



STUDYING THE EFFICACY OF SILODOSIN IN EARLY EXPULSION OF LOWER URETERIC CALCULI

Urology

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ABSTRACT

Aim: To study the role of silodosin augmentation along with the standard of care in management of lower ureteric calculus against standard of care alone.

Objectives: To observe the efficacy of silodosin in decreasing the time taken for the expulsion of stone. To observe the efficacy of silodosin in increasing the expulsion rate of stone.

Materials and methods: Patients presented to the Surgery OPD suggestive of renal colic were evaluated with history and physical examination. Ultrasound abdomen and pelvis, urinalysis and renal function tests were done. Patients with sonographic evidence of lower ureteric calculus of 4-8mm size were included in the study after consent. Patients were allotted to control-group A and cases-group B by simple randomization. Patients allotted in group A were given syrup citrate, tablet drotaverine 40mg and plenty of oral fluids. Patients allotted in group B were given tablet silodosin 4mg OD, syrup citrate, tablet drotaverine 40mg and plenty of oral fluids for a period of two weeks. Comparison of all variables was done using Z test and unpaired t test. P value less than 0.05 is considered significant.

Results: 124 patients (62 in group A+62 in group B) were studied from October 2019 to October 2021. Mean expulsion time in group A was 6.65+/-2.56 days and mean expulsion time in group B was 9.67+/-2.16 days. P value was <0.0001 which is statistically significant. Expulsion rate in cases was 88.7% and in control was 79.03% which was not statistically significant.

Conclusion: Silodosin is an efficacious drug for MET and decreases expulsion time in lower ureteric calculus of size 4-8mm.

KEYWORDS

Lower Ureteric Calculus, Silodosin, Medical Expulsion Therapy.

INTRODUCTION

Urolithiasis is a coalescence of crystals and salts formed in the kidney, impacting 12% of the population worldwide¹. It is associated with various complications when untreated, one of which being end stage renal failure². It has been documented since classical times³. It was once thought to be predominantly lower urinary tract disease with preponderance for males, however in recent times, the incidence and stone formation has shifted to upper urinary tract⁴. It is multifactorial with very high recurrence rates as much as 50% in 10 years⁵. The most common type of stone is calcium oxalate stone that is precipitated on the Randall's plaques, that are present on the renal papilla¹. Even though recent scientific techniques have made the stone removal as one of the easy procedures, there is still deficient learning and application to prevent recurrence or altering the course of the disease^{2,4}. Understanding the mechanism of formation of stone would help in preventing its recurrence⁵. According to EUA (European Urological Association) guidelines, MET (Medical Expulsive Therapy) is efficient in eliminating ureteric calculi at any level. Alpha blocker, Tamsulosin is the mainstay for MET specifically for distal ureteral stones >5mm. Oral chemolitholysis by alkalization of urine can be combined for a more synergistic effect by monitoring urinary pH⁶. The current study aims to a) validate Silodosin as an effective MET for distal ureteral calculus and b) to make this regimen the standard of care in Dr. D. Y. Patil Hospital, Kolhapur, Maharashtra. In this study, 124 patients with a distal ureteral calculus were studied over the period of two years from October 2019 to September 2021. This study was done to see the efficacy of silodosin augmentation along with the standard of care in management of lower ureteric calculus against standard of care alone.

There is evident male preponderance in urolithiasis in kind of chemical types of stones. The reason for higher incidence might be linked to urinary composition and pH of males as studied by Parks and Coe, who suggested that urinary solubility of calcium oxalate product in men is closer as compared to women⁷. Depending on the composition of minerals in the stone, they are classified as the following types. Calcium stones: calcium oxalate or calcium phosphate, Magnesium

ammonium phosphate or struvite stones, Uric acid or urate stones, Cystine stones, drug induced stones. Risk factors responsible for stone formation are diet, metabolic disorders, hypercalcemia, urine composition, low urine volume, recurrent UTI, hereditary, anatomic abnormalities, hypertension, obesity, climate change, IBD (inflammatory bowel disease), lithogenic drugs such as acyclovir, methotrexate, sulfonamides, antiepileptic drugs, vitamin D, loop diuretics, aluminium magnesium hydroxide and many other. There are various techniques available for stone analysis. The methods include chemical testing, optical method, physical method, infrared spectroscopy. Tamsulosin is extensively studied and is said to decrease expulsion time, increase expulsion rate. Therefore, MET is advised to patients with calculi size less than 10mm⁸. Although still controversial and failure to demonstrate similar results in different studies met is being used worldwide for smaller calculi that do not meet the AUA surgical intervention criteria^{6,9}, viz., Ureteric Stones >10mm, Ureteric stones <10mm but not passed even after 4-6 weeks with or without MET, Symptomatic patients, Pediatric patients, Pregnancy, when observation has failed.

MECHANISM OF ACTION OF SILODOSIN:

There is greater density of alpha 1 receptor in the distal ureter compared to the upper and middle. Alpha 1 blockers relax the ureteral muscles and reduce the spasm there by reducing colic pain. It reduces the amplitude of peristalsis and decreases the intraluminal pressure. This augments the transportational ability of the urine in the ureter, which increases the pressure proximal to the stone, thus propelling it⁹. Similar effect is seen at the level of neck of the urinary bladder and urethra facilitating expulsion. Alpha 1 blocker also c type of nerve fibers (fast) of the spinal cord, neurons of the postganglionic sympathetic neurons, thus also reducing the ureteric colic⁹.

MATERIALS AND METHODS:

The study was conducted for the period since October 2019. The trial protocol was approved by the ethics committee and the institutional research committee of D. Y. Patil Medical College, Kolhapur,

Maharashtra. Patients with urosepsis, presence of multiple calculi, severe hydronephrosis, known sensitivity to α blockers, nitrates for any co-morbidities, pregnancy, endoscopic procedures in the urinary tract, known ureteral stricture, severe back pressure changes with perinephric collection, known history of alternative medicine intake were excluded from the study. Patients presented to the Surgery OPD suggestive of renal colic are evaluated with history and physical examination. Ultrasound abdomen and pelvis, urinalysis and renal function tests were done. After sonographic proof of the stone size and location have met, written and informed consent was taken from the patients that meet the inclusion criteria. After consent, patients were allotted to control group (group A) and cases group (group B).

Table 1

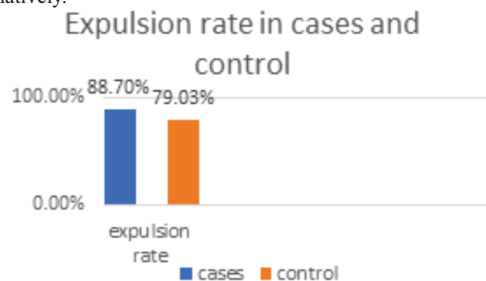
Patients allotted in GROUP A were given:	Patients allotted in GROUP B were given:
1. SYR. Citrate 2tsp+1 glass water twice a day +	1. TAB. Silodosin 4mg OD +
2. TAB. Drotaverine 40mg BD +	2. SYR. Citrate 2tsp+1 glass water twice a day +
3. Plenty of oral fluids.	3. TAB. Drotaverine 40mg BD +
	4. Plenty of oral fluids.

This regimen was given to the patients for a period of two weeks, and patients' statement was taken for stone expulsion and time taken for the same, in number of days. Sonography is done again for evidence of expulsion.

RESULTS

	cases	control
Patients with expulsion	n=55	n=49
Patients without expulsion	n=7	n=13
total	n=62	n=62

One hundred and twenty-four patients in age group of 22 to 59 years were assigned to group A (control n=62) and group B (cases n=62) alternatively.

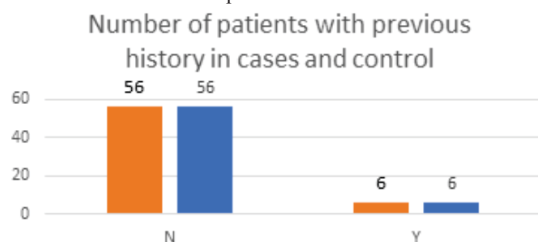


Out of 62 cases, 55 patients have had expulsion and 7 patients did not undergo expulsion within 2 weeks of treatment. Out of 62 controls, 49 patients have had spontaneous stone expulsion, 13 patients have not had stone expulsion within 2 weeks of study period. Expulsion rate in cases is 88.70% and 79.03%. z score is 1.465 and p value is 0.14 which is not statistically significant. In 62 cases, 53 were males and 9 were females. In 62 controls, 50 were males and 12 were females.

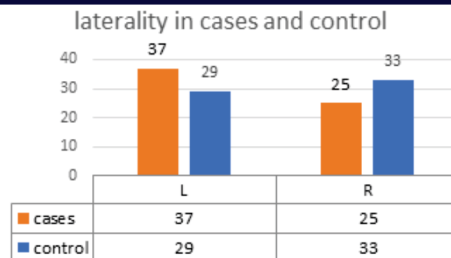
Table 2

Sex distribution	Cases	Control
Males	n=53	n=50
Females	n=9	n=12

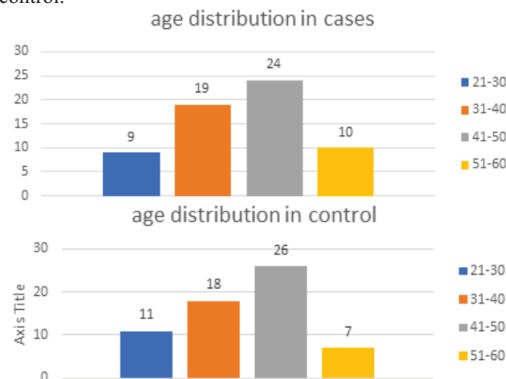
In 62 cases, 56 patients had previous history of stone disease and 6 patients were new stone formers. In 62 controls, 56 patients were recurrent stone formers and 6 patients were new stone formers.



In cases, 37 patients had left sided lower ureteric calculus and 25 patients had right sided lower ureteric calculus. Where as in control, 29 patients had left sided ureteric calculus and 33 patients had right sided ureteric calculus.



Peak age distribution was between the age group of 41-50 in both cases and control.



Average stone size in cases group is 6.19 mm. average stone size in control group is 6.05 mm.

size	cases	control
4.1-5.0 mm	n=12	n=9
5.1-6.0 mm	n=13	n=21
6.1-7.0 mm	n=21	n=20
7.1-8.0 mm	n=16	n=12

Expulsion time in cases is 6.65 +/- 2.56 (C.I = 5.96-7.34). Expulsion time in control is 9.67 +/- 2.16 (C.I = 9.05-10.29). p value is <0.0001 which is statistically significant.

	Cases	control	P value
Expulsion time	6.65 +/- 2.56	9.67 +/- 2.16	<0.0001
Confidence interval	5.96-7.34	9.05-10.29	

	Cases (n=62)	Control (n=62)	P value
Expulsion rate	88.7% (n=55)	79.03% (n=49)	0.14
Expulsion time	6.65 +/- 2.56	9.67 +/- 2.16	<0.0001
C.I	5.96-7.34	9.05-10.29	

DISCUSSION-

Since October 2019, an open labelled, prospective randomized controlled study was conducted to study the efficacy of Silodosin 4mg in expulsion of single distal ureteral calculus measuring 4-8mm in an outpatient setting. The trial protocol was approved by the ethics committee and the institutional research committee of D. Y. Patil Medical College, Hospital Kolhapur, Maharashtra. Patients with urosepsis, presence of multiple calculi, severe hydronephrosis, known sensitivity to α blockers, nitrates for any co-morbidities, pregnancy, endoscopic procedures in the urinary tract, known ureteral stricture, severe back pressure changes with perinephric collection, known history of alternative medicine intake were excluded from the study. Patients were allotted according to inclusion criteria. Patients presented to the Surgery OPD suggestive of renal colic were evaluated with history and physical examination. Ultrasound abdomen and pelvis, urinalysis and renal function tests were done. After sonographic proof of the stone size and location have met, written and informed consent was taken from the patients that meet the inclusion criteria. After consent for 2-week enrolment in the study, patients were allotted to control group (group A) and cases group (group B). This regimen was given to the patients for a period of two weeks, and patients' statement is taken for stone expulsion and time taken for stone expulsion in number of days with sonographic evidence of expulsion. All the data is entered into Microsoft excel sheet and analysed using SPSS version 23. Descriptive statistics of socio demographic and morbidity characteristics of the study sample are represented using frequencies & percentages for categorical data and mean & standard deviation for continuous data. Comparison of all variables was done using Z test and unpaired t test. P value less than 0.05 is considered as a significant.

Sex: In the current study, there is male preponderance, 85.4% in cases and 83.3% in control, which correlates with literature suggestive of higher affinity in males to form stones^{10,11,12}.

Age: In the current study peak age distribution was between 41-50 age group which co relates with studies conducted in Japan, USA and Iran^{13,14,15}. There were total of 9 patients in cases group within the age group of 21-30 years which account for 14.51% of total patients in cases group. There were 11 patients in control group within the 21-30 years' age group which sums up to 17.74% of control group. There were 19 patients in the cases group within the age range of 31-40 years which amounts to 30.64% of cases group. There were 18 patients in control group amounting to 29.03% of control group. There were 24 patients within the 41-50 years age group, that is 38.70% of cases and 26 patients in the control group of the same age group range, which amounts to 41.93% of control group population. There were 10 patients in the cases group of age range of 51-60 years which makes up 16.12% of cases group. And there were 7 patients in the control group of 51-60 age group range, making 11.29% patients of control group.

Laterality: There was no significant difference in laterality of the stone. In cases, 37 patients had left sided lower ureteric calculus which is 59.67% of cases and 25 patients had right sided lower ureteric calculus which is 40.32% of cases. In control group 29 patients had left sided lower ureteric calculus, 46.77% and 33 patients had right sided lower ureteric calculus that is 53.22%. preponderance to specific laterality is not seen.

Expulsion Rate: In the current study, expulsion rate in cases was 88.7% (n= 55) and expulsion rate in control was 79.03% (n=49) within two weeks of study period. P value was 0.14 which is not considered to be statistically significant. In the current study, expulsion rate in case of 4-6mm stone size in cases (n=21) is 84% and in control (n=22) is 73% which is also not significant. Expulsion rate is calculated among the cases and control in the stone size group of 6-8mm as well which showed 37 patients in cases with 34 patients with successful expulsion leading to 91% expulsion rate in cases and 32 patients in control group with 6-8mm size, among which 27 patients had expulsion which makes 84% expulsion rate in control which is also not statistically significant. In a study conducted in 2002 by **Cervenkov et al**, expulsion rate was 80.4% in tamsulosin group and 62.8% in control group¹⁶. In a study conducted by **Dellabella et al** in 2003 with 60 patients, expulsion rate was 100% in tamsulosin group and 70% in control group, p value was 0.001 which is statistically significant¹⁷. In 2011, **Yasunori Itoh et al** conducted a study with silodosin 8mg vs control in ureteric calculi where, expulsion rate was 52.2% in cases and 30.4% in control. P value was 0.036 which is significant¹⁸. In a 2015 study, conducted by **Roger L Sur et al** with 239 patients with silodosin 8mg vs control groups in a 4-10 mm ureteric calculi expulsion rate was 52% in cases and 44 % in control, p value was 0.2, which was not statistically significant, similar to the current study¹⁹. In a study conducted by **Cem Nedim Yuceturk et al** in 2017 with silodosin 4mg vs 8mg dosage groups, expulsion rate was 73.8% in 8mg group and 50.9% in 4mg group, p value was 0.002 which is statistically significant²⁰.

study	year	drug	cases	control	P value
Cervenkov	2002	Tamsulosin 0.4 mg	80.4%	62.8%	-
Dellabella	2003	Tamsulosin 0.4 mg	100%	70%	0.001
Yasunori	2011	Silodosin 8mg	52.2%	30.4%	0.036
Roger	2015	Silodosin 8mg	52%	44%	0.2
Yuceturk	2017	Silodosin 8mg	73.8%	50.9%	0.002
This study	2021	Silodosin 4mg	88.7%	79%	0.14

Expulsion time: In the current study, mean expulsion time for cases was 6.65 +/- 2.56 days and 9.67 +/- 2.16 days, confidence interval was 5.96-7.34 in cases and 9.05-10.29 in control group, **p value is <0.0001** which is statistically significant. It matches with the study conducted by **Dellabella et al** where p value for mean expulsion time was 0.02 which is statistically significant¹⁷. In a study conducted by **Yasunori Itoh et al**, in 2011 for distal ureteric calculi with silodosin 8mg OD group vs control group, expulsion time was 9.29 +/- 5.91 in cases and 13.4 +/- 5.9 in control. p value was 0.01 which is significant¹⁸. In a study conducted by **Roger L Sur et al**, in 2015 in 239 patients with silodosin 8mg. OD group vs control group in 4-10 mm ureteric calculi, there was statistically significant difference in mean expulsion time (p value=0.01)¹⁹. In a study conducted by **Chung Jing Wang et al** in 2016, with 198 patients of silodosin vs control group, mean expulsion time was 6.31 +/- 2.13 in cases and 9.73 +/- 2.76, p value <0.001²¹.

study	year	drug	cases	control	P value
Dellabella	2003	Tamsulosin 0.4mg	65.7 hours	111.1 hours	0.02
Yasunori itoh	2011	Silodosin 8mg	9.27 +/- 5.91	13.40 +/- 5.9	0.01
Roger L Sur	2015	Silodosin 8mg	NA	NA	0.01
Chung Jing Wang	2016	Silodosin 8mg	6.31 +/- 2.13	9.73 +/- 2.76	<0.001
This study	2021	Silodosin 4mg	6.65 +/- 2.56	9.67 +/- 2.16	<0.0001

CONCLUSION

In the current study, the peak age incidence of lower ureteric calculus was 41-50 years of age. The current study shows that there is higher incidence of lower ureteric calculus in males probably owing to more strenuous activity, dehydration and genetic predisposition and hormonal effect of stone formation. There is no predilection of stone toward one side either left or right, although certain literature shows preponderance to left side owing to the marginally higher location of left kidney and longer course of urine travel in the left ureter. The current drug of study, silodosin 4mg is an alpha blocker significantly reduces expulsion time in lower ureteric calculus of size 4-8mm by acting on the lower ureteric musculature and propelling the stone out. In this study most patients with lower ureteric calculi presented with colicky abdominal pain as the chief complaint demanding medical attention with size ranging from 4-8mm. In the present study, the average stone size in lower ureter was 6.12 mm. Medical expulsion therapy with alpha blocker silodosin 4mg is an efficacious drug in expulsion of lower ureteric calculus of size 4-8mm by decreasing the total time taken for the expulsion. 9.6% of patients had history of prior urolithiasis which suggests tendency for recurrence in stone formation.

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