. In conservative group 21 patients had burning micturition whereas 8 patients had complaint of vomiting. Similarly, 13 patients in silodosin group and 19 patients in silodosin + deflazacort group had burning micturition whereas 13 and 13 patients had vomiting in two respective groups. Out of total 180 patients 33, 36, and 41 patients presented with right iliac fossa pain in three consecutive groups, whereas left iliac fossa pain was present in 27, 24, and 19 patients.

	Right Ureter	Left Ureter
Conservative	33	27
Silodosin	36	24
Silodosin + Deflazacort	41	19

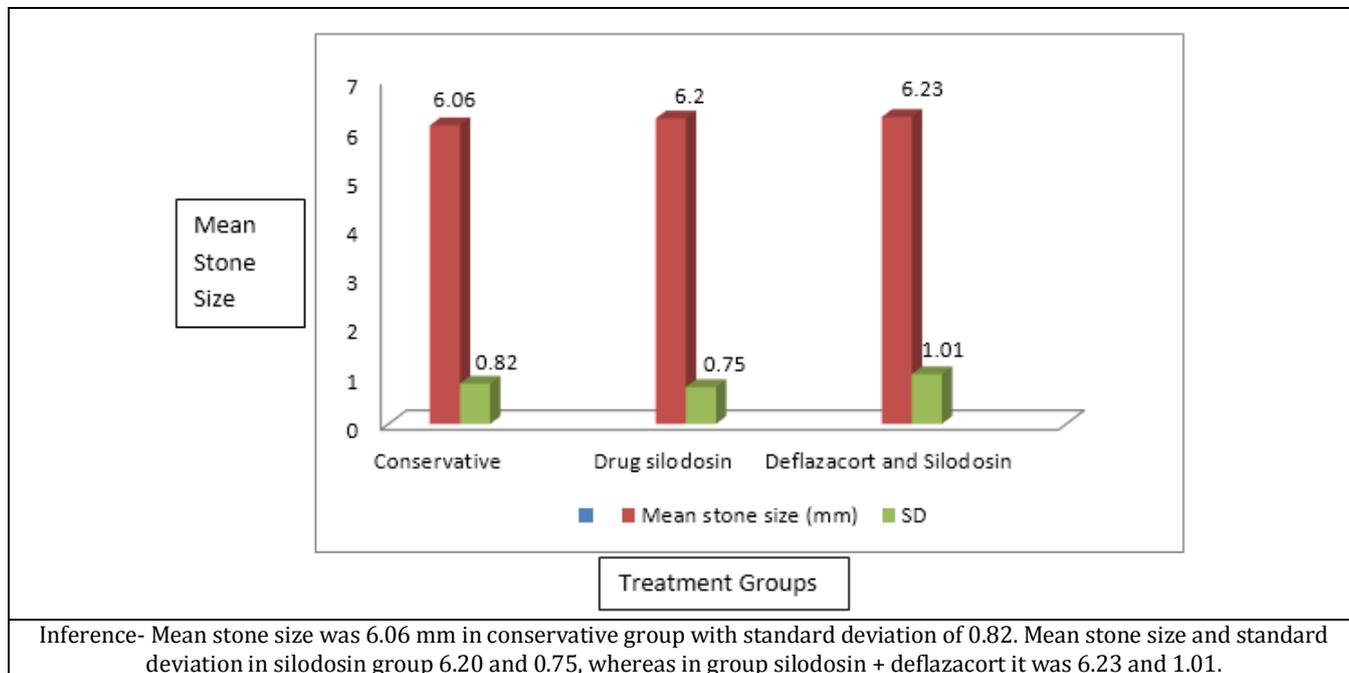
**Table 4. Site Wise Distribution of Stone in Different Treatment Groups**



Inference- Out of 180 patients, 110 patients were having stone in right lower ureter, and remaining 70 had stone in lower left ureter.  
 In conservative group, 33 patients had stone in right lower ureter whereas 27 patients had stone in left lower ureter.  
 In silodosin group, 36 patients had stone in right ureter and 24 in left ureter.  
 Silodosin + deflazacort group had 41 patients with right ureteric stone and 19 patients with left ureteric stone.

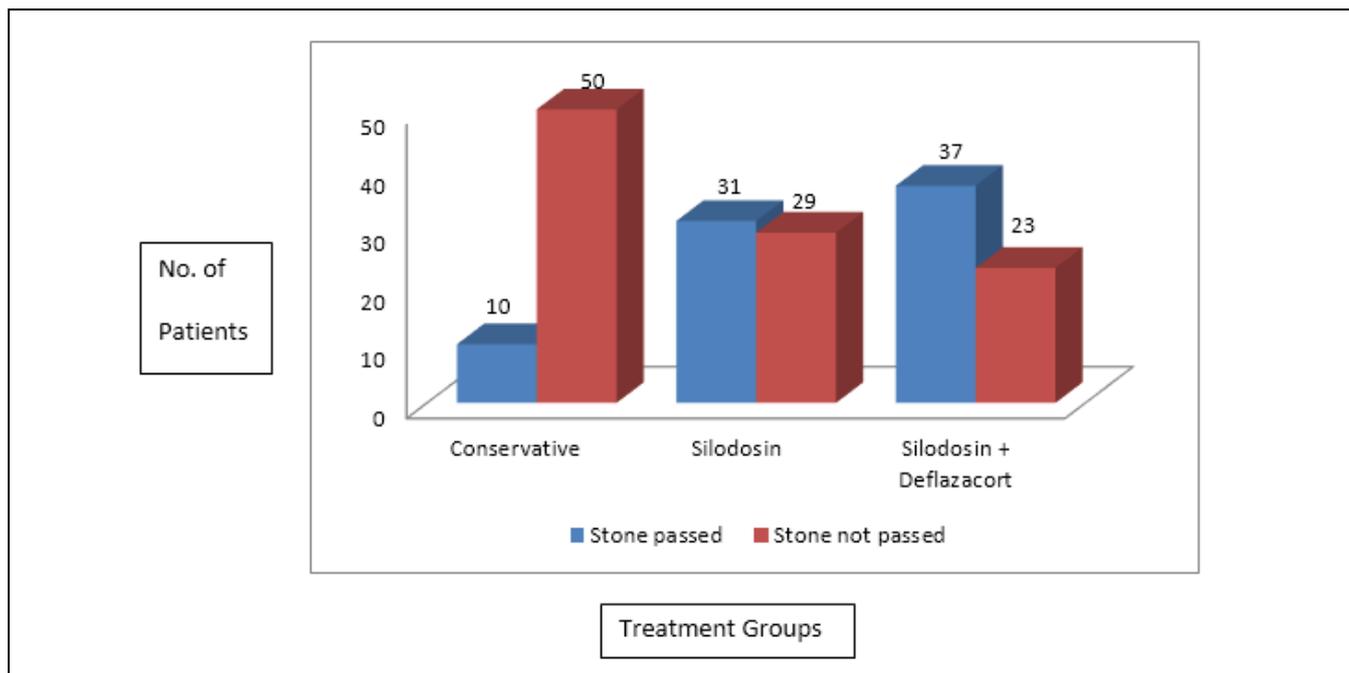
	n	Mean Stone Size (mm)	SD	Range	p-Value
Conservative	60	6.06	0.82	5.85-6.27	< 0.001
Drug Silodosin	60	6.20	0.75	6.05-6.39	
Deflazacort and Silodosin	60	6.23	1.01	5.97-6.49	

**Table 5. Mean Size of Stone in Different Treatment Groups**



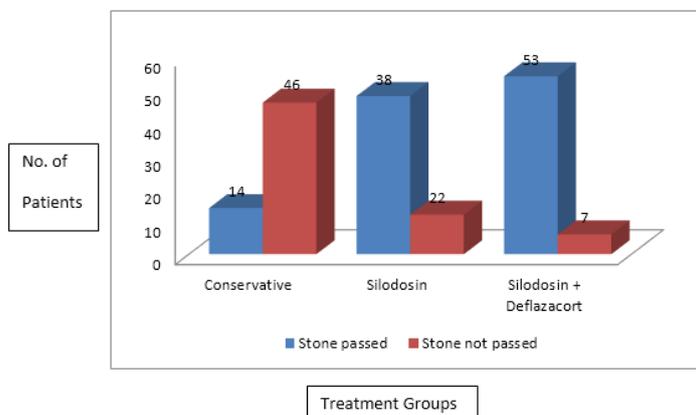
	Conservative		Silodosin		Silodosin + Deflazacort		p-Value
	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	
Stone Passed	10	16.66%	31	50.8%	37	61.6%	< 0.001 (Combination vs Conservative) 0.22 (Combination vs Silodosin)

**Table 6. Number of Patients Which Passed Stone Until 7<sup>th</sup> Day of Treatment**



	Conservative		Silodosin		Silodosin + Deflazacort		p-Value
	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	
Stone Passed	14	23%	38	63%	53	88%	< 0.001 (Combination vs Conservative) 0.001 (Combination vs Silodosin)

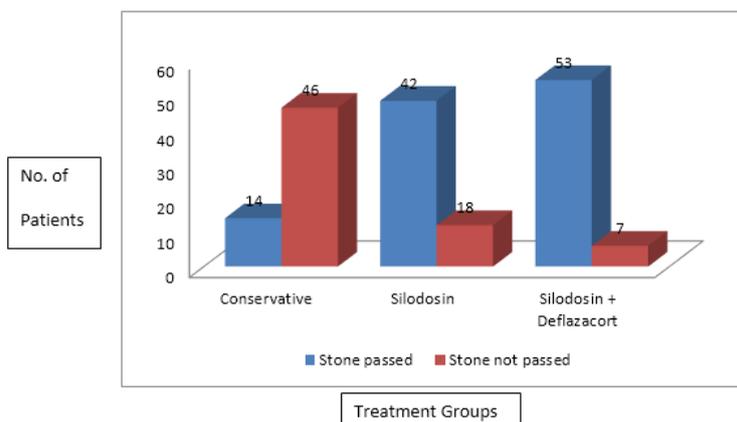
**Table 7. Number of Patients Which Passed Stone Until 14<sup>th</sup> Day of Treatment**



Inference- In conservative group out of 60 patients 14 (23.0%) patients had passed stone till 14th day. 38 (63.0%) patients passed stone in silodosin group where as 53 (88.0%) patients in silodosin + deflazacort group had passed stone till 14th day.

	Conservative		Silodosin		Silodosin + Deflazacort		p-Value
	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	
Stone Passed	14	23.0%	42	70.0%	53	88.0%	< 0.001 (Combination vs Conservative) 0.01 (Combination vs Silodosin)

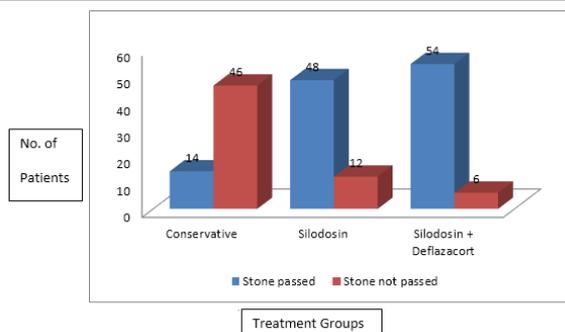
**Table 8. Number of Patients Which Passed Stone Until 21<sup>st</sup> Day of Treatment**



Inference- In conservative group out of 60 patients 14 (23.0%) patients had passed stone till 21st day. 42 (70.0%) patients passed stone in silodosin group where as 53 (88.0%) patients in silodosin + deflazacort group had passed stone till 21st day.

	Conservative		Silodosin		Silodosin + Deflazacort		p-Value
	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	No. of Patients (n)	% of Patients	
Stone Passed	14	23.0%	48	76.0%	54	90.0%	< 0.001 (Combination vs Conservative) 0.04 (Combination vs Silodosin)

**Table 9. Number of Patients Which Passed Stone Until 28<sup>th</sup> Day of Treatment**



Inference- In conservative group out of 60 patients 14 (23.0%) patients had passed stone till 28th day. 48 (76.0%) patients passed stone in silodosin group where as 54 (90%) patients in silodosin + deflazacort group had passed stone till 28th day. The P value is less than 0.001 between silodosin and silodosin + deflazacort. Therefore, it is considered to be statistically significant.

## DISCUSSION

Ureteric stones have emerged as a global health issue. Almost 20% of urinary tract stones are found in the ureter with majority (70%) being located in the lower third of the ureter. Medical Expulsive Therapy (MET) has its basis in several physiologic premises.

The ureter is lined by smooth muscle cells that respond to variations in calcium ion concentrations. An increase in calcium levels causes ureteric muscle contraction, conversely a decrease leads to relaxation. Furthermore, smooth muscle cells are densely populated with  $\alpha$ -1-adrenergic receptors, especially in the distal third of the ureter. Receptor blockade inhibits basal smooth muscle tone and hyper peristaltic uncoordinated frequency whilst maintaining tonic propulsive contractions.

MET has recently emerged as an alternative strategy for the initial management of small distal ureteral stones. The specific mechanism of action on the ureteral smooth muscle and the emerging evidence of the efficacy (Defined as either an increase in expulsion rate or a decrease in time to expulsion) and low-risk profile suggest that  $\alpha$ -adrenergic receptor antagonists ( $\alpha$ -blockers like silodosin) and calcium channel antagonists should be the initial medical treatment in patients amenable to conservative therapy.

Inflammation and edema pose a significant obstacle to the spontaneous passage of stones and anti-inflammatory drugs should be added. The most frequently used drugs in this context are corticosteroids, which are given in association with  $\alpha$ -1-adrenergic receptor antagonists and calcium-channel blockers because of their action of decreasing edema and inflammation and thereby facilitating the passage of the stone. MET should be offered as a treatment for patients with distal ureteric calculi who are amenable to a waiting management.

This study was conducted in People's College of Medical Sciences and Research Centre, Bhopal. A total of 180 patients with diagnosis of lower ureteric calculi were selected and were randomly divided into 3 equal treatment groups. 1st group comprising of 60 patients was managed with supportive and symptomatic therapy, whereas 2nd group comprising of 60 patients was given silodosin 8mg daily along with supportive medication. 60 patients of 3rd group were given silodosin and deflazacort in addition to symptomatic medication. Patients were followed up on 7th, 14th, 21st and 28th day for stone clearance and side effect of drugs.

Majority of the patients were in the age group of 15-30 years. Most of the studies have reported a male to female ratio between 3:1 and 2:1. In our study this ratio was 1.8:1. In the first group (Conservative) 66.6% (n=40) were male patients and 33.3% (n=20) were female patients.

In the second group (silodosin) male patients were 70% (n= 42) and females were 30.0% (n=18), in third group (Silodosin with deflazacort) male were 56.1% (n=34) and females were 42.9% (n=26).

Males are three times more likely to be afflicted for urinary stone disease. Men appear to excrete more oxalate in their urine and women excrete more citrate, that may explain low incidence of stone diseases in females. We had 110 patients with right lower ureteric calculi and 70 patients with left lower ureteric calculi. Most of the series found calculi with equal frequency on either side.

While alpha - blockers are currently the only recommended monotherapy, corticosteroids have received increased attention as a potential useful adjunct in the medical management of distal ureteric stones.

Medical expulsive therapy with alpha - blockers (Silodosin) is effective for management of lower ureteric calculi and avoids surgical intervention in many patients. Addition of a corticosteroid improves stone clearance rate significantly and hence addition of corticosteroid can be recommended as a standard medical expulsive therapy.

## CONCLUSION

1. Medical expulsive therapy with alpha-blockers (Silodosin) and corticosteroids (Deflazacort) is effective for management of lower ureteric calculi and avoids surgical intervention in many patients.
2. Silodosin alone or in combination with deflazacort significantly increases the stone expulsion rate of lower ureteric calculi in comparison to conservative management.
3. Silodosin alone or in combination with deflazacort also achieves earlier expulsion of stones from lower ureter as compared to conservative management.
4. Addition of deflazacort to silodosin apparently improves the stone clearance rate and decreases the time for stone expulsion.
5. Addition of deflazacort to silodosin improves the stone clearance rate and it is also statistically significant.
6. Addition of deflazacort beyond 14 days does not significantly increase stone expulsion rate.

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