

PROSPECTIVE STUDY OF TAMSULOSIN IN THE MANAGEMENT OF CALCULI IN LOWER THIRD OF URETERArunabha Sinha¹, Shirin Joshi², Shivkumar K. S³, R. N. Singh⁴, Nisith Ray⁵**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: INTRODUCTION: Urinary calculus disease is one of the 3 most common urological diseases. It affects about 12% of the world population and has become a worldwide health problem. Of all the urinary tract stones 20% are ureteral stones, of which 70% are found in the lower third of ureter. Patients with ureteric calculi have wide range of complications which includes acute pain necessitating hospitalization, urinary tract infection, anuria, acute renal failure, chronic renal failure, hydronephrosis, pyonephrosis, pyelonephritis. The objective of the study is, to study the effect of Tamsulosin in the passage of calculi in the lower one third of the ureter compared to NSAIDs and oral and IV fluids. **MATERIAL AND METHOD:** This study included a total of 82 patients between the study period from Nov 2010 to May 2013. 42 patients were chosen randomly and advised to take plenty of oral fluids and treated with NSAIDs (Diclofenac sodium) and the other 40 patients were treated with Tamsulosin (alpha blocker) 0.4mg HS for one month along with oral fluids and NSAIDs (Diclofenac sodium). **RESULTS:** Majority of the patients were in the age group of 20-40 yrs. The mean size of the calculus was 6.62 cms on the right side and 6.07 cms on the left side. Out of the 40 patients who were on alpha 1 blocker (Tamsulosin) 31 patients had passed the calculi and 9 patients had no results with a success rate of 77.5%. In the 42 patients who were not on Tamsulosin, 8 patients passed the calculi and 34 patients did not pass the calculi. 9 patients among the 42 underwent ureterorenoscopy (URS). **CONCLUSION:** Tamsulosin is an effective and safe drug in the management of calculi in the lower 1/3rd of the ureter. Most patients with ureteric calculi were rendered stone free with endourological procedures if conservative treatment failed.

KEYWORDS: Ureteric stones, Alpha 1 blocker, Tamsulosin, Ureteroscopy.

INTRODUCTION: Urinary stones have plagued mankind since ages, earliest recorded example being bladder stones detected in Egyptian mummies dated back to 4800 B. C. Urolithiasis was recognized as a major health problem even way back in 12 century BC when Susruta performed perineal lithotomy.¹

The etiology of the stones however remained obscure. Only in the last two centuries have studies resulted in the identification of composition of urinary stones.

Hereditary relationship of urinary stones was shown during the genetic studies performed by Resnik (1968) and McGeown (1960). Familial renal tubular acidosis is associated with nephrolithiasis and nephrocalcinosis in almost 70% of patients.¹ Males are more commonly afflicted than females (Male: Female = 3:1). Increased testosterone levels in men causing increased endogenous oxalate production by the liver and protective increased urinary citrate concentrations in women have been postulated as causes for the same.² Various studies over time have shown the cause of urinary stones to be multi-factorial.

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Stones do not usually form in the ureter, but drop down from the pelvi-calyceal system while they are still small. They tend to increase in size as they remain in the urinary passage. Most stones, smaller than 5 mm pass spontaneously.^{3,4} However some stones may arrest in the ureter producing complications such as obstruction, colic, infection, haematuria and acute renal failure. Therefore urgent relief is to be given to these patients.

The treatment of ureteral stones has undergone a remarkable evolution in the last 15yrs. At one time open uretero-lithotomy and blind stone basket manipulation were the mainstay of surgical management, they have now been superseded by an array of superior modalities. Among them Ureterorenoscopy (URS) and Extracorporeal shock wave lithotripsy (ESWL) are the two most favored methods for the treatment of Ureteric stones.^{5,6}

One of the major disorders of the Urinary System, causing concern to the Patient and the doctor is stone formation. Urinary calculus disease is one of the oldest known to man and affects about 3% of the population. The highest incidence of calculi occurs between the ages of 20 and 40 years with male: female ratio being 3:1. The severity of the condition can be judged from the fact that about 10 percent of the patients harboring a stone in the urinary system lose their kidney either by nephrectomy or as a result of subsequent destruction. The damaging effects of the calculi may result in obstruction with dilatation of the Urinary tract, leading to stasis and severe infection, with resultant fibrosis.

Ureter is the passage and the ureteric stone is just a passenger on its way from, the kidney, the site of its formation, to the urinary bladder. Many theories have been postulated to explain the aetiology of stone formation, but its exact cause still remains a mystery. Thus many times these stones may recur. Frere Jacques, the famous lithotomist, of middle ages has rightly exclaimed that "I have removed the stone but God will cure the patient" (Wagensteen OH et. al, 1969).

The treatment that can be offered to the patient depends on many factors such as the size of the stone, obstruction or infection and site of impaction. For stones up to 8mm size are generally treated by watchful expectancy but medical expulsion therapy is emerging as a better option.

AIMS AND OBJECTIVES: This study is to compare the effect of tamsulosin for the passage of calculi in the lower one third of the ureter to analgesics (NSAIDs) and oral fluids.

MATERIAL AND METHODS: This study included a total of 82 patients between the study period from Nov 2010 to May 2013. 42 patients were chosen randomly and advised to take plenty of oral fluids and treated with NSAIDs (Diclofenac Sodium) and the other 40 patients were treated with Tamsulosin (alpha blocker) 0.4mg HS for one month along with oral fluids and NSAIDs (Diclofenac Sodium).

The patients were then observed weekly and asked for any history of passage of calculi and ultrasound scan was repeated after 15 days to look for any passage of calculi. The findings were recorded and the patients were monitored and followed up for a period of one month. If the stone passed successfully, it was confirmed with ultrasonography. After 1 month if treatment failed, conservative management was discontinued and patient was advised surgery.

INCLUSION CRITERIA:

1. Patients with ureteric stone in the lower 3rd of ureter.
2. Stone sizes more than 4cm but less than 9 cm.

EXCLUSION CRITERIA:

1. Previous history of surgical intervention in the ureter.
2. Use of any other anti – hypertensive alpha blocker drug.
3. Congenital abnormality detected in the ultrasonography.

DISCUSSION: Ambrose Pare is credited with the first account of ureteral calculi in 1564 as he described “The cruel pain that tormented the patient in that place where the stone lodged”. Pare also stated that death was the consequence of having calculi impacted in both ureters.⁷ The earliest record establishing a difference between renal and ureteric calculi was the observation made by Avicenna (980-1037). He was aware of the fact that the migration of stone from the kidney to the bladder was accompanied by severe pain and also enlargement of the ureter.

At present there are many treatment modalities available in the armamentarium of the surgeon for the treatment of urinary calculus. Most ureteral stones can be observed with a reasonable expectation of uneventful stone passage and this strategy is generally less costly and less invasive than any other option, if successful.⁸ Ureteral stones with a diameter less than 5 mm will pass in up to 68% of cases. This is watchful expectancy, however, for stones with a greater diameter the overall chances of spontaneous passage are lower.⁹ Medical expulsion therapy (MET) has recently emerged as a appealing option for the initial management of ureteral stones.¹⁰ Several pharmacological approaches have been proposed in recent years aiming to act on possible causes of stone retention.¹¹ Both antagonists and calcium channel blockers have been shown to inhibit the contraction of ureteral muscle responsible for ureteral spasms while allowing ante grade stone progression.^{12,13}

Among all the agents available Tamsulosin fits the bill, more than the others, due to its unique properties. Tamsulosin is a competitive alpha 1 antagonist with a structure quite different from that of most other alpha 1 receptor blockers. It has high bioavailability and a long half-life of 9-15 hours. It is metabolized extensively in the liver. Tamsulosin has higher affinity for alpha 1 antagonists. Tamsulosin has less effect on standing blood pressure in patients.¹⁴

Alpha adrenergic receptors have been detected in the human ureter with a predominance of alpha 1A and alpha 1D receptor subtypes in the lower ureter. Alpha 1 adrenergic inhibition reduces the frequency and intensity of peristalsis of the ureter with an increase in the flow of urine.¹⁵ Tamsulosin therapy for uncomplicated distal ureteral calculi augments stone passage rate, shortens passage time and decrease need for analgesia. Particularly, tamsulosin shortens the passage time for smaller stones and augments the passage rate for larger stones.¹⁶

Tamsulosin exhibits high plasma-protein binding, largely to alpha (1) -acid glycoprotein. It is metabolized mainly by cytochrome P450 (CYP) 3A4 and CYP2D6 to compounds with low abundance, and 8, 7-15% of an oral dose is excreted renally as the parent compound. The pharmacokinetic of tamsulosin are not affected to a major extent by age and pharmacokinetic alterations in renally impaired patients relate largely to an increased concentration of alpha (1) -acid glycoprotein. Pharmacokinetic alterations with hepatic impairment are also only moderate, thus neither renal nor mild to moderate hepatic impairment necessitates dose adjustment. Concomitant exposure to potent CYP3A4 inhibitors can more than double the exposure of tamsulosin.¹⁷

The present study was done to study the effectiveness of Tamsulosin in MET compared to analgesics only. In this study which was conducted in MVJ MC & RH, Hoskote a total of 82 patients of

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20 to 40 years of age of whom 70% were male and had ureteric stone in the lower third of ureter. The size of the calculi were from 4 to 8 cm. in this study half the patients got analgesics only and the other group got analgesics and Tamsulosin. Out of the 40 patients who got Tamsulosin, 31 patients passed calculi. In the other 42 patients who were not on Tamsulosin 8 patients passed calculi.

In all our patients, who failed to pass the stones it was removed by ureterorenoscopy.

CONCLUSION:

- Incidence of ureteric calculi is common in the age group of 20-40 years.
- Incidence is common in males when compared to females, 57 males and 25 females.
- Incidence of ureteric calculi are more common in lower 1/3rd of the ureter, and more common in left side than right.
- Main symptoms of presentation are loin pain in 100% of patients, burning micturition in 12.19% patients, hematuria in 4.8%, vomiting in 7.3% and fever in none of the patients.
- Investigations to confirm the diagnosis of ureteric calculi are USG which is very sensitive and specific test than conventional X Rays.
- Majority of ureteric calculi of size 4mm -8mm will pass with alpha blocker drug (Tamsulosin).
- Ureterorenoscopy (URS) is a safe and effective minimally invasive surgery as complications are minimal with surgical expertise and proper case selection with present modalities of treatment.
- The common complications observed with tamsulosin are headache which was observed in 6 patients, dizziness was seen in 2 patients. Diarrhea and abnormal ejaculation like retrograde ejaculation are also the complications of Tamsulosin. None of our patients complained of retrograde ejaculation.

OBSERVATIONS AND RESULTS:

	Group 1	Group 2	%	Total
Female	12	13	30	25
Male	28	29	70	57

Table 1: Showing Distribution of Samples by Sex

30% of patients in this study group were female patients and 70% were male patients.

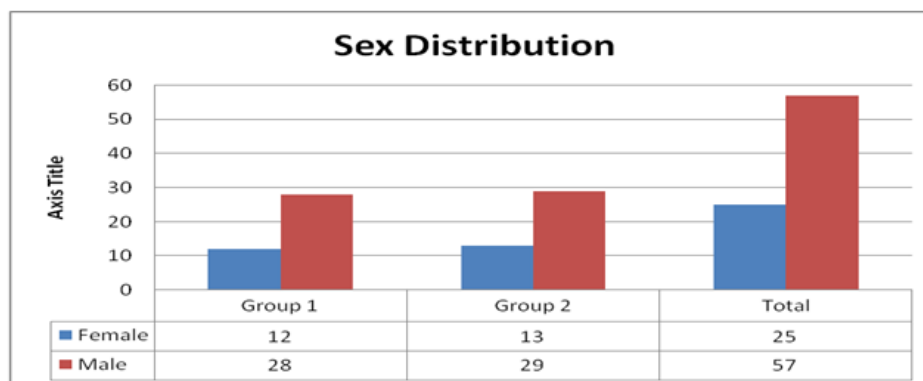


Chart No. 1

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Age	Female	Male	Total	Percentage
20-30	11	20	31	37.8%
30-40	6	16	22	26.8%
40-50	3	8	11	13.4%
50-60	3	6	9	10.9%
60-70	0	4	4	4.8%
70-80	2	3	5	6%

Table 2: Showing Distribution of Samples by Age

In this series majority of the patients were in the age group of 20-30 (31 patients) years followed by 30-40 years (22 patients). The mean age group was 36.44 years in females and 38.49 years in males.

37.8% were in the age group of 20-30 years, 26.8% of the patients were in the age group of 30-40 years, 13.4% of patients were in the age group of 40-50 years, 10.9% were in the age group of 50-60 years, 4.8% were in the age group 60-70 years, 6% of the patients were between 70-80 years.

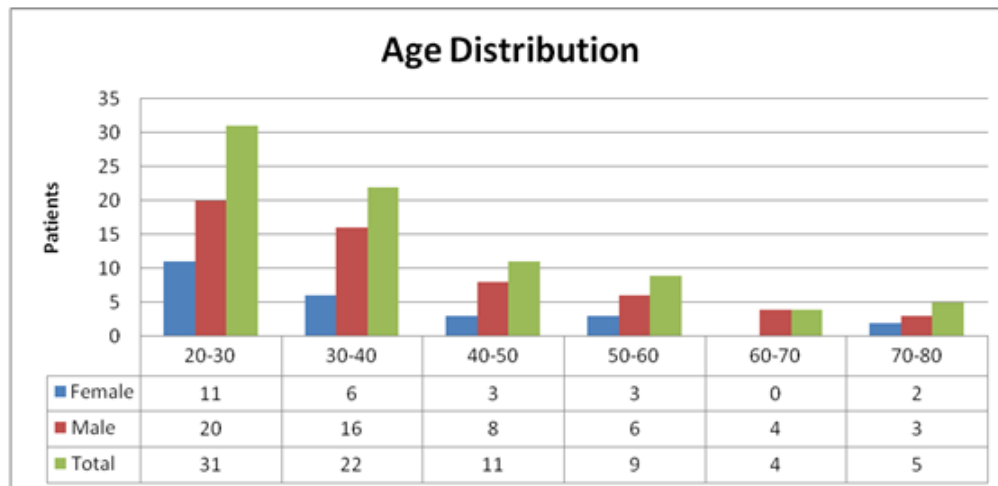


Chart No. 2

	Right	Left
Patients	33	49
Mean size	6.62	6.07
Percentage	40%	60%

Table 3: Showing Distribution of Samples by Laterality

In this series, 40% of the patients had right ureteric calculus and 60% of the patients had left ureteric calculus.

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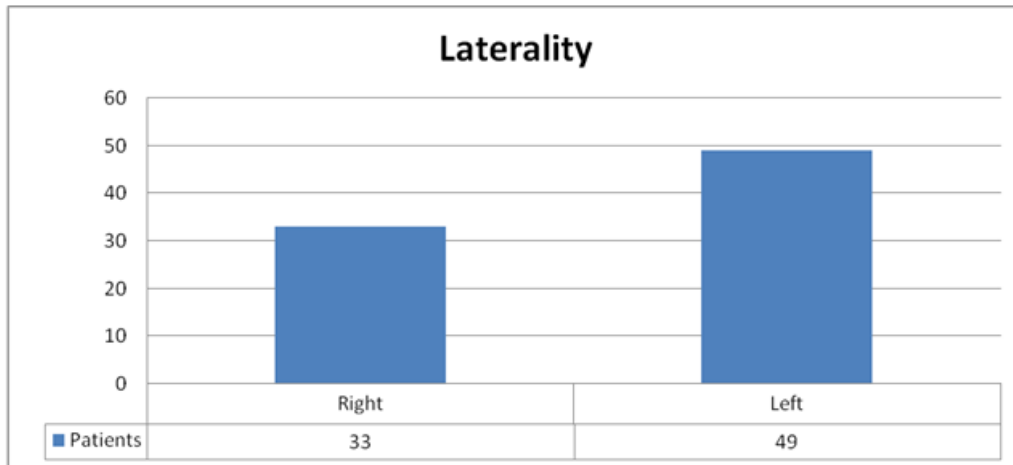


Chart No. 3

	Right	Left
Mean Size	6.62	6.07

Table 4: Showing Distribution of Samples by Size of Stones

In this series, the mean size of the calculus was 6.62 cms on the right side and 6.07 cms on the left side.

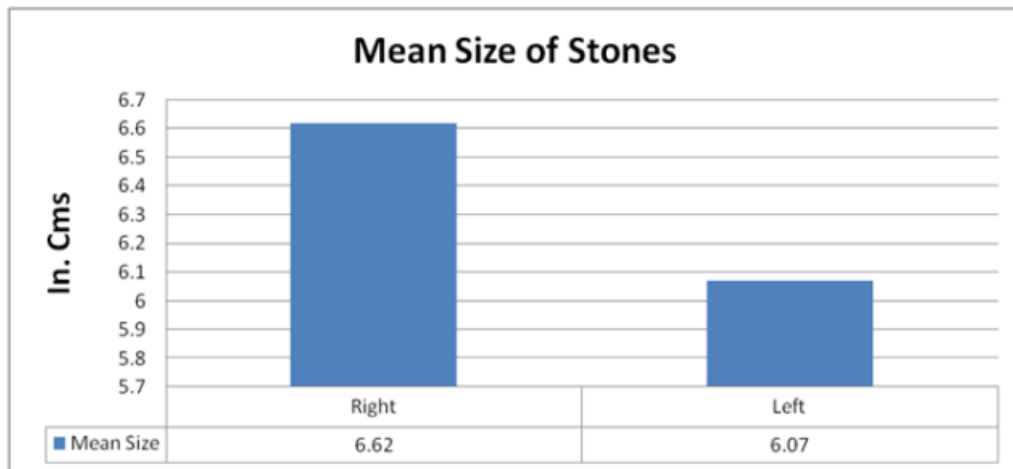


Chart No. 4

Symptoms	No. of patients	Percentage
PA	56	68%
PA+BM	13	16%
PA+V	8	10%

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PA+H	4	5%
PA+BM+H	1	1%
Total	82	100%

Table 5: Showing Distribution of Samples by Symptoms

In our study, 68% of the patients complained of only pain abdomen in the loin region, 16% of the patients had pain abdomen with burning micturition, 10% patients had associated vomiting with pain abdomen, 5% patients had hematuria associated with pain abdomen, and 1% patients had pain abdomen, burning micturition and hematuria.

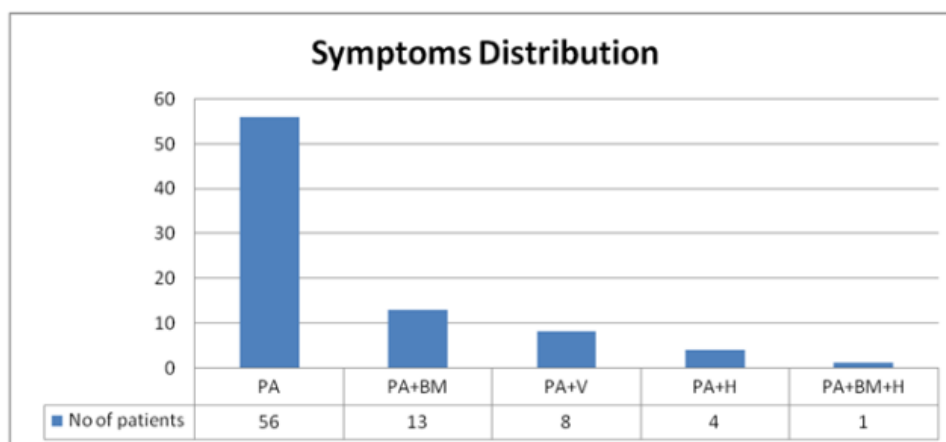


Chart No. 5

Hb%	Patients	Percentage
Below 10	2	2%
10-11	11	13%
11-12	14	17%
12-13	22	23%
>= 13	33	40%
Total	82	

Table 6: Showing Distribution of Samples by Hemoglobin

All the patients were tested to detect anemia. 40% of the patients had hemoglobin >13g%. 23% had hemoglobin in the range of 12-13g%. 17% of the patients had hemoglobin in the range of 11-12g%. 13% of the patients had hemoglobin in the range of 10-11g% and 2% patients had hemoglobin less than 10g%.

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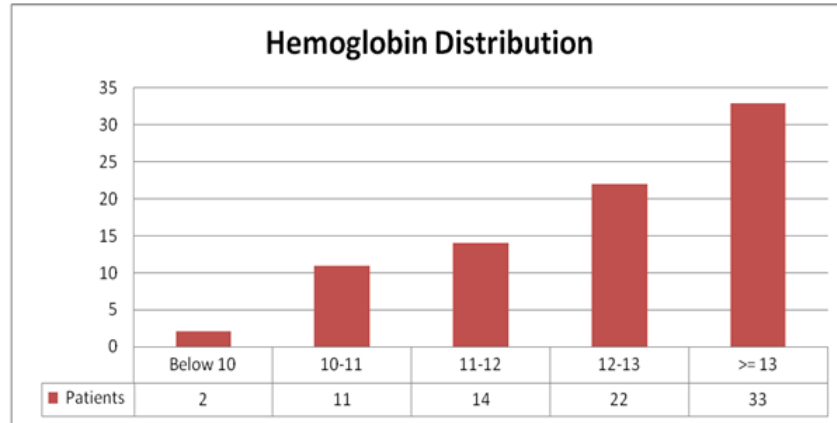


Chart No. 6

Status	Patients	Percentage
< 1	68	83%
>=1	14	17%
Total	82	

Table 7: Showing Distribution of Samples by Serum Creatinine

In this series 83% of the patients had serum creatinine <1mg% and 17% of the patients had serum creatinine >1mg%.

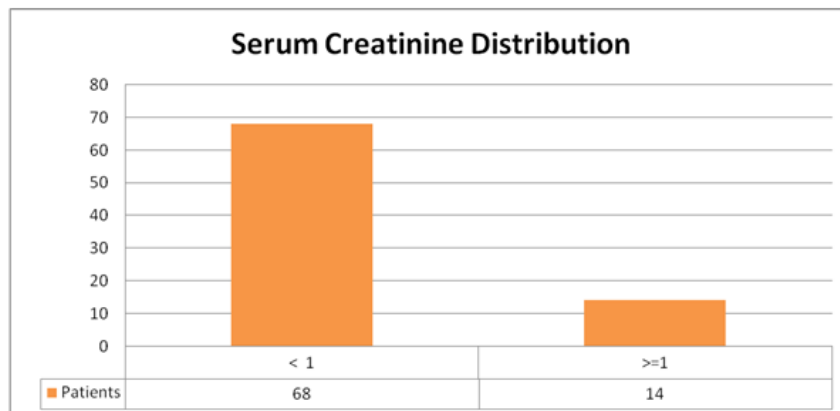


Chart No. 7

Urine routine		No. of patients
Albumin	Present	12
	Absent	70
Sugar	Present	0
	Absent	82

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Pus cells	Present	18
	Absent	64
RBC	Present	7
	Absent	75
Epithelial cells	Present	24
	Absent	58

TABLE 8

Urine routine results showed presence of Albumin in 12 patients, Pus cells in 18 patients, RBCs in 7 patients and epithelial cells in 24 patients.

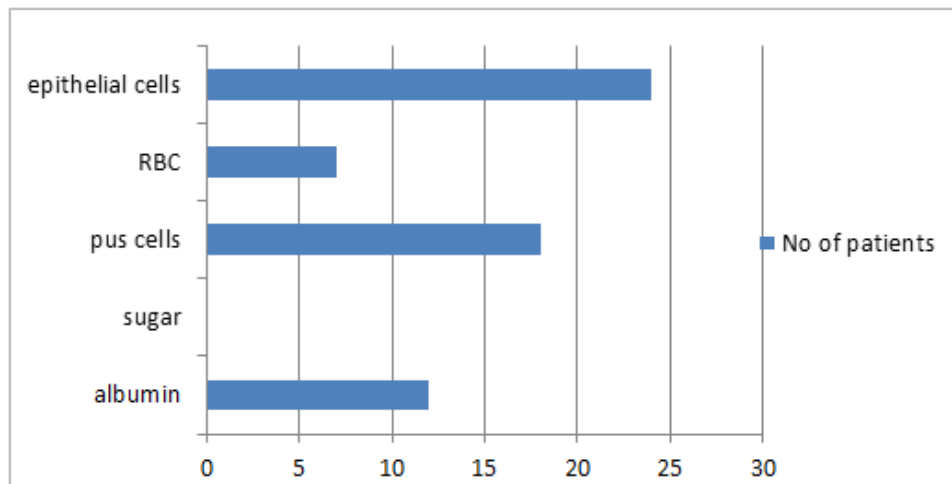


Chart No. 8

Total Cases	Follow up days	Percentages
7	7	18%
6	14	15%
5	21	13%
13	28	32.5%
9	0	22.5%

Table 9

In our study, in the group 1, 18% of patients passed the ureteric calculus within 7 days, 15% of the patients passed the calculus within 14 days, 13% of the patients passed the calculus within 21 days and 32.5% of the patients passed the calculus within 28 days of follow up and 22.5% patients did not pass the calculus. P value is less than 0.05, hence statistically significant.

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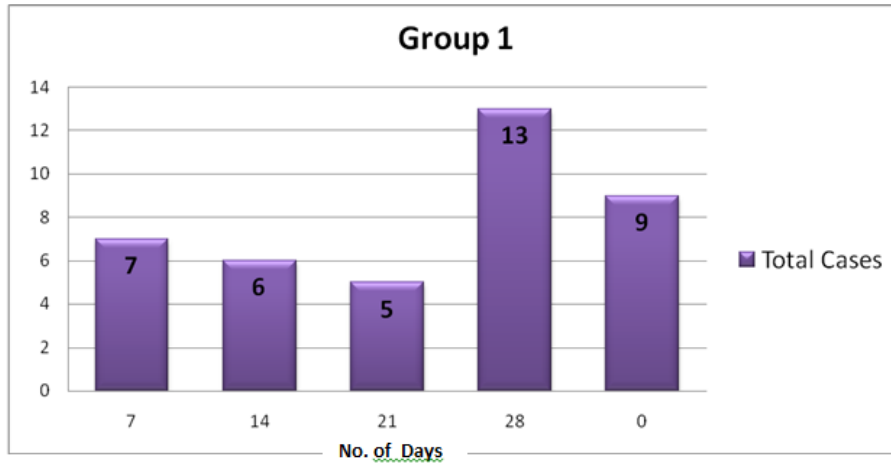


Chart No. 9

Total Cases	Follow up days	Percentages
2	7	5%
4	14	10%
2	21	5%
0	28	0
34	0	

TABLE 10

In the second group, 5% of the patients passed the calculus within 7 days, 10% patients passed the calculus within 14 days, 5% of the patients passed the calculus within 21 days and 0 patients passed the calculus within 28 days of follow up. 81% of the patients in the second group did not pass the calculus.

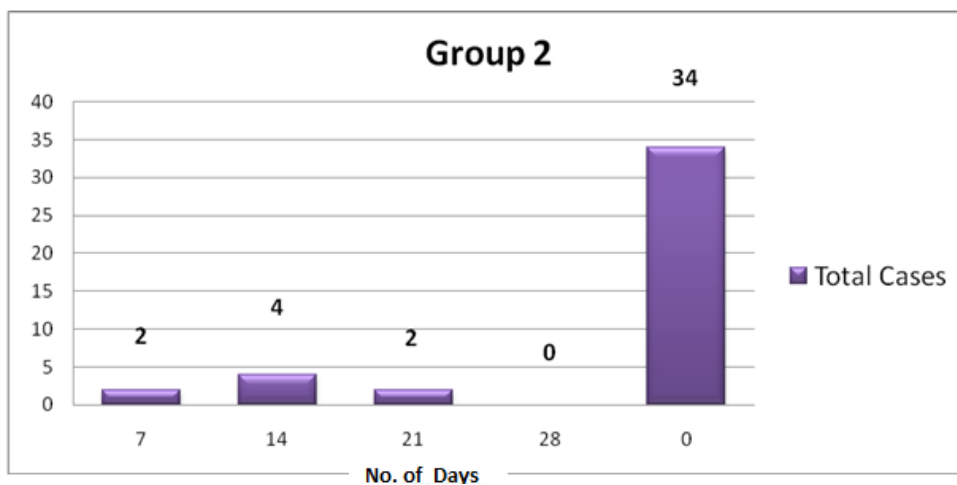


Chart No. 10

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Author	Year	No. of cases	Success rates
Kupeli B et al	2004	78	53.3%
Autorino R et al	2005	64	88%
Lojanapiwat et al	2008	75	68%
Francesco Porpiglia et al	2008	91	80%
Present series	2010	82	77.5%

Table 11: Comparison of success rate of treatment with Tamsulosin for ureteric calculi with other series

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