TAMSULOSIN VERSUS TADALAFIL AS MEDICAL EXPULSIVE THERAPY OF DISTAL URETERIC STONES: A COMPARATIVE STUDY

By

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In partial fulfilment
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GENERAL SURGERY

Under the guidance of:

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Date: **DR. HARDIK JAGJIVANBHAI PATEL**

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ABSTRACT

Introduction: The management of patients with ureteral calculi has changed dramatically in the current era, with the conservative approach being the primary focus, its main benefit being minimum patient morbidity. The use of the expectant approach for distal ureteric stones can be extended with the use of adjuvant medical expulsive therapy (MET), which is able to reduce symptoms and facilitate stone expulsion. The present study was thus conducted to determine single best monotherapy for medical expulsive therapy of distal ureteric stones by comparing Tadalafil and Tamsulosin.

Material & Methods: A hospital based comparative study was conducted at Department of Surgery of a tertiary care hospital. A total of 60 eligible cases of lower ureteric calculus were included in the study. These 60 patients were then divided into 2 groups of 30 each to receive one of the two medical therapy i.e. either Tadalafil or Tamsulosin. Data was analyzed using statistical software SPSS ver. 21.

Results: Mean expulsion of calculi was significantly earlier in patients managed by Tadalafil as compared to Tamsulosin (13.1 vs 16.92 days; $p<0.05$). Complete expulsion was seen in 86.7% cases on Tadalafil as compared to only 63.3% cases on Tamsulosin ($p<0.05$). Mean analgesic use (2.69 vs 1.81; $p<0.05$) and episodes of colicky pain (1.41 vs 0.43; $p<0.05$) were significantly higher in patients managed by Tamsulosin. The numbers of hospital visits required during treatment were also more with Tamsulosin, but the difference did not reach significance levels (2.56 vs 2.02 days; p-0.06). No difference was seen in the adverse effect profile of both drugs.

Conclusion: Our results showed that Tadalafil has a significantly higher ureteric stone expulsion rate. Tadalafil also provides early stone expulsion, a greater decrease in colicky pain episodes, and a greater decrease in analgesic requirement. Both drugs are safe, effective, and well tolerated with minor side effects. Thus Tadalafil is safe, efficacious, and well tolerated as medical expulsive therapy for distal ureteric stones.

Keywords: Medical expulsive therapy, Tadalafil, Tamsulosin, Lower Ureteric Calculi

INDEX

SR. NO.	TABLE OF CONTENTS	PAGE NO.
1	INTRODUCTION	1-5
2	REVIEW OF LITERATURE	6-43
3	AIMS	44
4	OBJECTIVES	45
5	MATERIALS & METHODS	46-48
6	STATISTICAL ANALYSIS	49
7	RESULTS & ANALYSIS	50-65
8	DISCUSSION	66-85
9	SUMMARY	86-87
10	CONCLUSION	88-90
11	REFERENCES	91-99
12	ANNEXURE	100-117
	I – LIST OF ABBREVIATIONS II - PARTICIPANT INFORMATION SHEET III - INFORMED CONSENT FORM IV- PROFORMA V- MASTER CHART	

LIST OF TABLES

Sr. No.	Tables	Page No.
1	COMPARISON OF STUDY GROUPS BASED ON AGE	50
2	COMPARISON OF STUDY GROUPS BASED ON GENDER	51
3	COMPARISON OF STUDY GROUPS BASED ON PRESENTING COMPLAINTS	52
4	DISTRIBUTION OF SUBJECTS AS PER OPACITY ON X-RAY-KUB	54
5	DISTRIBUTION OF SUBJECTS AS PER USG FINDINGS	55
6	DISTRIBUTION OF SUBJECTS AS PER CT-IVP RESULTS	57
7	COMPARISON OF STUDY GROUPS BASED ON STONE SIZE	58
8	COMPARISON OF STUDY GROUPS BASED ON STONE EXPULSION TIME	59
9	COMPARISON OF STUDY GROUPS BASED ON COMPLETE STONE EXPULSION RATE	60
10	COMPARISON OF STUDY GROUPS BASED ON ANALGESIC USE	61
11	COMPARISON OF STUDY GROUPS BASED ON COLIC PAIN EPISODES	62
12	COMPARISON OF STUDY GROUPS BASED ON HOSPITAL VISIT	63
13	COMPARISON OF ADVERSE EFFECTS AMONG STUDY GROUPS	64
14	MEAN AGE COMPARISION	67
15	GENDER COMPARISION	69
16	PRESENTING COMPLAIN COMPARISON	71
17	STONE SIZE COMPARISION	73
18	STONE EXPULSION TIME COMPARISION	75

19	STONE EXPULSION RATE COMPARISION	77
20	ANALGESIC USE COMPARISION	79
21	COLICKY EPISODE COMPARISON	81
22	HOSPITAL VISIT COMPARISON	83
23	ADVERSE REACTIONS	84

LIST OF FIGURES

Sr. No.	Figures	Page No.
1	Blood supply and lymphatic drainage	12
2	Arterial supply to the ureter	13
3	Five sites of narrowing where the stone may be arrested	16
4	Structure of Tamsulosin	23
5	Structure of Tadalafil	29

LIST OF GRAPHS

Sr. No.	Tables	Page No.
1	GRAPH SHOWING AGE DISTRIBUTION	50
2	GRAPH SHOWING GENDER DISTRIBUTION	51
3	GRAPH SHOWING PRESENTING COMPLAINTS	52
4	GRAPH SHOWING DISTRIBUTION OF SUBJECTS AS PER OPACITY ON X-RAY-KUB	54
5	GRAPH SHOWING DISTRIBUTION OF SUBJECTS AS PER USG FINDINGS	55
6	GRAPH SHOWING DISTRIBUTION OF SUBJECTS AS PER CT-IVP RESULTS	57
7	GRAPH SHOWING STONE SIZE	58
8	GRAPH SHOWING STONE MEAN EXPULSION TIME	59
9	GRAPH SHOWING COMPLETE STONE EXPULSION RATE	60
10	GRAPH SHOWING ANALGESIC USE	61
11	GRAPH SHOWING MEAN COLIC PAIN EPISODES	62
12	GRAPH SHOWING MEAN HOSPITAL VISITS	63
13	GRAPH SHOWING ADVERSE EFFECTS AMONG STUDY GROUPS	65
14	GRAPH SHOWING MEAN AGE COMPARISON	67
15	GRAPH SHOWING GENDER COMPARISION	69
16	GRAPH SHOWING PRESENTING COMPLAIN COMPARISION	71

17	GRAPH SHOWING STONE SIZE	73
18	GRAPH SHOWING STONE EXPULSION TIME COMPARISION	75
19	GRAPH SHOWING STONE EXPULSION RATE COMPARISON	77
20	GRAPH SHOWING ANALGESIC USE COMPARISON	79
21	GRAPH SHOWING COLICKY EPISODE COMPARISION	81
22	GRAPH SHOWING HOSPITAL VISIT COMPARISION	83
23	GRAPH ADVERSE REACTIONS	85

The formation of stone in the urinary system, i.e., in the kidney, ureter, and urinary bladder or in the urethra is called urolithiasis. 'Urolithiasis' = ouron (urine) and lithos (stone). Urolithiasis is one of the major diseases of the urinary tract and is a major source of morbidity. Stone formation is one of the painful urologic disorders that occur in approximately 12% of the global population and its re-occurrence rate in males is 70-81% and 47-60% in female. It is assessed that at least 10% of the population in industrialised part of the world are suffering with the problem of urinary stone formation.(1)

Ureteric calculi or stones are those lying within the ureter, at any point from the ureteropelvic junction (UPJ) to the ureterovesical junction (UVJ). They are the classic cause of renal colic-type abdominal pain. They are a subset of the broader topic of urolithiasis.

Patients with ureteric calculi may present with peristaltic pain (renal colic), haematuria, nausea and vomiting. The quality and location of pain is dependent on the location of the calculi within the ureter. Calculi within the ureteropelvic junction may cause deep flank pain due to distension of the renal capsule, without radiation to the groin, whereas pain from upper ureteral calculi radiates to the flank and lumbar areas. Calculi in the mid-ureter result in pain radiating anteriorly, while pain from distal ureteric calculi radiates to the groin via referred pain from the genitofemoral or ilioinguinal nerves. Calculi in the ureterovesical junction may also cause irritative voiding symptoms such as dysuria and urinary frequency.(2)

Each year throughout the world, people make more than a million visits to healthcare providers and to emergency rooms for urinary stone problems. The increasing prevalence of ureteric stones is a matter of concern in this era, and it could be linked

to improved quality of life. The incidence varies, with geographical location being higher in the Middle East, western India and southern USA, which probably reflects the water and soil content as well as the hot weather and dehydration that exist in these areas. Renal stones are most common in middle-aged people, and are threefold more common in men than women. A total of 22% of all urinary tract stones are found in the ureter, of which 68% are seen in the distal ureter. Colicky pain is an initial presentation of ureteric stones, and almost half of the patients present within 5 years of occurrence of calculi. (3) Most patients present between ages 30 and 60, with peak incidence between ages 35-45.(3)

Ureteral stones induce ureteral spasms that interfere with stone expulsion. Thus, reducing these spasms while maintaining normal peristaltic activity can facilitate stone expulsion. Almost 50% of ureteral stones will pass spontaneously over time and stone size is the key factor for success. Usually, stones smaller than 5 mm are expected to pass spontaneously, whereas only 20% of stones larger than 8 mm will pass. The best treatment modality depends upon various factors such as size, localization and composition of the stone, severity of obstruction, symptoms, and anatomy of the urinary system. The watchful waiting approach can result in complications, such as infection of the urinary tract, hydronephrosis, and deranged renal function. Ureteric stones have been treated traditionally with interventional techniques like ureteroscopy or open surgery.

Improvements in minimally invasive procedures in the last few decades have considerably changed the treatment of ureteral stones, but such procedures are not free of risks and are costly as well. A conservative approach through medical expulsive therapy (MET) as a supplement to conservative treatment has now become

an established treatment modality that employs various drugs acting on the ureter by different mechanisms(4)

The ureter is lined by smooth muscle cells with alpha-1 adrenergic receptors, especially in the distal third. Receptor blockade inhibits both basal smooth muscle tone and hyper peristaltic uncoordinated frequency in order to maintain tonic propulsive contractions. Ureteric calculi can induce ureteric spasms that interfere with expulsion; thus, muscle relaxation while maintaining normal peristaltic activity may facilitate passage. Ureteric stones at the impaction site produce noticeable pathological changes; that is, an intense inflammatory reaction with mucosal oedema that could further worsen the ureteric obstruction, increasing the risk of impaction and retention.

Therefore, alpha-1 adrenergic receptor antagonists work by creating an increased pressure gradient around the stone, which propels distal ureteral stones out of the ureter.(5)

The most frequently recommended agents are α-blockers, specifically Tamsulosin. Commonly used for benign prostatic hypertrophy, Tamsulosin acts at the α-1D adrenergic receptors present in the distal ureter.(6) Tamsulosin, a selective alpha-blocker with equal affinity for both α-1A and α-1D receptors, has a proven role in MET in increasing the stone expulsion rate and decreasing expulsion time.(7, 8).

α1D receptors are found in abundance in the detrusor and the intramural part of the ureter. α1A and α1D adrenergic receptors are present more densely in the distal 1/3 of ureter (including intramural part) than other adrenergic receptors. When stimulated, they inhibit the basal tone, peristaltic wave frequency and the ureteral contractions even in the intramural part of lower ureter. α1 antagonists have a crucial impact in

spontaneous painless elimination of the stones smaller than 8 mm located in the ureterovesical junction.(9) They may work on the obstructed ureter by inducing an increase in the intraureteral pressure gradient around the stone, that is, an increase in the urine bolus above the stone (and consequently an increase in intraureteral pressure above the stone) as well as decreased peristalsis below the ureter (and consequently a decrease in intraureteral pressure below the stone) in association with the decrease in basal and micturition pressures even at the bladder neck, thereby an increased chance of stone expulsion. Furthermore, the decreased frequency of phasic peristaltic contractions in the obstructed ureteral tract induced by Tamsulosin might determine a decrease in or the absence of the algogenic stimulus.(10)

Recently, phosphodiesterase-5 (PDE5) inhibitors have shown some benefit in stone expulsion. Phosphodiesterases are key enzymes regulating intracellular cyclic nucleotide metabolism (cyclic guanosine monophosphate (cGMP), cyclic adenosine monophosphate (cAMP)) and thus the contraction and relaxation of the muscle. In vitro studies have found that PDE5 inhibitors relax the ureteric muscle (8)

Tadalafil, which is a phosphodiesterase-5 (PDE5) inhibitor, was shown to act by a nitric oxide/cyclic guanosine monophosphate (cGMP)-signalling pathway, resulting in increased levels of cGMP, leading to smooth muscle relaxation in the ureter (8). Owing to its smooth muscle relaxation property, Tadalafil received approval from the Food and Drug Administration for lower urinary tract symptoms associated with benign prostatic hyperplasia and erectile dysfunction. Daily dosing with 10 mg has shown better results and tolerance than 20 mg per day (11).

Tadalafil has the longest duration of action (~36 hours) among the current PDE5 inhibitors. Although Tadalafil has been used in the treatment of erectile dysfunction

(ED) and lower urinary tract symptoms due to benign prostatic hyperplasia (BPH), its use in MET for ureteral stones is very limited in the Indian population.

On the other hand, Tamsulosin has been widely used for ureteral stones in our practice and has been found to be efficacious. This study aimed to analyse the safety and efficacy of Tadalafil in distal ureteral stones and also to compare the efficacy of Tadalafil with that of Tamsulosin.

Thus, by comparing drugs acting through different mechanisms, we aim to discover whether we can achieve better ureteric relaxation and reduction in intramural pressure in order to facilitate stone passage. Thus our main aim of comparing Tadalafil and Tamsulosin is to determine single best montherapy for medical expulsive therapy of distal ureteric stones.

HISTORICAL BACKGROUND

The history of urinary stones almost begins and goes parallel with the history of civilization. The roots of modern science and philosophy go back to the Ancient Egyptians, in whom we see the first signs of social and scientific developments. In 1901, the English archaeologist E. Smith found a bladder stone from a 4500–5000-year-old mummy in El Amrah, Egypt. Treatments for stones were mentioned in ancient Egyptian medical writings from 1500 BC.(12,13) The earliest literary quotations to stone disease, describing symptoms and prescribing treatments to dissolve the stone, are observed within the medical texts of Asutu in Mesopotamia between 3200 and 1200 BC. And the first descriptions of "cutting for the stone" are found in Hindu and Greek writings. Sushruta (around 600 BC) was a surgeon who lived in ancient India and is the author of the book Sushruta Samhita, in which he describes over 300 surgical procedures, including perineal lithotomy (14, 15). The formation of bladder stones was also described in these texts as follows. "Bladder stones are normally carried in to the bladder. If the internal channels are not kept clean or unwholesome food is eaten, the mixture of deranged Kapham (phlegm) and urine forms stones. Bigger stones form in the same fashion as the precipitate that occurs after some time when even clear water is kept in a new pitcher." A vegetarian diet, a urethral syringe of medicated milk, clarified butter, and alkalis were treatment recommendations for stone sufferers in the Ancient India. When these treatments failed, surgery was used, as described in detail in Sushruta's works (15).

Ancient Greeks, who settled down the basis of philosophy and science, did the first remarkable observations and documentations concerning urinary stone disease. Hippocrates (460–377 BC) described diseases of the kidney and defined symptoms of

bladder stones. In his famous Oath of Medical Ethics for physicians, he underlines "I will not cut for the stone, but will leave this to be done by practitioners of this work." At that time, lithotomy was practiced with only perineal incision by special lithotomists and Hippocrates adamantly stated that wounds of the bladder were lethal (16). This admonition to physicians about a very risky procedure was to be held for centuries.

Ammonius of Alexandria (276 BC) was the first person to suggest crushing the stone to facilitate its removal (17). The first recorded details of "perineal lithotomy" were those of Cornelius Celsus (25 BC–40 AD), who lived in Rome and wrote an encyclopedia of medicine (De Medicina) (12, 17, 18). Although he, as a physician, never performed the operation himself, his description of perineal lithotomy was a landmark in the history of urology. This technique, aptly called the "Operation Minor" or "petit appareil", was used with very little change, indeed if any, for the next 1500 years. (12, 17, 18).

Shortly afterwards, Albucasis (Ibn Abbas Alzahrawi, 930–1013 AD) from Cordova demonstrated considerable experience in surgery by modifying the technique of lithotomy as practiced by Ancient Greeks, (19). The operation was carried out through a perineal incision down to, then through, the bladder neck to reach the stone and extract it. Comparing the descriptions of the operative technique as carried out during ancient Indian and Greek civilizations, the description given by Albucasis in his book Al-Tasreef clearly shows how Albucasis remarkably improved the technique of this operation and reduced its risk (20). Albucasis also invented a new lithotomy scalpel, called "nechil", with 2 sharp cutting edges and being a novel instrument not known before him he made a drawing for it. Albucasis was also the first to use forceps to

extract a bladder stone. Before him, extraction of the stone was by an instrument similar to a small spoon that goes around the stone and scoops it out.

In the 14th century, Chauliac (1300–1367), considered as the father of French surgery, wrote the Chirugia Magma, combining surgical influences of the Arabs, the Greeks, and his experiences (21). He wrote much about stone disease but never performed lithotomy, which was a dangerous operation at that time. (22). The history of urinary stones is became more appealing with the famous persons harbouring the disease. Famous historical figures who developed bladder stones include King Leopold I of Belgium, Peter the Great, Louis XIV, George IV, Oliver Cromwell, Benjamin Franklin, the philosopher Bacon, the scientist Newton, the physicians Harvey and Boerhaave, and the anatomist Scarpa (23).

By modifying the "primitive lithotrite" developed by Albucasis, Jean Civiale introduced a trilabe, grasping, and fragmenting instrument in 1824 (24). This can be considered the beginning of the use of lithotripters and "endourology" in stone fragmentation. In 1874, Bigelow developed a stronger and harder lithotrite, which was introduced into the bladder with the help of anaesthesia (25). He filled the bladder, crushed the stones, and evacuated the fragments. This was called "litholopaxy." Suddenly, the mortality rate dropped from 25% to 2.4% (22).

Besides the developments in cystoscopic lithotrite, alternative surgical procedures for stone removal were being attempted. Gustav Simon performed the first planned nephrectomy for a fistula in 1869 (26). In 1873, Ingalls from Boston carried out the first nephrotomy. The first pyelotomy was performed by Heinecke in 1879, and the first nephrolithotomy was carried out in 1881 by Le Dentu (1, 27). On the other hand, Smith and Boyce from USA introduced and popularized anatrophic nephrolithotomy

for the treatment of staghorn stones in 1967 (28). This technique has further gained popularity, became treatment of choice for large staghorn stones in experienced hands, and is even applied during laparoscopic approaches (29).

With the increasing use of the Nitze cystoscope and the Hopkins rod-lens system, Young and Mckay (1870–1945) were able to develop the cystoscopic lithotrite. They were also the first to perform (1912) and report ureteroscopy (1929) (30). Before rigid ureteroscopy, advances in fiber optics led to the development of flexible ureteroscopes. In 1964, Marshall reported his first experience with flexible ureteroscopy using a 3 mm fiberscope (31).

Electrohydraulic lithotripsy was the first modern intracorporeal lithotriptor invented in 1954 by Yutkin, an engineer from Kiev (32). The first investigation of ultrasound for the destruction of urinary stones was undertaken by Mulvaney in 1953, and Kurth applied it to renal stones in 1977. The development of laser for the fragmentation of ureteral calculi was initiated in 1986 (32). Significant advances in laser fibers and power generation systems have propelled laser lithotripsy, in many practitioners' hands, as the treatment of choice for ureteral stones. The newest technique approved for the fragmentation of renal, ureteral, and bladder calculi is pneumatic lithotripsy. The first pneumatic device, the Lithoclast, was designed by a Swiss company in 1992 (32). Today, with the advances in flexible ureteroscopes and laser fibers, even stones in the renal calices can be treated by ureteroscopy (retrograde intrarenal surgery).

Improvements in intracorporeal lithotripsy also allowed renal stones to be treated by percutaneous renal surgery. Rupel and Brown removed a stone in 1941 through a nephrostomy tract that had previously been established surgically (36), and Trattner in 1948 used a cystoscope to examine the renal collecting system at open renal surgery

(37). Goodwin et al. were the first to place a nephrostomy tube to a grossly hydronephrotic kidney to provide drainage in 1955 (38). It was not until 1976 that Fernstrom and Johannson established percutaneous access with specific intention of removing a renal stone. Advances in endoscopes and other instruments allowed urologists to refine the percutaneous nephrolithotomy technique during 1970s and large series were reported in 1980s (39).

However, with the introduction of the first ESWL machine, Dornier HM-3, in 1980, a dramatic change in stone management was observed (40, 41). Probably, this was the outstanding invention in the management of urinary stones. The US Food and Drug Administration approved the use of ESWL machines in 1984, and thereafter it was used widespread all over the world (42). However, the limitations of this machine are underlined in recent studies, and ureteroscopy and percutaneous nephrolithotomy gained the position they deserve in current treatment guidelines.

With the subsequent developments in endourology (ureteroscopy, percutaneous surgery, and ESWL) there is an ongoing search for even less invasive treatments. And civilization in parallel with scientific developments has brought us to a point where we try not to "cut" our patients for stone disease, as Hippocrates admonishes, and rather manage them with minimal invasive alternatives. Currently, open surgery is performed in less than 4% of patients with urinary stones in reference centers (43).

ANATOMY

The ureters are paired muscular ducts with narrow lumina that carry urine from the kidneys to the bladder.

Embryology

The mesoderm gives rise to the kidney, ureter, bladder, and urethra. The metanephros is the principle excretory unit starting at week 8 of gestation, eventually becoming the mature kidney. Metanephric development is contingent on the ingrowth of the ureteric bud, which arises from the distal posteromedial mesonephric duct.

Absence of the ureteric bud leads to renal agenesis, whereas incomplete ingrowth or ureteral atresia results in multicystic dysplastic kidney. The ureteric bud bifurcates with ingrowth into the metanephric blastema, leading to division of the calyces. Premature bifurcation may lead to incomplete duplication of the ureter or bifid pelvis. Other abnormalities of ureteric bud formation may lead to anomalies of number or termination.(44)

Abdominal ureter

The ureter is roughly 25-30 cm long in adults and courses down the retroperitoneum in an S curve. At the proximal end of the ureter is the renal pelvis; at the distal end is the bladder. The ureter begins at the level of the renal artery and vein posterior to these structures. This ureteropelvic junction usually coincides with the second lumbar vertebra on the left, with the right being marginally lower. The ureter then continues anteriorly on the psoas major muscle, crossing under the gonadal vein at the level of the inferior pole of the kidney. The ureters course medial to the sacroiliac joint and then curve laterally in the pelvis. The colon and its mesentery are associated anterior

to the ureters. Specifically, the cecum, appendix, and ascending colon lie over the right ureter, and the descending and sigmoid colon lie over the left ureter.(45)

Pelvic ureter

The ureter enters the pelvis, where it crosses anteriorly to the iliac vessels, which usually occurs at the bifurcation of the common iliac artery into the internal and external iliac arteries. Here, the ureters are within 5 cm of one another before they diverge laterally.

The ovarian vessels travel in the suspensory ligament of the ovary (infundibulo pelvic ligament) and cross the ureter anteriorly and lateral to the iliac vessels. The ureters then course out to the ischial spines before coursing medially to penetrate the base of the bladder. The anteromedial surface of the ureter is covered by peritoneum, and the ductus deferens runs anteriorly. It travels with the inferior vesical neurovascular pedicle into the bladder. In females, the ureter runs posterior to the ovary and then deep to the broad ligament and through the cardinal ligament. The uterine artery crosses anteriorly in the rectouterine fold of peritoneum. (46)

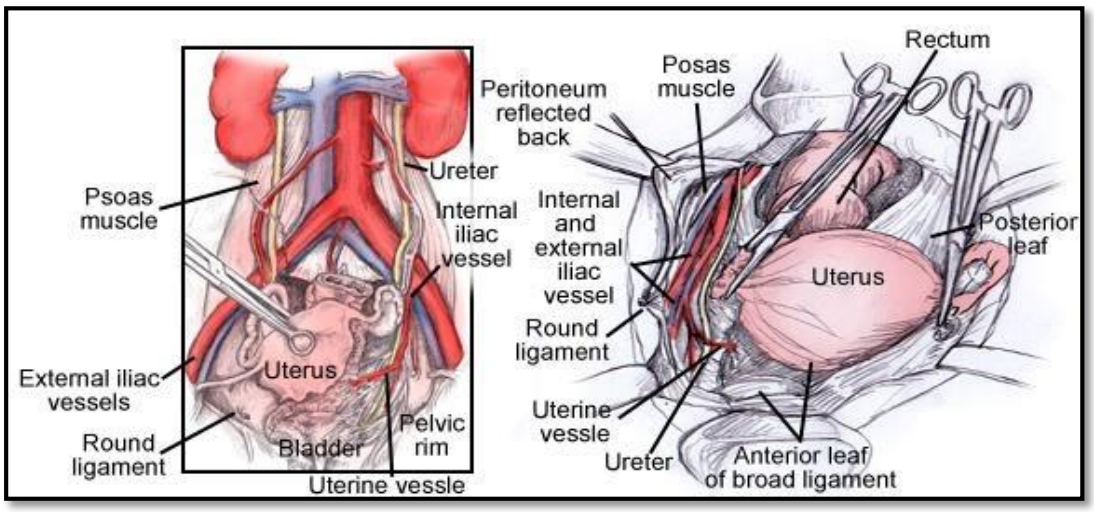


Figure 1: Blood supply and lymphatic drainage

The vascular supply and venous drainage of the ureter is derived from varied and numerous vessels. One critical feature is that the arterial vessels travel longitudinally in the periureteral adventitia. In the abdominal ureter, the arterial supply is located on the medial aspect of the ureter, whereas in the pelvis, the lateral aspect harbors the blood supply. The upper ureter is supplied by the renal artery and by branches from the gonadal artery and aorta. The arterial supply of the middle ureter is derived from the common iliac and gonadal arteries. Finally, the distal ureter is supplied by branches of the common iliac and internal iliac branches, particularly uterine and superior vesical arteries. The venous drainage is paired with the arteries. Knowledge of this vascular supply is crucial in ureteral surgery, because a devascularized ureter is subject to complications of stricture and leak. Lymphatic drainage of the upper ureter joins the renal lymphatics to the lumbar nodes. The middle ureter drains to the common and internal iliac nodes. The lymphatic vessels of the pelvic ureter drain to the internal iliac and vesical nodes.

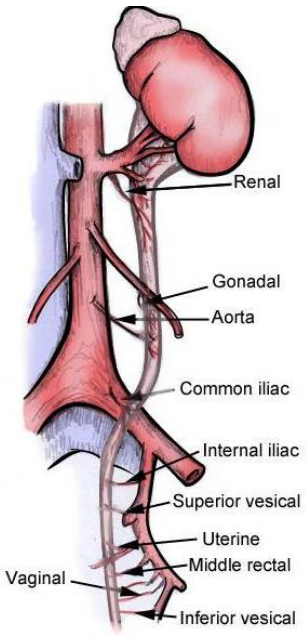


Figure 2 : Arterial supply to the ureter

The ureter has an intrinsic pacemaker that governs peristalsis but also has autonomic inputs. Thoracolumbar preganglionic inputs synapse with aorticorenal and inferior and superior hypogastric sympathetic plexuses before innervating the ureter. Parasympathetic inputs derive from the S2-S4 segments. Mucosal irritation and luminal distention stimulate nociceptors whose afferents travel with sympathetic nerves and confer the visceral-type referred pain that results in the manifestations of ureteral colic. Pain or hyperesthesia may be sensed from the region of the ipsilateral ribs down to the scrotum or labia.

Clinical corollaries

Close association of the abdominopelvic viscera places the ureter at risk for inflammatory, infectious, or malignant processes of the colon, appendix, oviducts, or ovaries. This may manifest as hematuria, pyuria, fistula, or obstruction. The mass effect of constipation, gravid uterus, or ovarian cysts may obstruct the ureter. The aorta and iliac vessels may exert deleterious effects on the ureter by mass effect or fibrotic reaction from the vasculopathy itself or by complications of the surgical management of aortoiliac disease.

The ureter has 3 physiologic narrowing's: (1) the ureteropelvic junction, (2) the crossing over the iliac vessels, and (3) the ureterovesical junction. This is crucial in the manifestations of calculus disease. These narrowing's may result in ureteral stones becoming trapped and obstructing at these specific levels. These narrowing's may also limit retrograde instrumentation performed for diagnostic or therapeutic purposes. The close association of the ovarian vessels at the level of the pelvic brim and the uterine artery in the rectouterine fold render the ureter subject to injury during oophorectomy or hysterectomy, as they are just deep to the crucial vasculature.(47)

URETERIC STONES

The stone that obstructs a patient's ureter originates in his kidney. Once it is free in his renal pelvis, it may pass into his ureter, and it can stick anywhere, but it is most likely to stick: (1) at his pelviureteric junction, (2) in the upper or (3) in the lower third of his ureter, or (4) at the entry of his ureter into his bladder. A stone is usually rough, so that some urine can usually leak past it to begin with. Later, obstruction becomes complete, so that after some weeks or months, he develops a hydronephrosis or a hydroureter, which may become infected.

Epidemiology

The lifetime prevalence of ureteric calculi is relatively high, occurring in approximately 12% of men and 7% of women (48). The risk is increased with a past history of ureteric calculi and with positive family history. Most patients present between ages 30 and 60 2, with peak incidence between ages 35-45. Initial calculus presentation occurring past age 50 is uncommon. (49)

Clinical features

A stone passing down the ureter often causes intermittent attacks of ureteric colic.

Ureteric colic

The waves of agonizing loin pain are typically referred to the groin, external genitalia and the anterior surface of the thigh. As the stone enters the bladder, the pain can be referred to the tip of the penis.

Impaction

There are five sites of narrowing where the stone may be arrested. An impacted stone causes a more consistent dull pain, often in the iliac fossa and increased by exercise and lessened by rest. Distension of the renal pelvis due to obstruction may cause loin pain. The stone may become embedded as the adjacent ureteric wall becomes eroded and oedematous as a result of pressure ischaemia. Perforation of the ureter and extravasation of urine is a rare complication.

Severe renal pain subsiding after a day or so suggests complete ureteric obstruction. If obstruction persists after 1–2 weeks, the calculus should be removed to avoid pressure atrophy of the renal parenchyma.

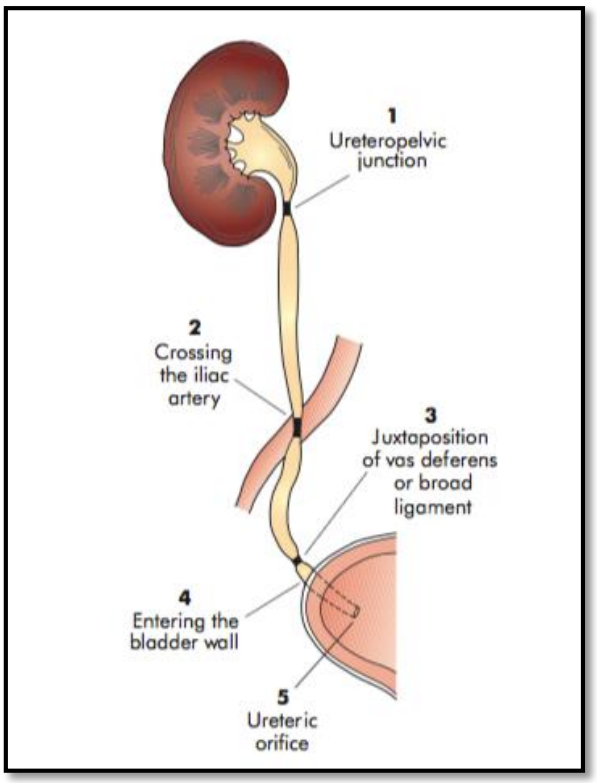


Figure 3 : Five sites of narrowing where the stone may be arrested

Haematuria

Almost all ureteric colic is associated with transient microscopic haematuria. Serious bleeding is uncommon and should suggest clot colic.

Patients may also present with nausea and vomiting. The quality and location of pain is dependent on the location of the calculi within the ureter. Calculi within the ureteropelvic junction may cause deep flank pain due to distension of the renal capsule, without radiation to the groin, whereas pain from upper ureteral calculi radiates to the flank and lumbar areas. Calculi in the mid-ureter result in pain radiating anteriorly, while pain from distal ureteric calculi radiates to the groin via referred pain from the genitofemoral or ilioinguinal nerves. Calculi in the ureterovesical junction may also cause irritative voiding symptoms such as dysuria and urinary frequency. (50)

Pathology

Up to 80% of renal calculi are formed by calcium stones 3. Other types include struvite, uric acid and cystine stones. In specific patient groups, mucoprotein (matrix), xanthine or indinavir stones may be (rarely) encountered. Calculi formation is likely due to two mechanisms. The first is where stone forming substances such as calcium or uric acid supersaturate the urine beginning crystal formation. The other mechanism depends on stone forming substances depositing in the renal medullary interstitium forming a Randall plaque 4 and eventually eroding into the papillary urothelium, creating a calculus. In addition to history of prior ureteric calculi and family history, other risk factors for ureteric calculi include low fluid intake, frequent urinary tract infections and medications that may crystalise the urine.(51)

Abdominal Examination

There is tenderness and some rigidity over some part of the course of the ureter. The presence of haematuria does not rule out appendicitis because an inflamed appendix can give rise to a local ureteritis leaking some red cells into the urine. The patient with acute ureteric colic is usually in greater pain and less ill than one with appendicitis or acute cholecystitis.

Imaging

Most urinary calculi are radio-opaque. Stones are difficult to see if small or obscured by bowel contents or nearby bones. IVU while the patient has pain can confirm the diagnosis, although spiral CT is preferable. In ureteric colic, there will probably be little or no excretion on the affected side. Occasionally, there is an extravasation of contrast from the dilated system. Late x-rays, taken up to 36 hours after the injection of contrast, may show dilatation of the ureter down to an obstructing calculus. A radiolucent uric acid stone may be demonstrated as a filling defect in the contrast-filled system. Analgesic abusers occasionally fake symptoms to obtain drugs, and emergency imaging is useful in excluding renal colic. If the CT or urogram is normal during an attack, the patient does not have renal colic. The absence of blood in the urine makes colic less likely but its presence can be simulated. Cystoscopy is not indicated routinely but may reveal oedema around the ureteric orifice when the stone is nearby. Retrograde ureterography is performed as an immediate preliminary to an endoscopic operation to remove a calculus.(52)

CT - IVP is the gold standard for imaging ureteric stones, with the vast majority (99%) being radiodense. Stones > 1 mm in size are visualized, with the specificity of helical CT as high as 100% 5. Scanning the patient in the prone position is preferred

as this gives certainty as to whether a stone remains impacted within the ureterovesical ostium or if it has passed freely into the bladder (53). A stone will always fall dependently and sit along the anterior bladder wall once it is free of the ostium in a prone patient. Alternatively, some centers will 'flip' the patient and re-scan the pelvis if a stone is identified at the ureterovesical junction/bladder base on the supine scan. The choice is often one of practicalities depending on the list supervision and staff involved.

CT - IVP can also detect secondary signs of urinary tract obstruction, including ureterohydronephrosis and perinephric stranding. In patients with little pelvic fat, distinguishing a ureteric calculus from a phlebolith can be challenging. Two signs have been found helpful:

- comet-tail sign: favours a phlebolith
- soft-tissue rim sign: favours a ureteric calculus

Ultrasound

While CT is the gold standard test, there is recent evidence that screening patients with ultrasound in the emergency department can help avoid CT in more half of patients leading to reduced cumulative radiation dose without increasing complications, pain scores, emergency department visits or hospitalizations.(54)

Ultrasound may be used for patients who need to avoid radiation, such as pregnant women. It is also useful for assessing for complications, such as hydronephrosis or pyonephrosis and in aiding percutaneous nephrostomy tube insertion in septic patients. Features include:

- echogenic foci
- acoustic shadowing
- twinkle artefact on colour Doppler
- colour comet-tail artefact

Treatment

Most patients presenting with acute renal colic due to ureteric calculi can be managed conservatively with hydration and analgesia until the calculi pass. NSAID's are as effective as opioids (55). Hospitalization may be required where oral analgesia is insufficient, in patients with a solitary kidney or in patients with urosepsis or acute kidney failure.

Calculus size and location as well as ureter anatomy are important factors in determining the likelihood of spontaneous calculus passage (56). Spontaneous passage by 20 weeks has been reported at the following rates (axial dimension) (57):

- 0-3 mm: 98%
- 4 mm: 81%
- 5 mm: 65%
- 6 mm: 33%
- >6.5 mm: 9%

In calculi >10 mm or with failed conservative management, urological procedures such as extracorporeal shockwave lithotripsy (ESWL), ureteroscopic lithotripsy, or percutaenous nephrostomy may be required.

Endoscopic stone removal

Dormia basket

The use of wire baskets under image intensifier control has been replaced by ureteroscopic techniques but they may be useful when the instruments and expertise are not available. There is a danger of ureteric injury even with small stones.

Ureteric meatotomy

Endoscopic incision with a diathermy knife will enlarge the opening and free a stone lodged in the intramural ureter. The consequent urinary reflux rarely causes problems.

Ureteroscopic stone removal

A ureteroscope is introduced transurethrally across the bladder into the ureter to remove stones impacted in the ureter. Stones that cannot be caught in baskets or endoscopic forceps under direct vision are fragmented using an electro-hydraulic, percussive or laser lithotripter.

A stone in the middle or upper part of the ureter can often be flushed back into the kidney using a ureteric catheter. A J-stent secures the calculus in the kidney for subsequent treatment with ESWL. A flexible fibreoptic ureteroscope can be used for laser destruction of calculi in the renal collecting system or ureter and to retrieve small stones from the kidney.

Lithotripsy in situ a stone in a part of the ureter that can be identified by the imaging system of the lithotripter can be fragmented in situ. This form of treatment is not appropriate if there is complete obstruction or if the stone has been impacted for a long time.

Open surgery

Ureterolithotomy

An x-ray confirms the position of the stone immediately before surgery.

The skin incision must be appropriate for the position of the stone. Calculi in the upper third of the ureter are approached through a loin or upper quadrant transverse incision as used for a stone in the renal pelvis. Access to midureteric stones is through a muscle-cutting iliac fossa incision; lower ureteric stones are best reached through a Pfannenstiel incision. For stones close to the bladder, exposure is improved by ligating and dividing the superior vesical vascular pedicle. The ureter is exposed in the retroperitoneum and slings are applied above and below the calculus to stop it from escaping. The ureter is incised longitudinally, directly on to the stone, which is freed by blunt dissection and removed with stone forceps. Soft catheters are passed upwards and downwards to ensure that the ureter is clear. The ureterotomy is closed with interrupted absorbable sutures and a drain left to drain urine leakage. The operation can be performed laparoscopically, but alternative minimal access techniques described above are usually preferable.(52)

Medical expulsive therapy

This treatment comprises the use of drugs to help the spontaneous passage of ureteral calculi. Several drugs including calcium channel blockers (nifedipine), steroids, and α adrenergic blockers have recently been investigated. (58) The rationale for using α blockers is based on the presence of large numbers of α1 adreno receptors in the distal ureter. These blockers inhibit basal ureteral tone and peristaltic frequency and decrease the intensity of ureteral contractions. A recent prospective randomised study

compared three drugs as medical expulsive therapy for distal ureteral calculi. (59) Two hundred and ten patients with symptomatic distal ureteral stones >4 mm were randomly assigned to three treatment groups: phloroglucinol and corticosteroid, Tamsulosin and corticosteroid, or nifedipine and corticosteroid. Tamsulosin and corticosteroid was the most efficacious combination—stones were passed more quickly and the need for analgesics was reduced. A randomised controlled prospective study has also shown Tamsulosin to be a useful addition to shock wave lithotripsy. (60)

Once the calculus is passed out, should be sent for analysis to evaluate for possible underlying causes of stone disease and better plan for future prevention.

Tamsulosin (61)

Tamsulosin , a benzensulfonamide , is an α_1 receptor antagonist with some selectivity for α_{1A} (and α_{1D}) subtypes as compared to the α_{1B} subtype.(uroselective)

Structure :

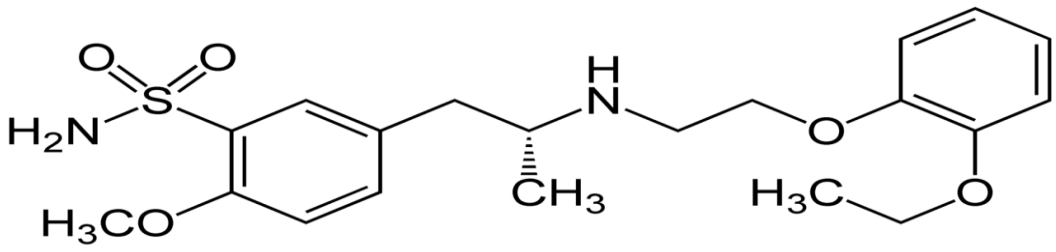


Figure 4 : Structure of Tamsulosin

Chemistry :

Chemically, it is (R)-5-(2-{(2-(2-ethoxyphenoxy) ethyl) amino} propyl) – 2 - methoxybenzene - 1-sulfonamide . Tamsulosin is a white crystalline powder which is

soluble in water. It is available in hydrochloride form. Its empiric formula is $C_{20}H_{28}N_2O_5S$•HCl and its molecular weight is 408.51 daltons.

Mechanism of action:

There are 2 component bladder outlet obstruction with BPH: static (related to the mechanical obstruction caused by the enlarged prostate) and Dynamic (determined primarily by smooth muscle tone in the prostate, prostatic urethra and bladder base). α_1- adrenoceptors predominate in the prostate and bladder base, and contraction of prostatic smooth muscle is mediated by sympathetic nervous system stimulation of these receptors. Pharmacological (functional and ligand binding) and molecular cloning studies have revealed a number of different α_1 adrenoceptor subtypes.

α_{1A} adrenoceptors appears to be the predominant α_1 adrenoceptor subtype in human prostate. Furthermore, α_{1A} adrenoceptors appear to mediate human prostatic smooth muscle contraction induced by α_1 adrenoceptor activation. Evidence suggest that the α_{1B} and α_{1D} adrenoceptors subtypes are involved in smooth muscle contraction of large arteries, and that both α_{1A} and α_{1B} adrenoceptors subtypes may coexist in the prostate.

Tamsulosin is the only clinically available α_1 adrenoceptor antagonist that shows selectively for a $\alpha_1$adrenoceptor subtype. The drug has 7 to 38 times greater affinity for α_{1A} than α_{1B} adrenoceptors. In radioligand binding studies, Tamsulosin had greater affinity for the cloned α_{1A} and α_{1D} adrenoceptors than for the α_{1B} adrenoceptors. In contrast , binding affinities of Alfuzosin , Doxazosin, Prazosin and Terazosin were equipotent for the 3 receptors. The rank order of selectivity of Tamsulosin for cloned α_1 adrenoceptor subtypes is $\alpha_{1a} > \alpha_{1d} > \alpha_{1b}$.

Tamsulosin is a stereoisomer. The binding affinity of the R (-)-isomer of Tamsulosin to α_1 adrenoceptor subtypes is greater than that of the S (+)-isomer

Pharmacokinetic properties:

Tamsulosin, as controlled release oral formulas, is suitable for once-daily administration. It is gradually absorbed, with bioavailability of almost 100%. The extent and rate of absorption are reduced by food. The maximum plasma concentration (Tmax) occurred at 0.96 to 1.25 hr with single oral doses of a conventional formulation of Tamsulosin 0.05, 0.1 and 0.2 mg. It is 99% plasma protein binding. Tamsulosin has a volume of distribution of 16 L and t1/2 9 hr.

Tamsulosin is slowly metabolized in the liver by cytochrome P450 isoenzyme, CYP3A4 and CYP2D6. The Predominant metabolites are M-1-Sul ,AM-1,M-1 and M-2. Metabolites retain the selective α_{1A} and α_{1D}-adrenoceptor antagonistic activity of the parent compound.

Tamsulosin is excreted mainly as metabolites in the urine (76%) and in faeces (21%). Systematic clearance is relatively slow i.e. 2.88L/h and elimination half life is 9 hours.

Uses

BPH:

Until recently, nonselective α adrenergic antagonists (phenoxybenzamine) and short acting (Prazosin, Alfuzosin) and long acting (Terazosin , Doxazosin) nonsubtype–selective α_1 adrenoceptor were available. However, Vasodilator cardiovascular

adverse events, especially postural hypotension and syncope, due to blockage of vascular α_1 adrenoceptors have been problematic with these agents.

The identification of multiple α_1 adrenoceptor subtypes and the finding that α_{1A} adrenoceptors appear to play a major role in mediating human prostate smooth muscle contraction have aided in developing an α_1 adrenoceptors antagonist with specificity for the prostate. Tamsulosin is the first clinically available α_1 adrenoceptor antagonist to selectively antagonize an α_1 adrenoceptor subtype. This agent consequently has greater affinity for α_1 adrenoceptors in the prostate than in the vasculature. This properties gives Tamsulosin a major potential clinical advantage over other less – selective α_1 adrenoceptor antagonists, as the drugs shows minimal cardiovascular effects.

Bladder Outlet Obstruction:

Tamsulosin is a selective antagonist of alpha-1A and alpha-1B-adrenoceptors in the prostate, prostatic capsule, prostatic urethra, and bladder neck. At least three discrete alpha1-adrenoceptor subtypes have been identified: alpha-1A, alpha-1B and alpha-1D; their distribution differs between human organs and tissue. Approximately 70% of the alpha1-receptors in human prostate are of the alpha-1A subtype. Blockage of these receptors causes relaxation of smooth muscles in the bladder neck and prostate.

Ureteral Calculus:

Tamsulosin has equal affinity for α1a and α1d receptors. The α1d receptor is the most common receptor in the ureter and is most concentrated in the distal ureter. It reduces ureteral spasm, increase pressure proximal to the stone, and relax the ureter in the region of and distal to the stone. The rationale in using it in MET has been that they

are capable of decreasing the force of ureteral contraction, decreasing the frequency of peristaltic contractions, and increasing the fluid bolus volume transported down the ureter. It increases rates of spontaneous stone expulsion and decreases the time to stone expulsion. Importantly, it decreases the amount of pain patients suffer while passing their stones. (62)

Thus, the main potential advantages of Tamsulosin are:

- Selectivity for α_{1A} adrenoceptor and greater affinity for α_1 adrenoceptor in the prostate than in the vasculature.
- No clinically relevant effect on blood pressure or heart rate and minimal vasodilatory cardiovascular adverse events
- Lack of need for dose titration to minimize adverse events
- Once-daily administration

Dosage form and route of administration:

Tamsulosin is available in the form of capsule. It is given orally. It is available in the strength of 0.2 mg and 0.4 mg given once a day. Dose titration is not necessary.

Dosage adjustment are not required in patients with coexisting renal impairment or mild to moderate hepatic impairment; however, there are no pharmacokinetic data available specifically in patients with a creatinine clearance of < 10 ml/min. Tamsulosin is contraindicated in patient with sever hepatic insufficiency because there was no data available in this patient group.

Adverse effects:

Abnormal ejaculation is an adverse effect of Tamsulosin, experienced by ≈ 18% of patient receiving the higher doses. It may cause dizziness.

Precaution:

- If you are allergic to Tamsulosin, sulfa medications, or any other medications.
- Ever had prostate cancer or liver or kidney disease.
- That Tamsulosin may cause dizziness, lightheadedness, a spinning sensation, and fainting, especially when get up too quickly from a lying position. This is more common when first start taking Tamsulosin or after dose is increased.
- During Cataract surgery. It may cause intraoperative floppy iris syndrome.

Drug interactions:

There is potential for interaction between Tamsulosin and other CYP- mediated compounds. In vitro testing with Amitryptaline, Salbutamol, Glibenclamide and Finasteride disclosed no clinically significant metabolic interaction, but the results are equivocal between Tamsulosin and Diclofenac or Warfarin. more over, Amitryptaline, Diclofenac, Glibenclamide, Simvastatin , Warfarin, Diazepam, Propranolol, Trichlormethiazide did not affect the extent of binding of Tamsulosin to plasma protein , and Tamsulosin did not affect the binding of these drugs, in two-way in vitro studies (Boehringer Ingelheim., 2000). In controlled clinical trials, no clinically significant interaction occurred when Tamsulosin was administered with Nifedipine, Atenolol or Enalapril. There is no significant effect of Tamsulosin over oral Anticoagulant, Digoxin, and Theophylline, Furosemide.

Tadalafil (63)

Tadalafil is an orally adminstered drug used to treat male erectile dysfunction. It is marketed worldwide under the brand name Tadalafil. It is a phosphodiesterase 5 (PDE5) inhibitor. Tadalafil's distinguishing pharmacologic feature is its longer half-life (17.5 hours) compared with Viagra and Levitra (4-5 hours). This longer half-life results in a longer duration of action and is, in part, responsible for the Tadalafil nickname of the "weekend pill." This longer half-life also is the basis of current investigation for Tadalafil's use in pulmonary arterial hypertension as a once-daily therapy.

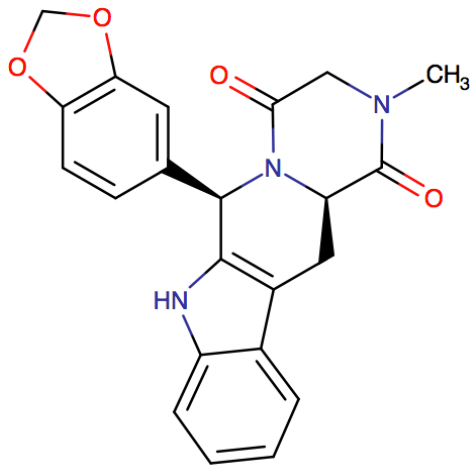


Figure 5 : Structure of Tadalafil

Structure

Chemistry

C22H19N3O4

The chemical designation is pyrazino(1′,2′:1,6)pyrido(3,4-b)indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

It is available as film-coated, almond-shaped tablets for oral administration. Each tablet contains 5, 10, or 20 mg of Tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

Pharmacokinetics

Over a dose range of 2.5 to 20 mg, Tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once-daily dosing, and exposure is approximately 1.6-fold greater than after a single dose. Tadalafil is eliminated predominantly by hepatic metabolism, mainly by cytochrome P450 3A4 (CYP3A4). The concomitant use of potent CYP3A4 inhibitors such as ritonavir or ketoconazole resulted in significant increases in Tadalafil AUC values.

Tadalafil is used to treat male erectile dysfunction and pulmonary arterial hypertension (PAH). Part of the physiological process of erection involves the release of nitric oxide (NO) in the corpus cavernosum. This then activates the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation in the corpus cavernosum, resulting in increased inflow of blood and an erection. Tadalafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. This means that, with Tadalafil on board, normal sexual stimulation leads to increased levels of cGMP in the corpus cavernosum which leads to better erections. Without sexual

stimulation and no activation of the NO/cGMP system, Tadalafil should not cause an erection.

Mechanism of action

Tadalafil inhibits the cGMP specific phosphodiesterase type 5 (PDE5). It is a carboline-based compound with vasodilatory activity. Tadalafil selectively inhibits the cyclic guanosine monophosphate (cGMP)-specific type 5 phosphodiesterase-(PDE-5)-mediated degradation of cGMP, which is found in the smooth muscle of the corpus cavernosa and corpus spongiosum of the penis. Inhibition of cGMP degradation by Tadalafil results in prolonged muscle relaxation, vasodilation, and blood engorgement of the corpus cavernosa, and, so, prolonged penile erection.

It is responsible for degradation of cGMP in the corpus cavernosum located around the penis. Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) by Tadalafil enhances erectile function by increasing the amount of cGMP.

Dosage and Route of Administration

The recommended starting dose of Tadalafil in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

Tadalafil was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of this drug, this should be taken into consideration. It may be taken without regard to food.

Uses

Benign Prostatic Hyperplasia (BPH)

Erectile Dysfunction (ED)

Pulmonary Arterial Hypertension (PAH)

Tadalafil is a prescription medicine used to treat impotence, known medically as erectile dysfunction (ED), and symptoms of enlarged prostate (benign prostatic hyperplasia, or BPH).

It is also is used to improve the ability to exercise in people with pulmonary arterial hypertension, or PAH. PAH is high blood pressure in the vessels carrying blood to the lungs, causing shortness of breath, dizziness, and tiredness.

Medical Expulsive Therapy (MET) for lower ureterolithiasis with Tadalafil 10mg during watchful waiting period is proved safe and effective as demonstrated by the absence of serious side effects and increased stone expulsion rate with early time in a study. MET with Tadalafil 10mg affords an outstanding control of pain for patients while waiting for stone expulsion.(64)

Adverse Drug Reactions

The most common side effects with Tadalafil are:

- headache
- indigestion
- back pain
- muscle aches
- flushing
- stuffy or runny nose

Uncommon side effects include:

- an erection that won't go away (priapism). If you get an erection that lasts more than 4 hours, get medical help right away. Priapism must be treated as soon as possible or lasting damage can happen to your penis, including the inability to have erections.
- color vision changes, such as seeing a blue tinge (shade) to objects or having difficulty telling the difference between the colors blue and green

PRECAUTIONS

Evaluation of erectile dysfunction should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options. Before prescribing Tadalafil, it is important to note the following:

Alpha-blockers

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly which may lead to symptomatic hypotension (e.g., fainting).

Renal Insufficiency

It should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. The starting dose of Tadalafil in patients with a moderate degree of renal insufficiency should be 5 mg not more than once daily, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency.

Hepatic Impairment

In patients with mild or moderate hepatic impairment, the dose of it should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of Tadalafil in this group is not recommended.

Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)

Tadalafil is metabolized predominantly by CYP3A4 in the liver. The dose of Tadalafil should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and Itraconazole.

General

As with other PDE5 inhibitors, Tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, Tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects.

While this effect should not be of consequence in most patients, prior to prescribing Tadalafil, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with significant left ventricular outflow obstruction or severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators.

The safety and efficacy of combinations of Tadalafil and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Tadalafil should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

When administered in combination with aspirin, Tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. Tadalafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although Tadalafil has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

Drug Interactions

Cytochrome P450 Inhibitors

Tadalafil is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase Tadalafil exposure.

Ketoconazole - Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased Tadalafil 20-mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for Tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased Tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for Tadalafil 10 mg alone.

HIV Protease inhibitor - Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased Tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for Tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased Tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for Tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase Tadalafil exposure.

Based upon these results, in patients taking concomitant potent CYP3A4 inhibitors, the dose of Tadalafil should not exceed 10 mg, and Tadalafil should not be taken more frequently than once in every 72 hours

Other cytochrome P450 inhibitors — although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, Iitraconazole, and grapefruit juice, would likely increase Tadalafil exposure.

Cytochrome P450 Inducers

Studies have shown that drugs that induce CYP3A4 can decrease Tadalafil exposure.

Rifampin — Rifampin (600 mg daily), a CYP3A4 inducer, reduced Tadalafil 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for Tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease Tadalafil exposure. No dose adjustment is warranted.

Gastrointestinal Drugs

H_2 antagonists - An increase in gastric pH resulting from administration of Nizatidine had no significant effect on Tadalafil pharmacokinetics.

Antacids - Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and Tadalafil reduced the apparent rate of absorption of Tadalafil without altering exposure (AUC) to Tadalafil.

Effects of Tadalafil on Other Drugs

Drugs Metabolized by Cytochrome P450

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have

shown that Tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 substrate — Tadalafil had no clinically significant effect on the pharmacokinetics of theophylline. When Tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP3A4 substrates - Tadalafil had no clinically significant effect on exposure (AUC) to midazolam or lovastatin.

CYP2C9 substrate - Tadalafil had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did Tadalafil affect changes in prothrombin time induced by warfarin.

Alcohol

Alcohol and PDE5 inhibitors, including Tadalafil, are mild systemic vasodilators. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect Tadalafil plasma concentrations. Both alcohol and Tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with Tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Anti-Hypertensives

PDE5 inhibitors, including Tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of Tadalafil on the potentiation of the blood-pressure-lowering effects of selected anti-hypertensive medications.

Tamsulosin - A single oral dose of Tadalafil 10, 20 mg, or placebo was administered in a 3-period, crossover design to healthy subjects taking 0.4 mg once-daily Tamsulosin, a selective alpha (1A)-adrenergic blocker (N=18 subjects). Tadalafil or placebo was administered 2 hours after Tamsulosin following a minimum of seven days of Tamsulosin dosing.

Epidemiological Review

Global

Parsons JK et al. (2007) performed meta-analysis of randomized clinical trials of α-blockers for the treatment of ureteral stones. The primary outcome was overall stone expulsion rate. Pooled analysis demonstrated significantly increased rates of stone expulsion with α-blocker therapy. Compared to patients receiving conservative therapy only, patients receiving conservative therapy plus α-blockers were 44% more likely to spontaneously expel the stones (RR 1.44, 95% CI 1.31 to 1.59, p <0.001), and stone expulsion incidence increased significantly (RD 0.28, 95% CI 0.22 to 0.34, p <0.001). Sensitivity and subgroup analyses categorized by specific α-blocker, prior use of shock wave lithotripsy and stone size produced similar effect estimates, but were generally less precise due to smaller sample sizes. The largest subgroup of trials (664 participants) studied Tamsulosin without prior shock wave lithotripsy. α-Blocker

therapy was seen to associated with significantly increased rates of distal ureteral stone expulsion.(65)

KC HB et al. (2016) conducted a prospective randomized study was performed in a tertiary care hospital in Kathmandu, Nepal, from June 2015 to May 2016. The study aimed to compare the safety and efficacy of Tamsulosin and Tadalafil as medical expulsive therapy for distal ureteral stones. Altogether 85 patients, 41 in group A and 44 in group B, were enrolled in the study. The patients' average age was 31.72±12.63 years, and the male-to-female ratio was 1.5:1. Demographic profiles, stone size, and baseline investigations were comparable between the 2 groups. The stone expulsion rate was significantly higher in the Tadalafil group than in the Tamsulosin group (84.1% vs. 61.0%, p=0.017). Although the occurrence of side effects was higher with Tadalafil, this difference was not significant (p=0.099). There were no serious adverse effects. Tadalafil has a significantly higher stone expulsion rate than Tamsulosin when used as a medical expulsive therapy for distal ureteral stones sized 5–10 mm. Both drugs are safe, effective, and well tolerated with minor side effects.(66)

India

Kumar S et al. (2015) conducted a pilot study to evaluate the role of Tamsulosin, Tadalafil, and Silodosin as the medical expulsive therapy in lower ureteric stone. 285 patients presenting with distal ureteric stones of size 5-10 mm were on consent randomly assigned to 1 of 3 outpatient treatment arms: Tamsulosin (group A), Silodosin (group B), and Tadalafil (group C). Therapy was given for a maximum of 4 weeks. Stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow-up, and endoscopic treatment and adverse effects of drugs were noted. All 3 groups were compared. They observed a statistically

significant expulsion rate of 83.3% in group B compared with 64.4% and 66.7% in groups A and C, respectively, with lower time of stone expulsion (*P* value = .006 and *P* value = .016, respectively). Statistically significant differences were noted in colicky episodes and analgesic requirement in group B than groups A and C. There was no serious adverse event. Medical expulsive therapy for the distal ureteric stones using Tamsulosin, Silodosin, and Tadalafil is safe, efficacious, and well tolerated. The result of this pilot study showed that Silodosin increases ureteric stone expulsion quite significantly along with better control of pain with significantly lesser analgesic requirement.(67)

Jayant K et al.(2014) conducted a study to compare the efficacy of Tamsulosin versus Tamsulosin plus Tadalafil as medical expulsive therapy for lower ureteric stones. Stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow up, endoscopic treatment and adverse effects of drugs were recorded. Patients presenting with distal ureteric stones (size 5–10 mm) were randomized equally to Tamsulosin (group A) or Tamsulosin plus Tadalafil (group B). There was a statistically significant higher expulsion rate in group B compared with group A (83.6% *vs* 65.5%; *P*-value = 0.031) and a shorter time to expulsion. Statistically significant differences were noted in terms of the number of hospital visits and analgesic requirement in favor of group B. There was no serious adverse event. An improvement in erectile function was noted in patients of group B compared with those of group A. Medical expulsive therapy for distal ureteric stones using Tamsulosin plus Tadalafil is safe, effective and well tolerated. Furthermore, Tadalafil provides the additional advantage of improving erectile dysfunction when this condition coexists with a lower ureteric stone.(68)

Puvvada S et al. (2016) conducted a study in Bangalore, Karnataka, India, to compare the safety and efficacy of a phosphodiesterase-5 inhibitor (Tadalafil) and an α-1 blocker (Tamsulosin) as medical expulsive therapy for distal ureteric calculi. Patients who presented with distal ureteric stones of size 5–10 mm were randomly divided into two groups: Tadalafil (Group A) and Tamsulosin (Group B). Therapy was given for a maximum of 4 weeks. Stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow-up, endoscopic treatment and adverse effects of drugs were noted. They observed statistically significant expulsion rate of 84.0% in Group A compared with 68.0% in Group B (*P* value = 0.0130), and shorter stone expulsion time in Group A (14.7±3.8) in comparison to Group B (16.8 ±4.5) was observed. Statistically significant differences were noted in renal colic episodes and analgesic requirement in Group A than Group B. No serious adverse effects were noted. They concluded that Tadalafil is safe, efficacious, and well tolerated as medical expulsive therapy for distal ureteric stones. This study showed that Tadalafil increases ureteric stone expulsion quite significantly along with better control of pain and significantly lower analgesic requirement.(69)

Girish TD et al. (2016) conducted study in Mysore, India to compare the safety and efficacy of Tamsulosin, Tadalafil, and combination of Tamsulosin with Tadalafil as medical expulsive therapy for lower ureteric stones. A total of 90 patients who presented with distal ureteric stones between September 2013 and August 2015 were simply randomised equally based on a computer generated table into three groups, group A received Tamsulosin, group B patients Tadalafil alone, and group C patients received a combination of Tamsulosin with Tadalafil. Therapy was given for a maximum of 4 weeks. The stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow-up endoscopic treatment, and adverse

effects of the drugs were noted. There was a higher expulsion rate 78% in group C, which received combination therapy compared to 75% in group B and 70% in group A. There was an increase in expulsion rate in patients with combination therapy, though statistical significance could not be demonstrated in this sample size. The analgesic requirement and hospital visits due to colic were decreased significantly in the combination therapy group and time to expulsion was also lesser in group C compared to group A and B. There were no serious adverse effects noted. Medical expulsive therapy for distal ureteric stones using combination of Tamsulosin and Tadalafil is safe and efficacious compared to monotherapy with either of the drugs alone. It significantly decreases the analgesic dose requirement and aids in pain relief as well.(70)

To compare Tadalafil and Tamsulosin in terms of medical expulsive therapy of distal ureteric stones

1. To evaluate its role in medical expulsive therapy in lower ureteric stones.
2. To review Outcome and complications of Tadalafil and Tamsulosin.
3. Compare the efficacy of Tadalafil and Tamsulosin in terms of the

    a) Stone expulsion rate.

    b) Time of stone expulsion.

STUDY SITE: - Dhiraj hospital

STUDY DESIGN: - Comparative study

SAMPLE SIZE: - 60 patients. 1st group and 2nd group- 30 each

STUDY PROCEDURE: - comparative study between efficacy of 2 drugs in terms of

Stone expulsion rate.

Time of stone expulsion.

STUDY PERIOD: - From date of approval of study – SEPTEMBER 2017

INCLUSION CRITERIA

1. Male or female patients aged 20 and over.
2. Patients having ureteral calculi located in lower ureter
3. Patients whose calculi measures 10 mm and less.
4. Patients who voluntarily decide to take part in this study and give written consent.

EXCLUSION CRITERIA

1. Patients who do not want to undergo expectant treatment.
2. Pregnant women or nursing mothers.
3. Patients with febrile UTI or severe hydronephrosis, hydroureter or ulcerative disease or hypotension.
4. Patients with severe hepatic dysfunction (e.g. Hepatic Cirrhosis, Hepatic failure).
5. Patients on α-blockers or α/β blockers or CCB or steroid.

6. Patients whose urinary tracts are anatomically deformed or stenosed.
7. Patients who underwent invasive operation on their ureter before.
8. Patients whose blood creatinine levels are 2mg/dl and over.
9. Patients who take part in clinical trials other than the present study.
10. Patients who are hypersensitive to drugs used in study.
11. Patients having lower ureteric calculi more than 1 cm.
12. Complex stone
13. Patients having severe clinical symptoms
14. Patients with co morbid condition.
15. Patients with age less than 20
16. Non compliance
17. Patient not willing for study.

METHOD OF STUDY

The present study is a prospective, randomized controlled trial. Between from the date of approval up to September 2017. After taking the consent from all the patients, each enrolled patient will be assessed by physical examination, serum creatinine, urine culture, X-Ray KUB, ultra- sonography and CT-IVP of the kidneys, ureters and bladder region as required and then 60 patients will be selected applying inclusion-exclusion criteria. These patients will be divided into two groups each of 30 patients, based on odd and even number of presentation. Patients in group A (odd no) will be given Tamsulosin 0.4 mg once daily, and those in group B (even no) will be given Tadalafil 10 mg once daily.

Patients will be instructed to take plenty of fluids, to take adequate analgesic orally during episodes of pain and filter their urine by using a standard mesh net to detect stone expulsion.

The patients were given treatment for a maximum period of 3 weeks or early till stone expulsion. Expulsion of the stone was confirmed with CT-IVP. Follow up is done in weekly intervals and data were recorded in a specially designed proforma. Stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow up, and adverse effects of drugs were recorded. It was transfer to a master chart then subjected to statistical analysis.

Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Data were tested first for normal distribution by Klomogorov – Smirnov test. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. Mann–Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21

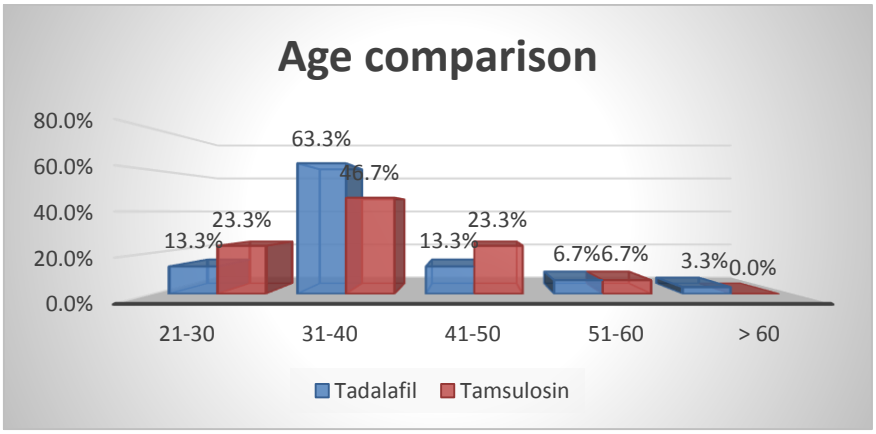
1) AGE DISTRIBUTION

TABLE 1:- COMPARISON OF STUDY GROUPS BASED ON AGE

Age Group	Group		Total
	Tadalafil	Tamsulosin	
21-30	**4**	**7**	**11**
	13.3%	23.3%	18.3%
31-40	19	14	33
	63.3%	46.7%	55.0%
41-50	4	7	11
	13.3%	23.3%	18.3%
51-60	2	2	4
	6.7%	6.7%	6.7%
> 60	1	0	1
	3.3%	0.0%	1.7%
Total	30	30	60
	100.0%	100.0%	100.0%
p- value - 0.49			

Out of 60 patients enrolled 18.3% were from 21-30 yrs and 41-50 yrs. Of age, 55% i.e. the maximum from 31-40 years of age, 6.7% from 51-60 years of age and 1.7% i.e. lowest from >60 years of age.

Most common age group affected by Lower ureteric calculus was between 31-40 years. Amongst that 55%, 63.3% were in Tadalafil group and 46.7% were in Tamsulosin group.



GRAPH 1: - GRAPH SHOWING AGE DISTRIBUTION

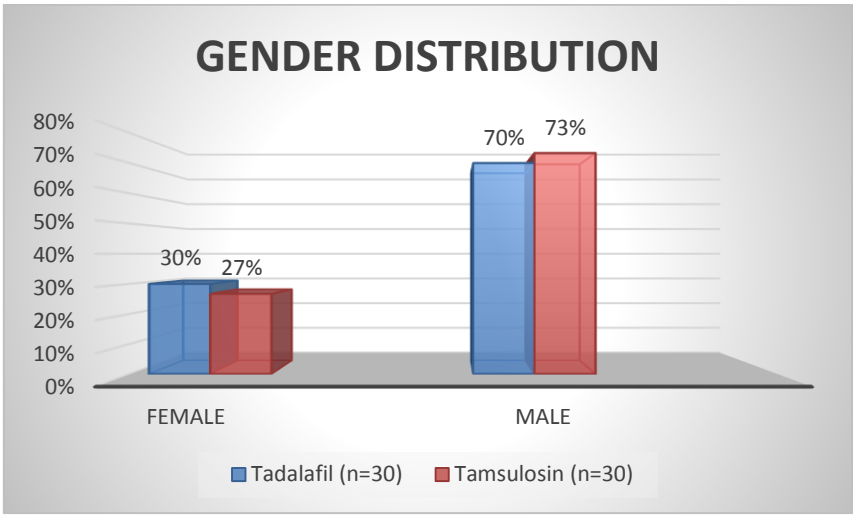
2) GENDER DISTRIBUTION

TABLE 2: - **COMPARISON OF STUDY GROUPS BASED ON GENDER**

Gender	Group		Total
	Tadalafil (n=30)	**Tamsulosin (n=30)**	
Female	9	8	17
	30.0%	26.7%	28.3%
Male	21	22	43
	70.0%	73.3%	71.7%
Total	30	30	60
	100.0%	100.0%	100.0%
p- value - 1.0			

Out of 60 patients 71.7% of them were males with only 28.3% as females. Amongst them in Tadalafil group 30% were females and 70% were males and in Tamsulosin group 26.7% were female and 73.3% were male.

This showed the male preponderance in the study population. It can be due to males working out in fields in hot environment which leads to dehydration. The quality of water can also affect the study population.

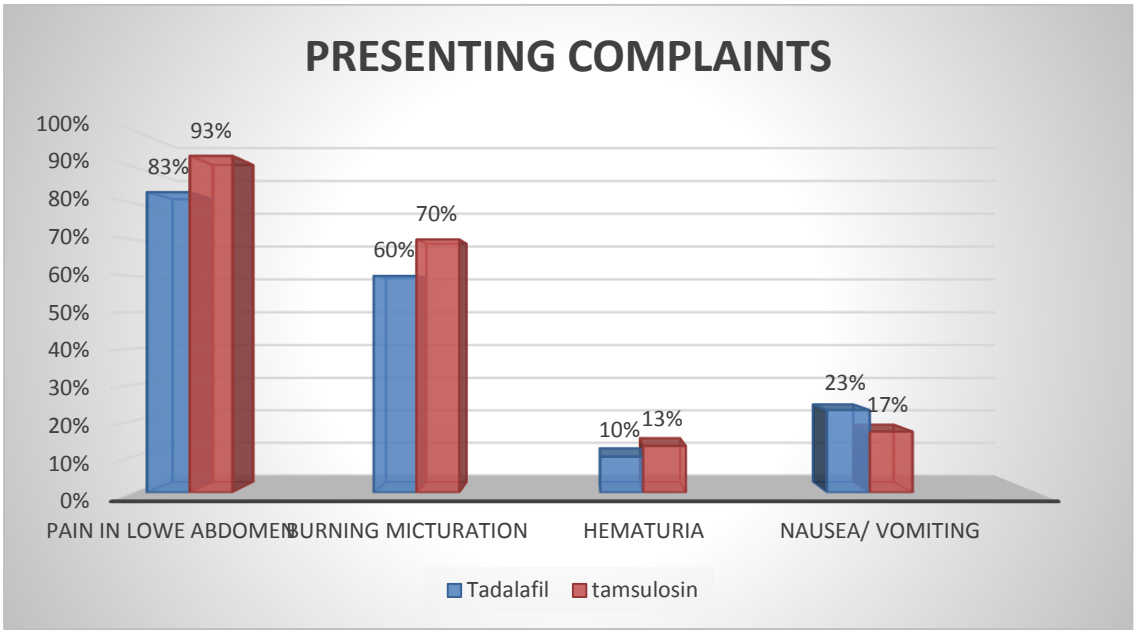


GRAPH 2:- GRAPH SHOWING GENDER DISTRIBUTION

3) PRESENTING COMPLAIN

TABLE 3:- COMPARISON OF STUDY GROUPS BASED ON PRESENTING COMPLAINTS

PRESENTING COMPLAINTS	GROUP		TOTAL
	Tadalafil (n=30)	Tamsulosin (n=30)	
Pain in Lower Abdomen	**25**	**28**	**53**
	83%	93%	88%
Burning Micturation	**18**	21	39
	60%	**70%**	65%
Hematuria	**3**	4	7
	10%	**13%**	12%
Nausea/Vomiting	**7**	5	11
	23%	**17%**	18%



GRAPH 3:- GRAPH SHOWING PRESENTING COMPLAINTS

This table shows the frequency and percentage of patients having different symptoms in both group.

Pain in lower abdomen was found in 88% (n=53) of which 83% were from Tadalafil group and 93% from Tamsulosin group keeping n=30 in each group.

Patients presenting with complaints of burning micturation were 60% and 70% respectively in Tadalafil and Tamsulosin group.

Hematuria was seen in only 10% of patients in Tadalafil group and 13% in Tamsulosin group while nausea or vomiting was seen in 23% and 17% respectively in Tadalafil and Tamsulosin group. The maximum no. of patients came to opd with the complaint of lower abdominal pain i.e. 88% with decreasing frequency, Burning micturation(65%), nausea/vomiting(18%) and hematuria (12%).

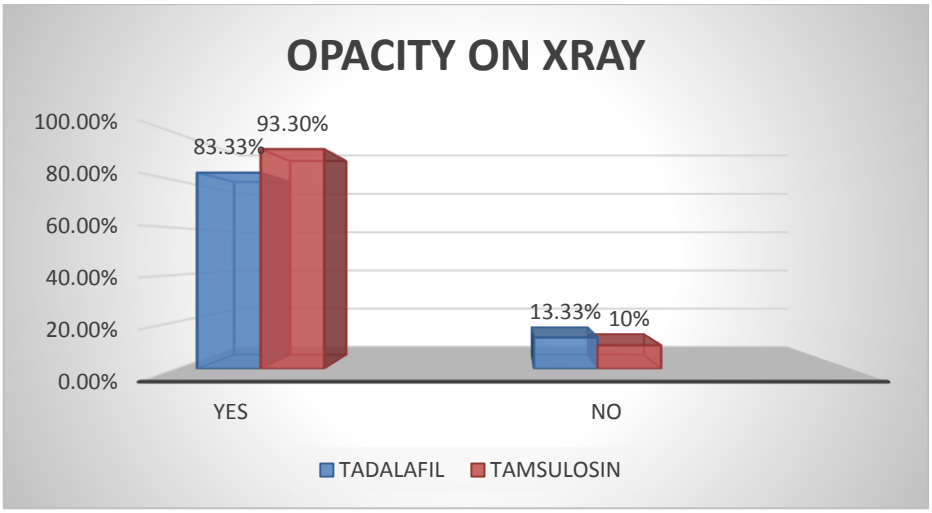
4) X-RAY

TABLE 4. DISTRIBUTION OF SUBJECTS AS PER OPACITY ON X-RAY-KUB

OPACITY ON XRAY	GROUP		TOTAL
	TADALAFIL	TAMSULOSIN	
YES	25	28	53
	83.33%	93.30%	88%
NO	4	3	7
	13.33%	10%	23.33%

Out of 60 patients 88 % (n=53) had radio-opaque shadow on X-ray KUB. In Tadalafil group 83.3% had opacity on X-ray-KUB and 13.3% didn't had while in Tamsulosin group 93.3% of patients had opacity on X-ray-KUB and 10% didn't had.

As X-ray KUB is easy, confirmatory, early and affordable test for for the patient it was done to see the size and location of the stone.

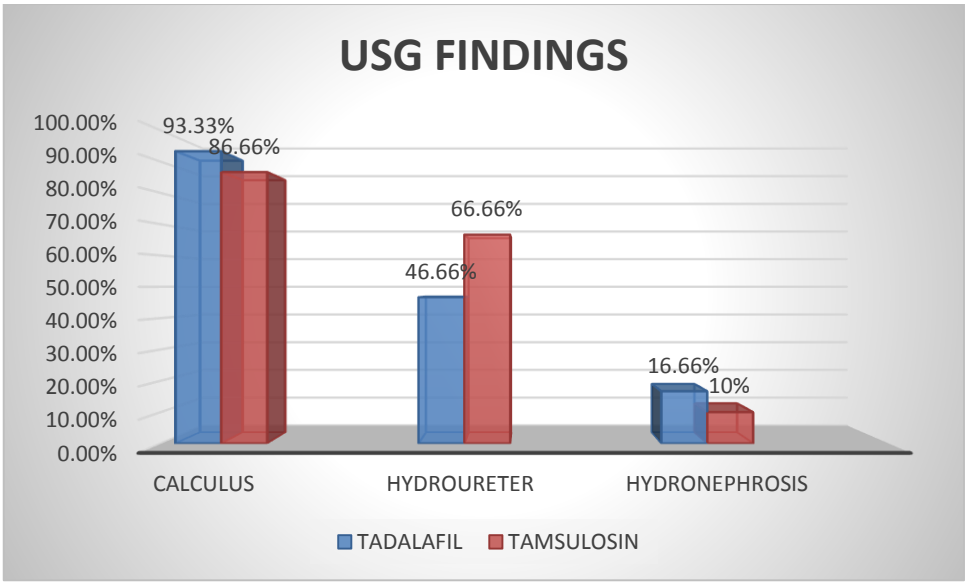


GRAPH 4:-GRAPH SHOWING DISTRIBUTION OF SUBJECTS AS PER OPACITY ON X-RAY-KUB

5) USG

TABLE 5. DISTRIBUTION OF SUBJECTS AS PER USG FINDINGS

USG	GROUP		TOTAL
	TADALAFIL (n=30)	TAMSULOSIN (n=30)	
CALCULUS	28	26	54
	93.33%	86.66%	90%
HYDROURETER	14	20	34
	46.66%	66.66%	56.70%
HYDRONEPHROSIS	5	3	8
	16.66%	10%	13.30%



GRAPH 5:- GRAPH SHOWING DISTRIBUTION OF SUBJECTS AS PER USG FINDINGS

Distribution of patients according to the evidence on USG findings of calculus, hydroureter and hydronephrosis is shown in the above table. 90% of the patients had calculus on USG with decreasing percentage of patients having hydroureter and hydronephrosis i.e. 56.7% and 13.3% respectively. Calculus was seen in 93.3% of Tadalafil group and 86.6% of Tamsulosin group. 46.66% and 66.66% had hydroureter in Tadalafil and Tamsulosin group respectively. Hydronephrosis was seen in 16.66% in Tadalafil group and 10% in Tamsulosin group.

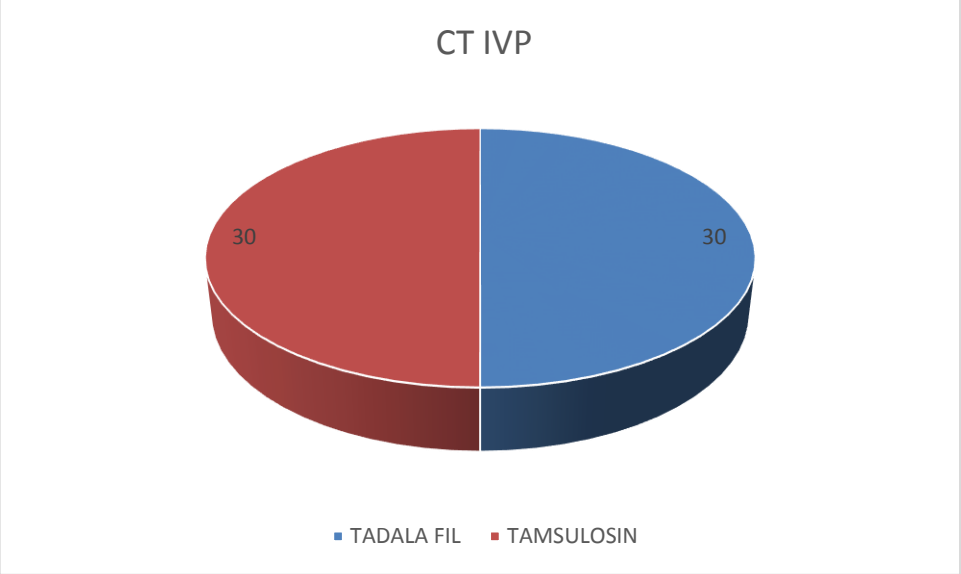
It is easier to see the hydroureter and hydronephrosis on USG (ultrasonography of kidneys, ureter and urinary bladder) than x-ray and so it was performed to rule out the same.

6) CT-IVP

TABLE 6. DISTRIBUTION OF SUBJECTS AS PER CT-IVP RESULTS

CT IVP	GROUP(N=60)		TOTAL
	TADALAFIL	TAMSULOSIN	
CALCULUS PRESENT	30	30	60

The inclusion criteria for present study was with the evidence of calculus on CT Intravenous Pyelogram (IVP). Thus only patients with lower ureteric calculi as evident on CT-IVP were included in the study equally in each group.



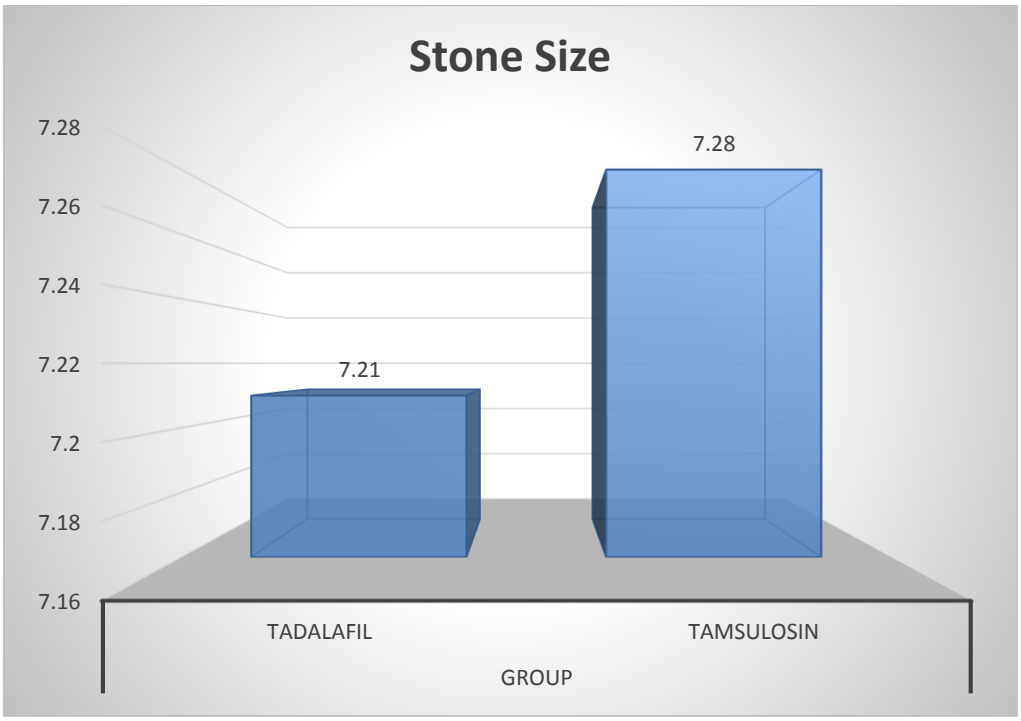
GRAPH 6: - GRAPH SHOWING DISTRIBUTION OF SUBJECTS AS PER CT-IVP RESULTS

7) STONE SIZE

TABLE 7: - COMPARISON OF STUDY GROUPS BASED ON STONE SIZE

	Group	N	Mean	SD	p- value
Stone size (mm)	**Tadalafil**	30	7.21	1.55	**0.54**
	Tamsulosin	30	7.28	1.28	

Mean ± SD of stone size in cases of Tadalafil and Tamsulosin group was 7.21 ± 1.55 mm and 7.28 ± 1.28 mm respectively. Thus, no significant difference was observed between the study groups with respect to mean stone size (p-0.54).



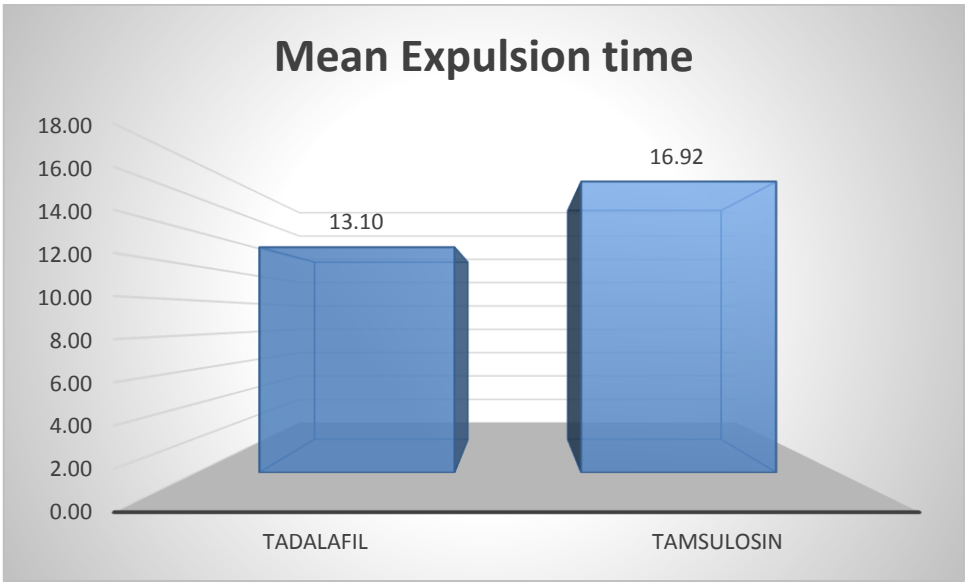
GRAPH 7: - GRAPH SHOWING STONE SIZE

8) STONE EXPULSION TIME

TABLE 8: - COMPARISON OF STUDY GROUPS BASED ON STONE EXPULSION TIME

Variables	Group	N	Mean	SD	p- value
Expulsion Time (days)	**Tadalafil**	30	13.10	3.99	**<0.05**
	Tamsulosin	30	16.92	4.21	

The Mean ± SD of expulsion of stone in Tadalafil group was 13.10 ± 3.99 vs 16.92 ±4.21 in Tamsulosin group with the p value of <0.05. Therefore Mean expulsion of calculi was significantly earlier in patients managed by Tadalafil as compared to Tamsulosin (p<0.05).



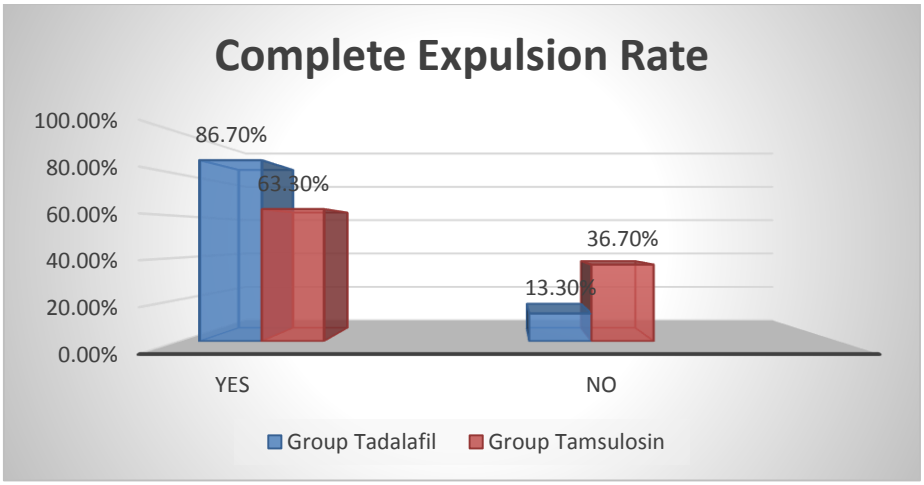
GRAPH 8:- GRAPH SHOWING STONE MEAN EXPULSION TIME

9) COMPLETE STONE EXPULSION RATE

TABLE 9: - COMPARISON OF STUDY GROUPS BASED ON COMPLETE STONE EXPULSION RATE

Complete Expulsion	Group		Total
	Tadalafil (n=30)	Tamsulosin (n=30)	
Yes	26	19	45
	86.7%	63.3%	75.0%
No	4	11	15
	13.3%	36.7%	25.0%
Total	30	30	60
	100.0%	100.0%	100.0%
p- value <0.05			

Complete expulsion by the end of 1 month was seen in 75% of patients out whole study population. 86.7% cases on Tadalafil as compared to only 63.3% cases on Tamsulosin out of 30 patients each had complete expulsion of stone at the end of 1 month. P-value ($p<0.05$) was found to be significant showing the better activity of Tadalafil on Tamsulosin.



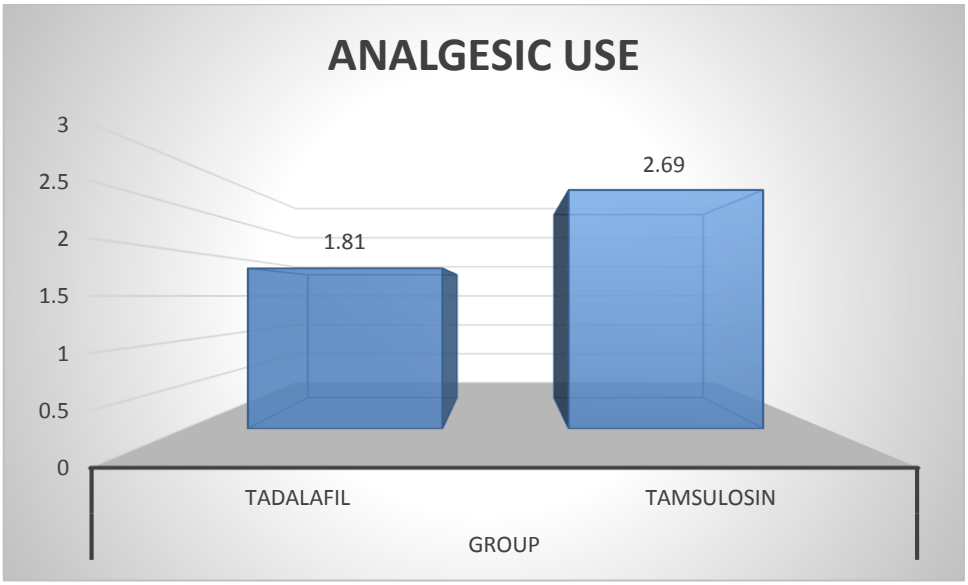
GRAPH 9: - GRAPH SHOWING COMPLETE STONE EXPULSION RATE

10) ANALGESIC USE

TABLE 10:- COMPARISON OF STUDY GROUPS BASED ON ANALGESIC USE

Variables	Group	N	Mean	SD	p- value
Analgesic Use	**Tadalafil**	30	1.81	0.54	**<0.05**
	Tamsulosin	30	2.69	0.73	

Mean ± SD of using analgesics in study population was 1.81± 0.54 vs 2.69 ± 0.73 in Tamsulosin group. This suggests that there was significantly higher use of analgesics in patients managed by Tamsulosin (p= <0.05).



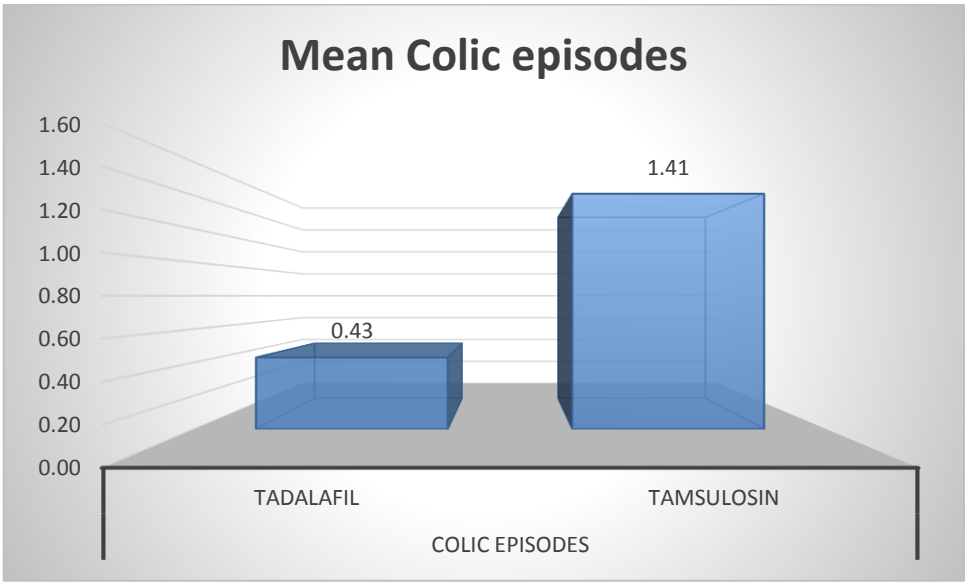
GRAPH 10: - GRAPH SHOWING ANALGESIC USE

11) COLIC EPISODES

TABLE 11:- COMPARISON OF STUDY GROUPS BASED ON COLIC PAIN EPISODES

Variables	Group	N	Mean	SD	p- value
Colic episodes	**Tadalafil**	30	0.43	0.79	**<0.05**
	Tamsulosin	30	1.41	0.88	

Mean ± SD of episodes of colicky pain was significantly higher in patients managed by Tamsulosin i.e. 1.41 ± 0.88 than in Tadalafil group i.e. 0.43 ± 0.79 with the significant p value of <0.05



GRAPH 11:- GRAPH SHOWING MEAN COLIC PAIN EPISODES

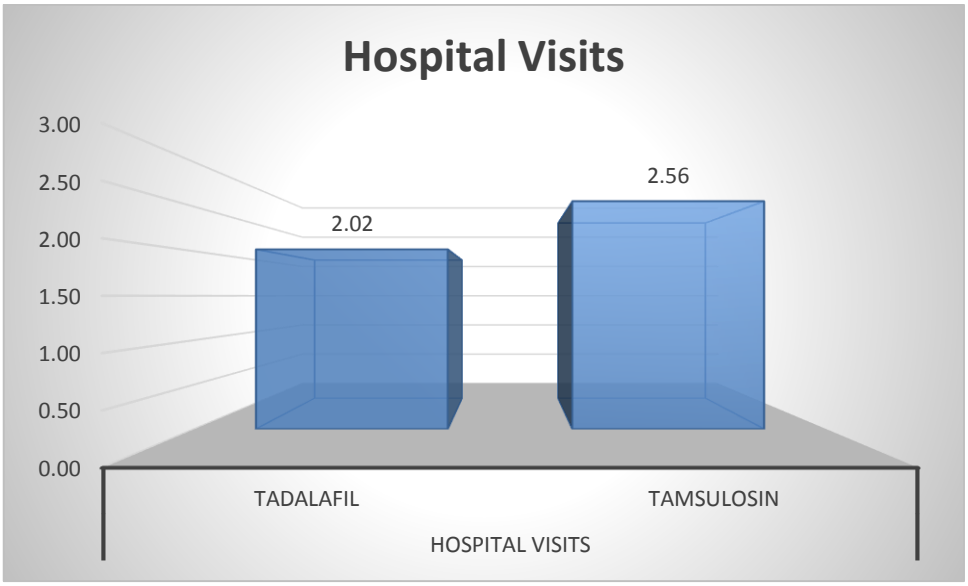
Table 10 and 11 suggests that the Tadalafil has better control of pain and colic episodes than Tamsulosin group with p <0.05 in each.

12) HOSPITAL VISITS

TABLE 12: - COMPARISON OF STUDY GROUPS BASED ON HOSPITAL VISIT

Variables	Group	N	Mean	SD	p- value
Hospital Visits	**Tadalafil**	30	2.02	0.90	**0.06**
	Tamsulosin	30	2.56	0.70	

The number of hospital visits required during treatment were also more with Tamsulosin showing Mean ± SD of 2.56 ± 0.70 vs than Tadalafil having 2.02 ± 0.90 but the difference did not reach significance levels (2.56 vs 2.02 days; p-0.06).



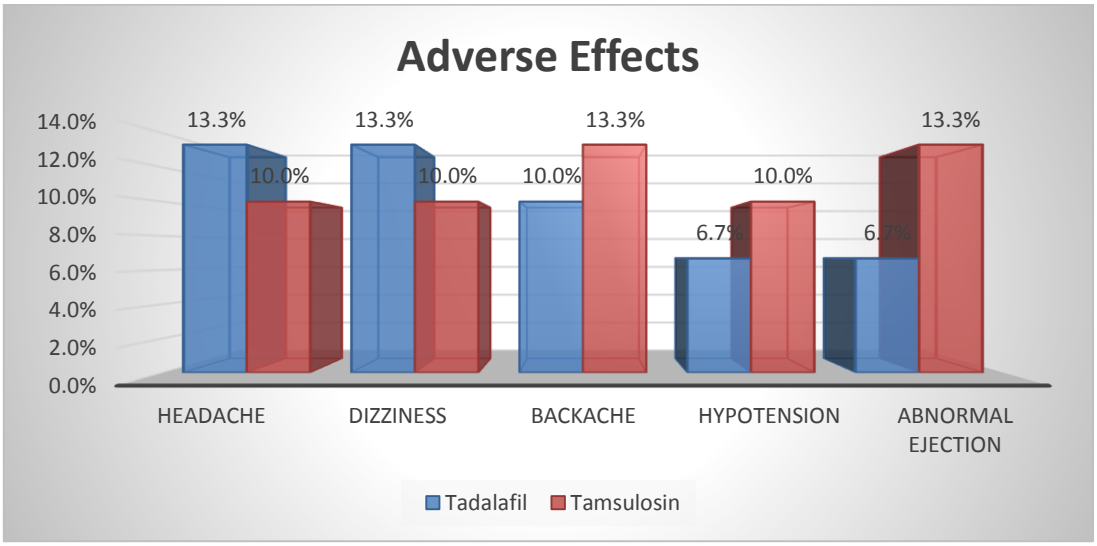
GRAPH 12:- GRAPH SHOWING MEAN HOSPITAL VISITS

13) ADVERSE EFFECTS

TABLE 13. COMPARISON OF ADVERSE EFFECTS AMONG STUDY GROUPS

Adverse Effects	Group		Total	p- value
	Tadalafil	**Tamsulosin**		
Headache	4	3	7	**1.00**
	13.3%	10.0%	11.7%	
Dizziness	4	3	7	**1.00**
	13.3%	10.0%	11.7%	
Backache	3	4	7	**1.00**
	10.0%	13.3%	11.7%	
Hypotension	2	3	5	**1.00**
	6.7%	10.0%	8.3%	
Abnormal ejection	2	4	6	**0.67**
	6.7%	13.3%	10.0%	

The various side effects noted during the study period in patients on Tadalafil and Tamsulosin group were headache (13.3% vs 10%), dizziness (13.3% vs 10%), backache (10% vs 13.3%), hypotensive episodes (6.7% vs 10%) and abnormal ejection (6.7% vs 13.3%). No difference was seen in the adverse effect profile of both drugs.



GRAPH 13: - GRAPH SHOWING ADVERSE EFFECTS AMONG STUDY GROUPS

The advances in minimally invasive techniques have led to a decrease in the treatment related morbidity associated with management of ureteric calculi. These advances include shock wave lithotripsy and ureteroscopic lithotripsy. Although these approaches are less invasive than traditional open surgical methods, they are expensive and have inherent risks. Hence, observation has been advised for small ureteral stones, which have a high probability to pass spontaneously. The use of the expectant approach for distal ureteric stones can be extended with the use of adjuvant medical expulsive therapy (MET), which is able to reduce symptoms and facilitate stone expulsion.

The factors influencing expulsion of calculi include stone size, shape, and location, ureteric edema, and ureteric convolutions. Of these, the location of the calculus and its size are the most important factors.

The management of patients with ureteral calculi has changed dramatically in the current era, with the conservative approach being the primary focus, its main benefit being minimum patient morbidity. Conservative nonsurgical approaches are usually implemented in the treatment plan of distal ureteral stones of size 5–10 mm as these are less likely to pass spontaneously [6,7].

According to earlier studies, the expulsion rate of distal ureteric stone by watchful waiting is 25–54% with mean expulsion time >10 days and is associated with high analgesic requirement even for stones <5 mm. To improve the expulsion rate and reduce analgesic requirement, medical therapy is considered for distal ureteral stones [8, 9].

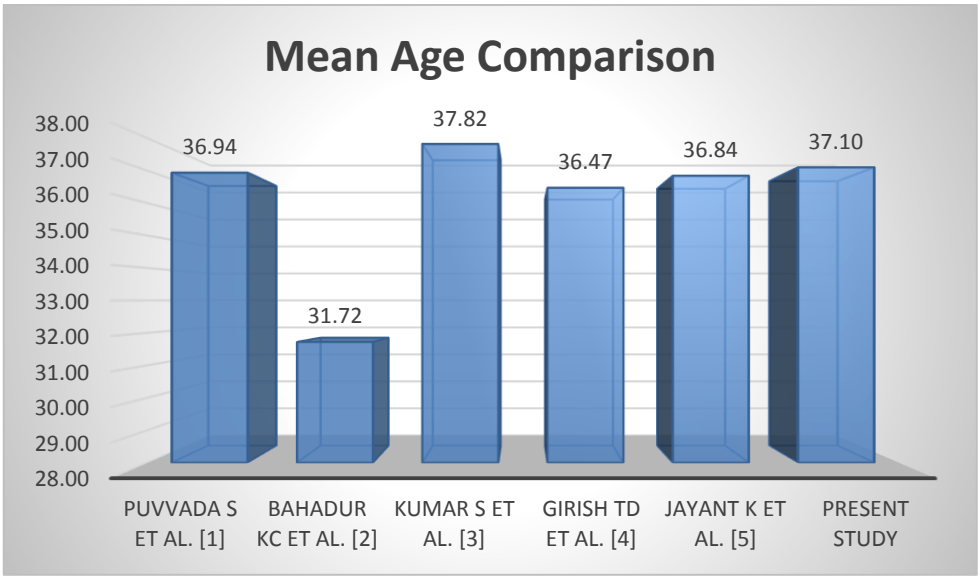
The present study was thus conducted to determine best treatment for medical expulsive therapy of distal ureteric stones by comparing Tadalafil and Tamsulosin.

1) AGE COMPARISION

>50% of the cases in present study were between 31-40 years of age with 6.7% and 1.7% cases between 51-60 years and above 60 years of age. Mean age of the study subjects was 37.1 ± 10.97 years.

TABLE 14: - MEAN AGE COMPARISION

Author	Mean Age (yrs)
Puvvada S et al. [1]	36.94
Bahadur KC et al. [2]	31.72
Kumar S et al. [3]	37.82
Girish TD et al. [4]	36.47
Jayant K et al. [5]	36.84
Present study	37.10



GRAPH 14: GRAPH SHOWING MEAN AGE COMPARISON

According to the study done by Puvvada S et al. the mean age of patients having ureteric stones was 36.94 years. Bahadur KC et al. study had 31.72 as a mean age of patients having ureteric stones.

The study done by Girish TD et al. and jayant K et al. showed mean age of 36.47 and 36.84 respectively.

The maximum mean age was seen in Kumar S et al. – 37.82 years which is approximately same as the present study (37.1 years).

Our results are in accordance with the past literature where most cases of uretric calculus were in their 4th decade of life.

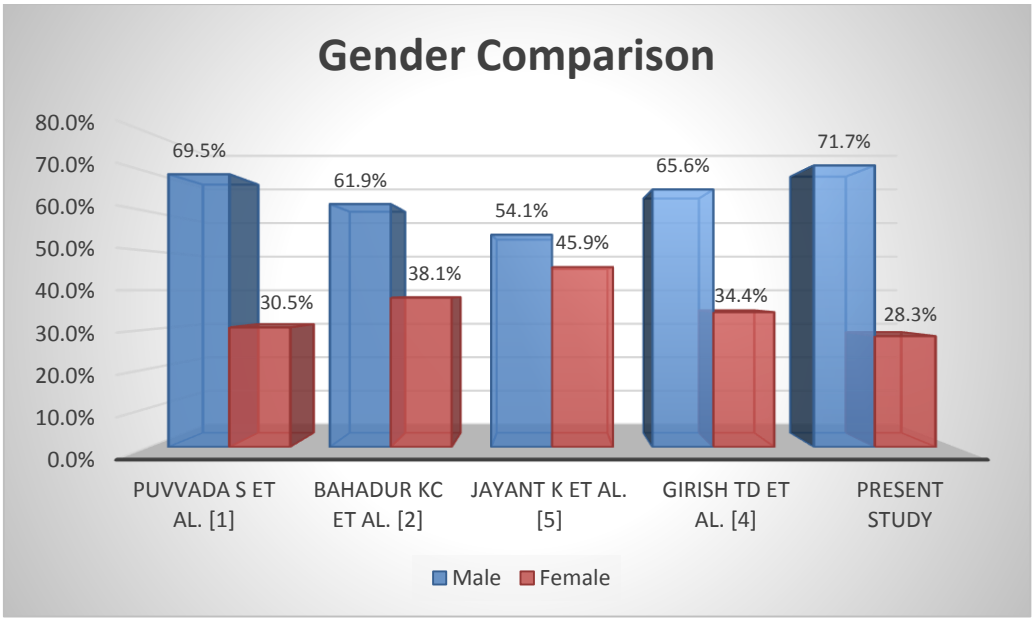
Most of the patients affected are in age group of 31-40 years which can be because of the young working people who have decrease amount of water intake in there day to day life.

2) GENDER COMPARISION

Male predominance was seen in present study with 71.7% males to 28.3% females.

TABLE 15: - GENDER COMPARISION

Author	Male	Female
Puvvada S et al. [1]	69.5%	30.5%
Bahadur KC et al. [2]	61.9%	38.1%
Jayant K et al. [5]	54.1%	45.9%
Girish TD et al. [4]	65.6%	34.4%
Present study	71.7%	28.3%



GRAPH 15: - GRAPH SHOWING GENDER COMPARISION

The percentage of male & female in Puvvada S et al. was 69.5% vs 30.5% while with Bahadur KC et al.; jayant K et al and Girish TD et al. showed 61.9% of male vs 38.1% of females; 54.1% of males vs 45.9% of females and 65.6% of males vs 34.4% of females respectively.

Our results are in accordance with the past literature where males were generally more affected than females [1-5].

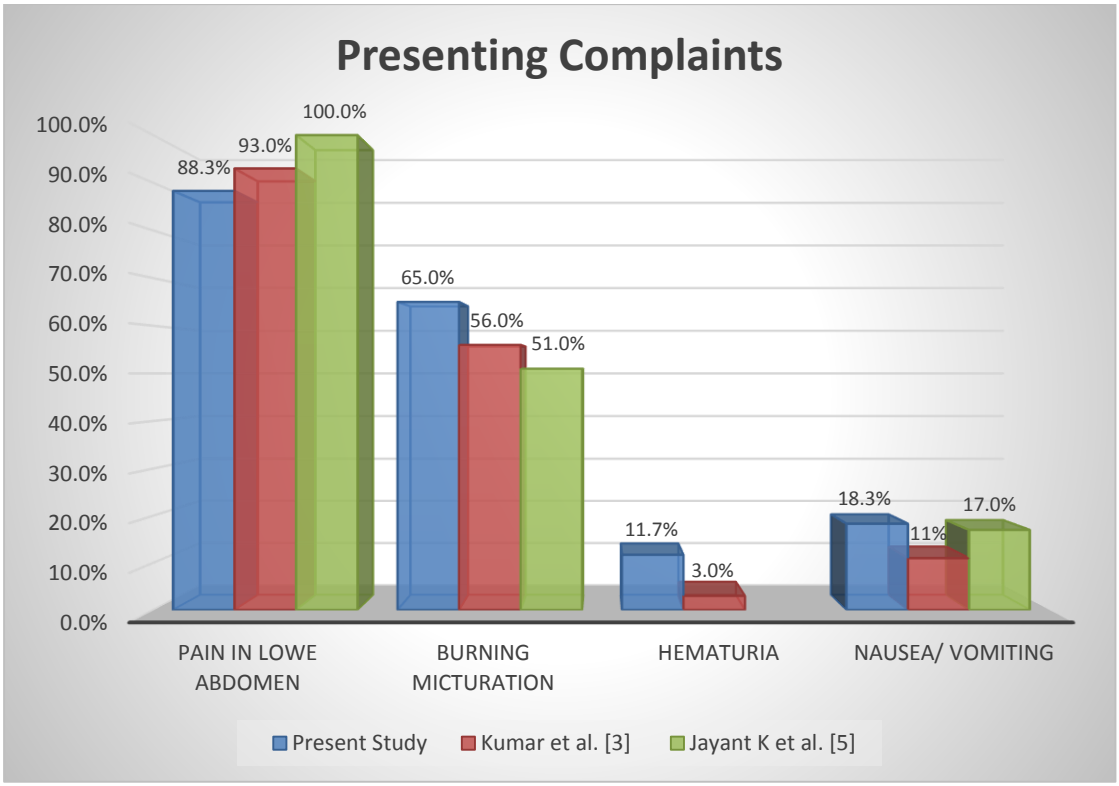
This showed the male preponderance in the study population. It can be due to males working out in fields in hot environment which leads to dehydration. The quality of water can also affect the study population.

3) PRESENTING SYMPTOMS

Most common presenting complaints were pain in lower abdomen (88.3%) followed by burning micturition (65%), nausea/ vomiting (18.3%) and hematuria (11.7%).

TABLE 16: - PRESENTING COMPLAIN COMPARISON

Complaints	Present Study	Kumar et al. [3]	Jayant K et al. [5]
Pain in Lower Abdomen	88.3%	93.0%	100.0%
Burning Micturation	65.0%	56.0%	51.0%
Hematuria	11.7%	3.0%	
Nausea/ Vomiting	18.3%	11.0%	17%



GRAPH 16:- GRAPH SHOWING PRESENTING COMPLAIN COMPARISION

According to the Kumar et al. and Jayant K et al. both the maximum no. of patients had complaint of lower abdominal pain (93%) which is quite similar to the present study.

The no. of patients having burning micturation in Kumar et al was 56% vs 51% in Jayant K et al. which was less than the present study. The no of patients having hematuria was more(11.7%) in the present study as compared to the Kumar et al. which was 3.0% while the patients coming with complaint of nausea or vomiting was almost equal in present study(18.3%) and Jayant k et al (17%) while it was only 11% in Kumar et al.

Various studies have shown that colicky pain in the flank and ipsilateral lower abdomen with radiation to the testicles or the vulvar area is a characteristic feature of ureteric calculus. In most of the cases pain in lower abdomen is the only presenting complaint [1, 2, 4].

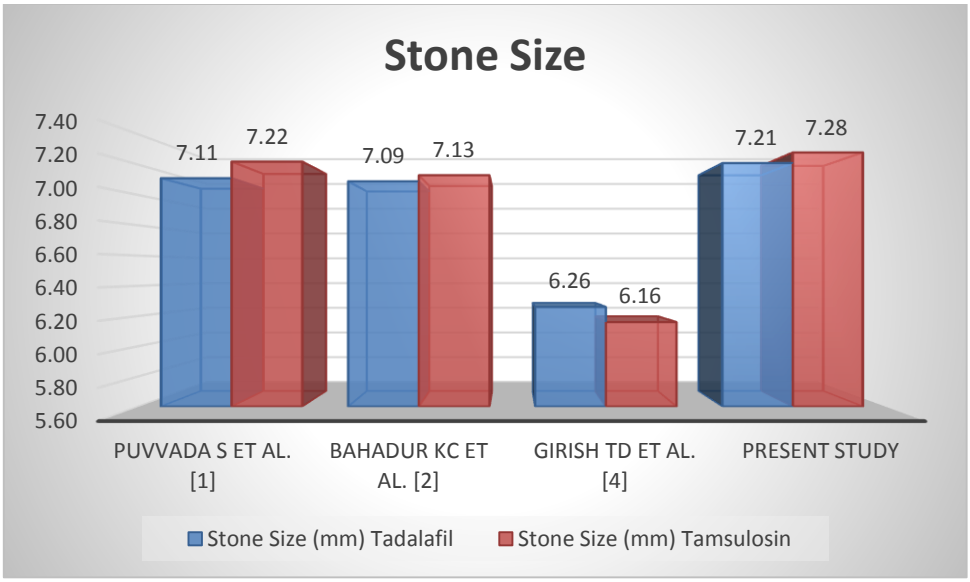
Pain in lower abdomen is seen as major complaint in such patients as the stone of >5mm while propulsion pass through the ureter which is of maximum 5 mm diameter and so causing spasmodic pain and due the passage of stone the epithelium lining of the ureter gets abraded due to which haematuria occurs. Burning micturation occurs due to the infection. Nausea and vomiting are also because of the unbearable pain and infection.

4) STONE SIZE

Most of the cases in present study had calculi measuring between 5-10 mm with mean size in cases of Tadalafil and Tamsulosin group as 7.21 mm and 7.28 mm respectively. The comparison of stone size as observed in the studies by other authors is as follows:

TABLE 17: - STONE SIZE COMPARISION

Author	Stone Size (mm)	
	Tadalafil	Tamsulosin
Puvvada S et al. [1]	7.11	7.22
Bahadur KC et al. [2]	7.09	7.13
Girish TD et al. [4]	6.26	6.16
Present study	7.21	7.28



GRAPH 17:- GRAPH SHOWING STONE SIZE

According to the European Association of Urology Guidelines (2015) on Urolithiasis, there exists a high likelihood of spontaneous passage of stones up to ~5 mm, hence MET is less likely to increase the stone-free rate. The best results from MET were seen in cases with size ranging from 5-10 mm.

According to the study by Puvvada et al. the patients in Tadalafil had mean size 7.11 mm stone vs 7.2 mm stone in Tamsulosin group.

In Bahadur KC et al. study the mean size was 7.09 mm in Tadalafil vs 7.13 mm in Tamsulosin group.

In Girish TD et al. study the mean size of stone was 6.26 mm in Tadalafil vs 6.16 mm in Tamsulosin group. As compared to the other studies the mean size of stone was almost equal with the present study.

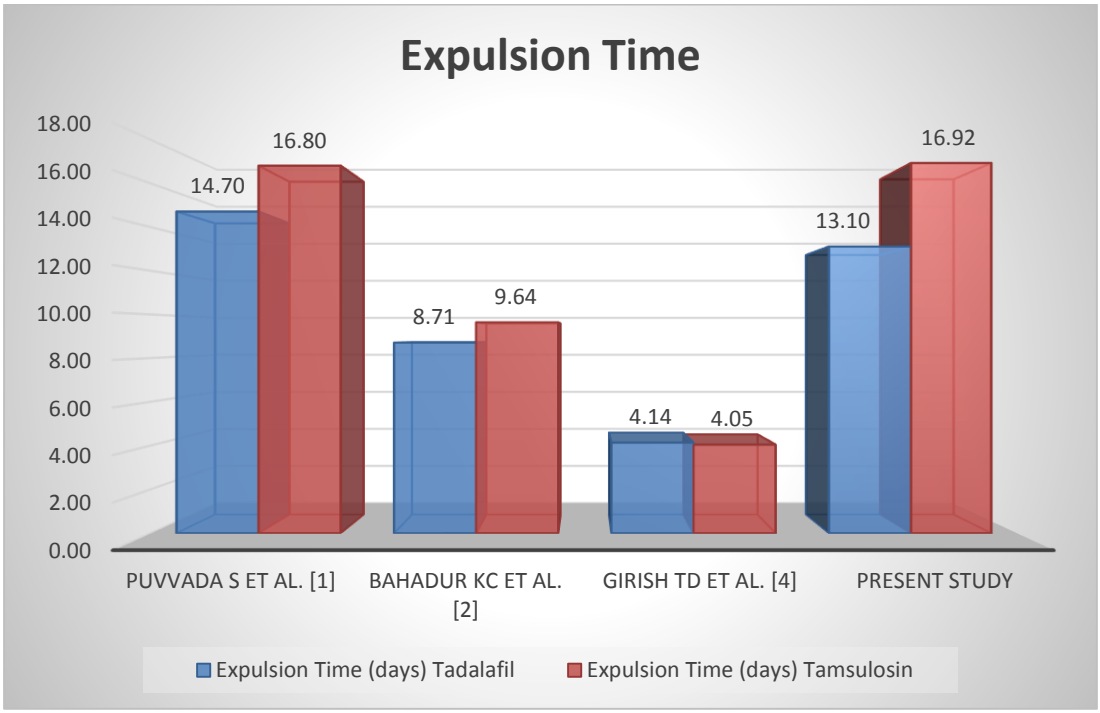
Stone size larger than 10 mm doesn't pass through ureter thus most of the patients with ureteric calculi presented to us and in other study with colicky pain with mean stone size 7.2 mm.

5) STONE EXPULSION TIME

Mean expulsion time of calculi in the present study was significantly earlier in patients managed by Tadalafil as compared to Tamsulosin (13.1 vs 16.92 days; $p<0.05$).

TABLE 18:- STONE EXPULSION TIME COMPARISION

Author	Expulsion Time (days)	
	Tadalafil	Tamsulosin
Puvvada S et al. [1]	14.70	16.80
Bahadur KC et al. [2]	8.71	9.64
Girish TD et al. [4]	4.05	4.14
Present study	13.10	16.92



GRAPH 18:- GRAPH SHOWING STONE EXPULSION TIME COMPARISION

According to the study done by Puvvada S et al. the time for expulsion in days was more in Tamsulosin (16.80 days) than Tadalafil (14.70 days).

Similarly, findings were seen in Bahadur KC et al. study where expulsion time in days was 8.71 vs 9.64 in Tadalafil and Tamsulosin group.

While in Girish TD et al the expulsion time in days was not significantly different in Tadalafil (4.05 day) and Tamsulosin group (4.14 days).

So, the present study shows similar findings as of in study done by Puvvada et al & Bahadur KC et al.

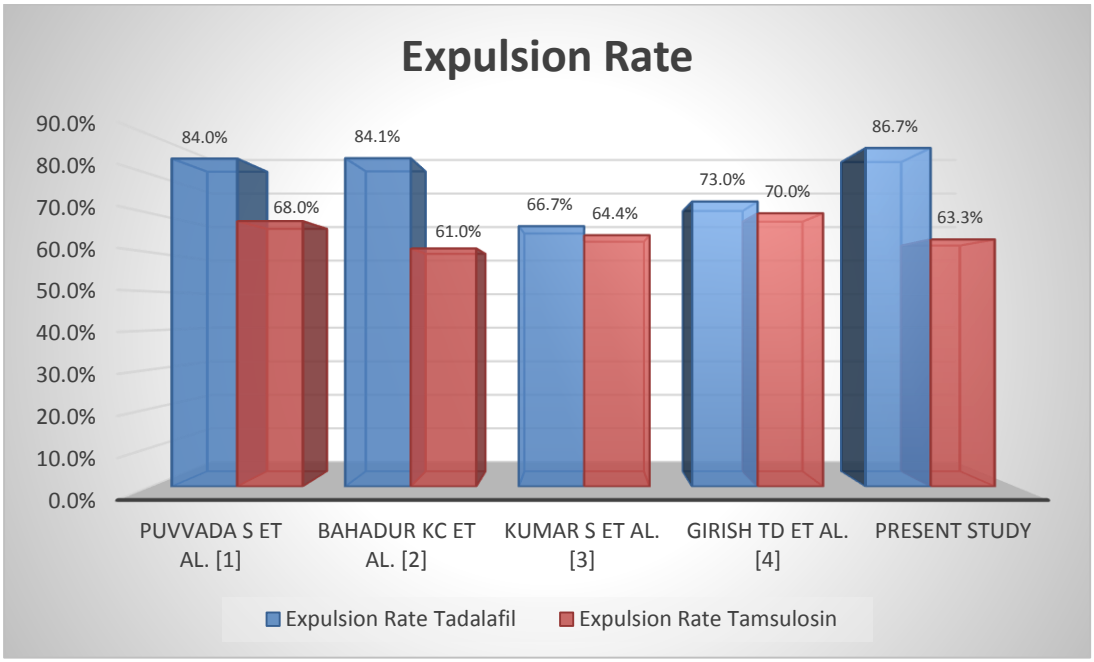
Tadalafil is PDE5 inhibitor which are abundant in ureter leading to more smooth muscle relaxation than Tamsulosin whose effect are sympathetic nervous system mediated on blocking of alpha 1 A and 1 D receptors which are more in distal ureter thus less expulsion rate by Tamsulosin.

6) STONE EXPULSION RATE

Complete expulsion was seen in 86.7% cases on Tadalafil as compared to only 63.3% cases on Tamsulosin ($p<0.05$).

TABLE 19:- STONE EXPULSION RATE COMPARISION

Author	Expulsion Rate	
	Tadalafil	Tamsulosin
Puvvada S et al. [1]	84.0%	68.0%
Bahadur KC et al. [2]	84.1%	61.0%
Kumar S et al. [3]	66.7%	64.4%
Girish TD et al. [4]	73.0%	70.0%
Present study	86.7%	63.3%



GRAPH 19:- GRAPH SHOWING STONE EXPULSION RATE COMPARISON

In Puvvada et al. [1] the expulsion rate in Tadalafil group was 84% than in Tamsulosin group 68%.

In Bahadur KC et al.[2] the expulsion rate was 84.1% vs 61% in Tadalafil and Tamsulosin group (p=0.017).

In a randomized study with 285 patients, Kumar et al. [3] compared the efficacy of 3 drugs, Tamsulosin, Silodosin, and Tadalafil, as MET for lower ureteral stones. The expulsion rate was 64.4%, 83.3%, and 66.7%, respectively, but there was no significant difference between the Tamsulosin and Tadalafil groups (p=0.875).

In Girish TD et al.[4] the expulsion rate of stone was 73% in Tadalafil group vs 70% in Tamsulosin group.

According to the Puvvada et al.[1] and Bhadur et al.[2] the expulsion rate of lower ureteric stone was significantly higher in Tadalafil group than in Tamsulosin group has also seen in present study.

Jayant et al. [5] in their study compared the stone expulsion rate of Tamsulosin with the Tamsulosin and Tadalafil combination. The expulsion rate was 74.2% versus 83.9% (p=0.349) and 65.5% versus 83.6% (p=0.031), respectively.

In another study, Hasan et al. [10] found that Tadalafil had an expulsion rate of 93% compared with 67% for a placebo group.

The rate of expulsion was observed to be significantly faster with Tadalafil in most of the studies [1-5].

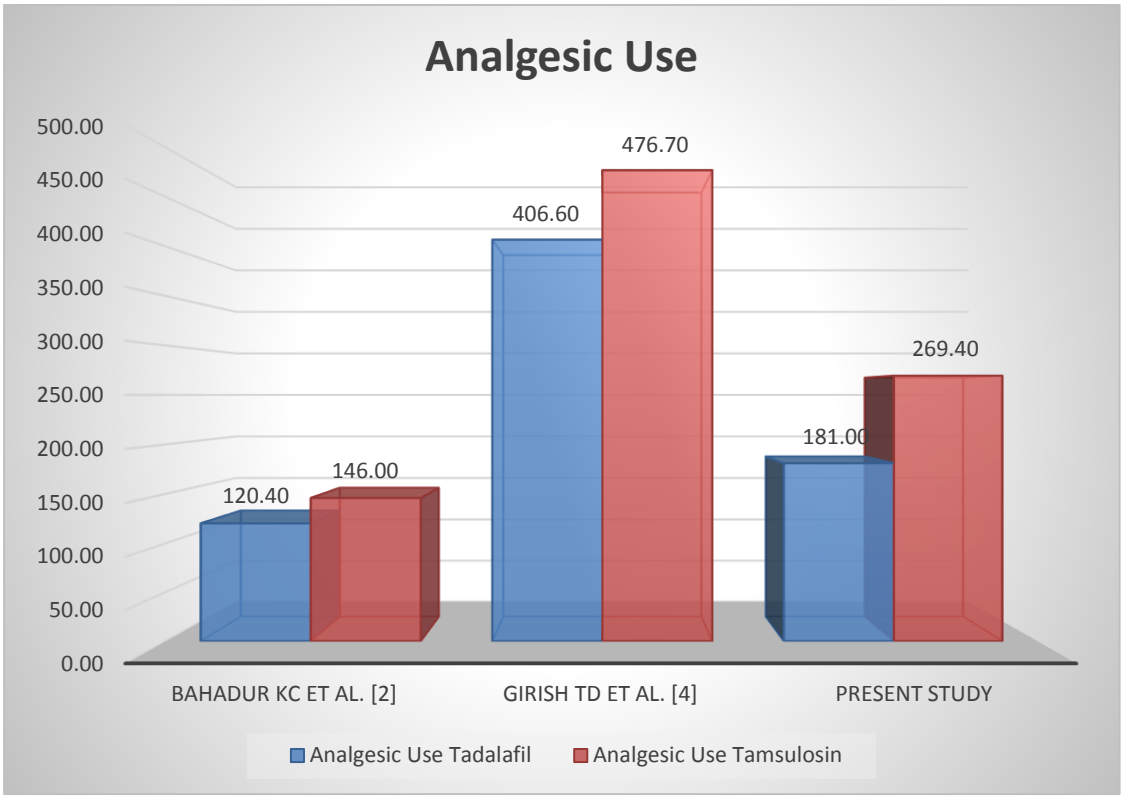
Tadalafil is PDE5 inhibitor which are abundant in ureter leading to more smooth muscle relaxation than Tamsulosin whose effect are sympathetic nervous system mediated on blocking of alpha 1 A and 1 D receptors which are more in distal ureter thus Tamsulosin taking more time than Tadalafil.

7) ANALGESIC USE & COLICKY EPISODES COMPARISION

Mean analgesic use (269.4 vs 181.0 mg; $p<0.05$) was significantly higher in patients managed by Tamsulosin.

TABLE 20:- ANALGESIC USE COMPARISION

Author	Analgesic Use	
	Tadalafil	Tamsulosin
Bahadur KC et al. [2]	120.40	146.00
Girish TD et al. [4]	406.60	476.70
Present Study	181.00	269.40



GRAPH 20:- GRAPH SHOWING ANALGESIC USE COMPARISON

Bahadur KC et al. [2] showed less use of analgesic in Tadalafil group (120.40) vs (146.0) in Tamsulosin group.

In the study done by Girish TD et al [4] the use of analgesic was just little less in Tadalafil group (406.60) than in Tamsulosin group (476.70).

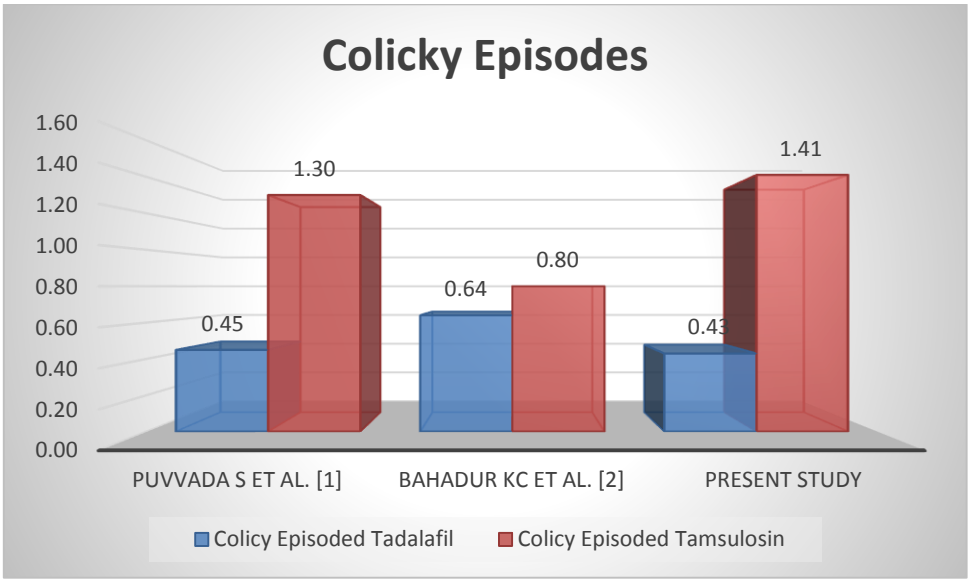
The mean analgesic use was less compared to Tamsulosin group in Tadalafil group in Bahadur KC et al. and in Girish TD et al. which corresponds with the results of present study.

Colicky pain is due to increased intra-ureteral pressure. Alpha blockade by Tamsulosin blocks C fibre mediated pain which are more concentrated in lower ureter while PDE5 mediated Tadalafil causes dilatation of whole of ureter thus decreases intraluminal pressure and faster expulsion. Hence less pain.

Mean episodes of colicky pain (1.41 vs 0.43; p<0.05) was significantly higher in patients managed by Tamsulosin.

TABLE 21:- COLICKY EPISODE COMPARISON

Author	Colicky Episodes	
	Tadalafil	Tamsulosin
Puvvada S et al. [1]	0.45	1.30
Bahadur KC et al. [2]	0.64	0.80
Present Study	0.43	1.41



GRAPH 21: - GRAPH SHOWING COLICKY EPISODE COMPARISION

Mean episodes of colicky pain in patients with Tamsulosin was in Puvvada S et al. [1] was 0.45 in Tadalafil group and 1.30 in Tamsulosin group.

MET not only facilitates stone passage, but also decreases the colicky pain episodes and analgesic requirement.

In the study by Bahadur KC et al. [2], 48 of 85 patients on Tadalafil (56.47%) had no episodes of colicky pain and 52 of 85 patients (61.17%) did not require any analgesics for pain during the study period. The number of episodes of colicky pain, the pain score, and the analgesic requirement were less in patients on Tadalafil as compared to Tamsulosin.

Jayant et al. [5], who had compared Tamsulosin with the combination of Tamsulosin and Tadalafil, demonstrated a significantly decreased expulsion time (16.7±4.8 vs. 14.9±4.4 days, p=0.003), significantly fewer colicky pain episodes (1.60±1.0 vs. 0.45±0.68, p=0.000), and significantly less analgesic use (2.90±0.90 vs. 1.87±0.8, p=0.000). Colicky pain in ureteral stones occurs owing to an increase in intraureteral pressure above the site of ureteral obstruction.

Kinnman et al. [25] demonstrated that α-blockade relieves ureteric colic by blocking the C-fibers responsible for mediating pain. Both drugs are thought to decrease the frequency and amplitude of phasic peristaltic contractions that accompany ureteric obstruction and to decrease the need for analgesia. In the present study, these parameters were lower in Tadalafil group.

Hasan et al. [22] reported a significantly lower pain score of 3.9 versus 7.9 ($p<0.01$) and a significantly lower analgesic requirement in the Tadalafil group than in the placebo group.

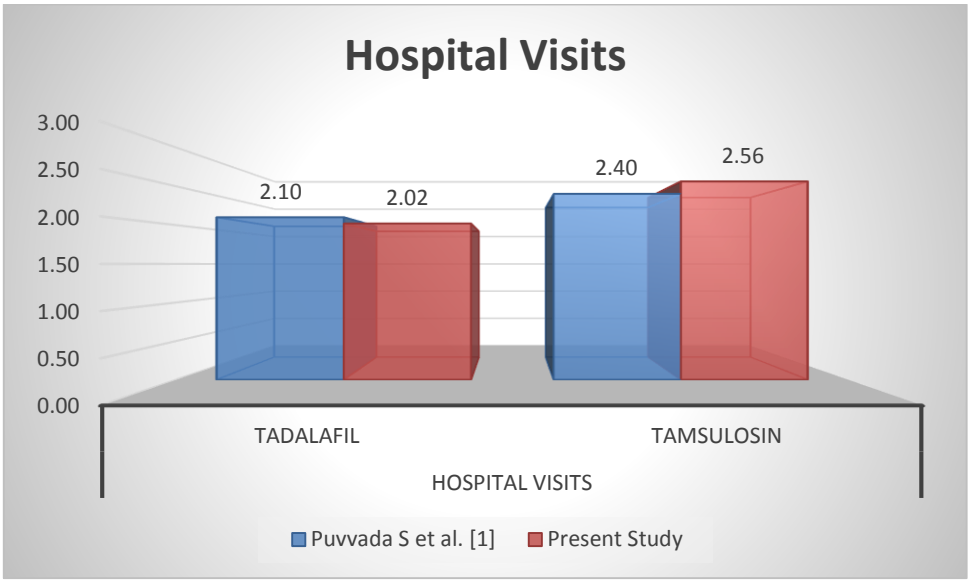
Mean episodes of colicky pain in patients with Tamsulosin was more in study done by Puvvada et al.[1] which corresponds to the findings analysed in the present study suggesting that the Tadalafil is better in controling pain too and so the no. of colicky episodes are less as well as the use of analgesic is also low.

8) HOSPITAL VISITS

The number of hospital visits required during treatment were also more with Tamsulosin, but the difference did not reach significance levels (2.56 vs 2.02 days; p-0.06).

TABLE 22: - HOSPITAL VISIT COMPARISON

Author	Hospital Visits	
	Tadalafil	Tamsulosin
Puvvada S et al. [1]	2.10	2.40
Present Study	2.02	2.56



GRAPH 22: - GRAPH SHOWING HOSPITAL VISIT COMPARISION

9) ADVERSE REACTIONS

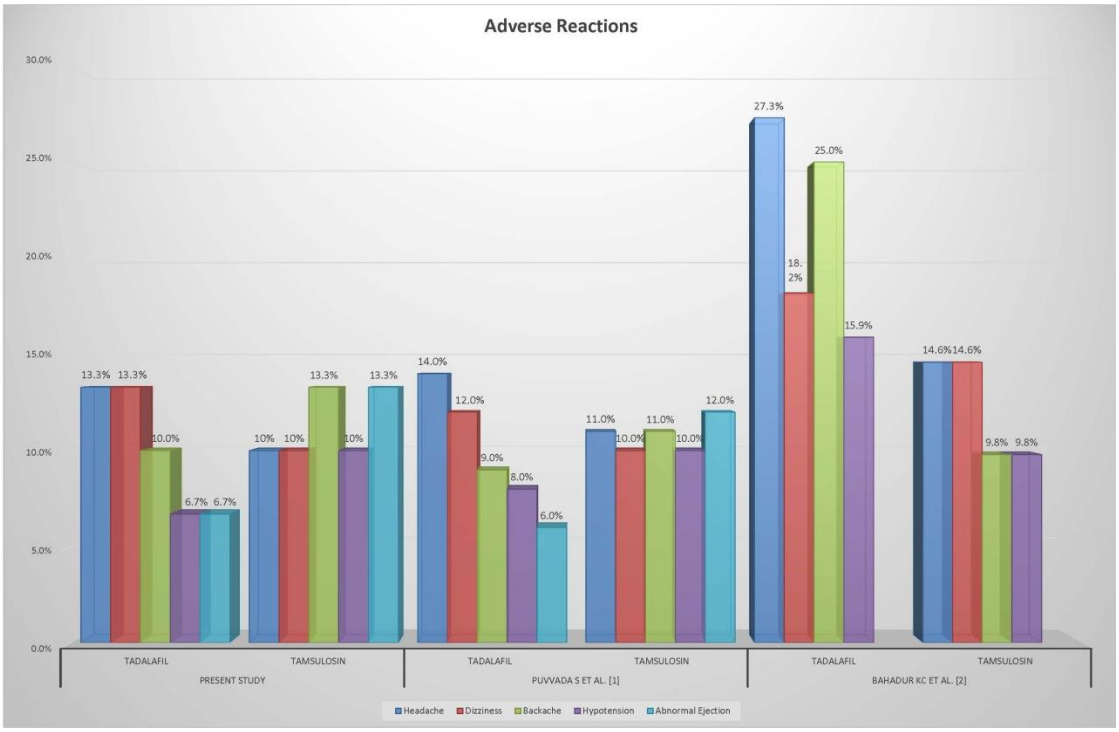
The various side effects noted during the study period in patients on Tadalafil and Tamsulosin group were headache (13.3% vs 10%), dizziness (13.3% vs 10%), backache (10% vs 13.3%), hypotensive episodes (6.7% vs 10%) and abnormal ejection (6.7% vs 13.3%). No difference was seen in the adverse effect profile of both drugs.

TABLE 23 : - ADVERSE REACTIONS

Adverse Reactions	Present Study		Puvvada S et al. [1]		Bahadur KC et al. [2]	
	Tadalafil	Tamsulosin	Tadalafil	Tamsulosin	Tadalafil	Tamsulosin
Headache	13.3%	10.0%	14.0%	11.0%	27.3%	14.6%
Dizziness	13.3%	10.0%	12.0%	10.0%	18.2%	14.6%
Backache	10.0%	13.3%	9.0%	11.0%	25.0%	9.8%
Hypotension	6.7%	10.0%	8.0%	10.0%	15.9%	9.8%
Abnormal Ejection	6.7%	13.3%	6.0%	12.0%		

In the study by Bahdur KC et al. [2], the incidence of side effects were similar in both groups.

Similar results were demonstrated in studies by Kumar et al. [3] and Jayant et al. [5]. No serious adverse effects were encountered in either group in our study and all reported side effects were mild and well tolerated.



GRAPH 23: - GRAPH ADVERSE REACTIONS

A hospital based comparative study was conducted at Department of Surgery of a tertiary care hospital to determine single best monotherapy for medical expulsive therapy of distal ureteric stones by comparing Tadalafil and Tamsulosin. A total of 60 patients were randomly divided into 2 groups of 30 each to receive one of the above medical therapy and results were compared at the end of 2 weeks. Following observations were made during the study:

1. Over half of the cases in present study were between 31-40 years of age with 6.7% and 1.7% cases between 51-60 years and above 60 years of age.
2. Female predominance was seen in present study with 71.7% males to 28.3% females.
3. Most common presenting complaints were pain in lower abdomen (88.3%) followed by burning micturition (65%), nausea/ vomiting (18.3%) and hematuria (11.7%).
4. Mean stone size in cases of Tadalafil and Tamsulosin group was 7.21 mm and 7.28 mm respectively.
5. Amongst 60 patients 88% of them had radio opaque shadow suggesting lower ureteric stone on X-ray KUB
6. On USG-KUB findings the percentage of calculus seen in patients was 90%
7. All patients on CT-IVP confirmed lower ureteric stone on the basis of which the patients were divided equally
8. No significant difference was observed between the study groups with respect to mean stone size, age and gender distribution.
9. Mean expulsion of calculi was significantly earlier in patients managed by Tadalafil as compared to Tamsulosin (13.1 vs 16.92 days; $p<0.05$)

10. Complete expulsion was seen in 86.7% cases on Tadalafil as compared to only 63.3% cases on Tamsulosin ($p<0.05$).
11. Mean analgesic use (2.69 vs 1.81; $p<0.05$) and episodes of colicky pain (1.41 vs 0.43; $p<0.05$) were significantly higher in patients managed by Tamsulosin.
12. The number of hospital visits required during treatment were also more with Tamsulosin, but the difference did not reach significance levels (2.56 vs 2.02 days; p-0.06).
13. The various side effects noted during the study period in patients on Tadalafil and Tamsulosin group were headache (13.3% vs 10%), dizziness (13.3% vs 10%), backache (10% vs 13.3%), hypotensive episodes (6.7% vs 10%) and abnormal ejection (6.7% vs 13.3%). No difference was seen in the adverse effect profile of both drugs.

- Our study confirms that most common age group affected was 31-40 years of age because of young working people who have decrease amount of water intake in there day to day life.

- Male predominance was seen in our study can be due to males working out in fields in hot environment which leads to dehydration. The quality of water can also affect the study population.

- Most common presenting complaints were pain in lower abdomen followed by burning micturition, nausea/ vomiting and hematuria because stone of >5mm while propulsion pass through the ureter causing spasmodic pain and due the passage of stone the epithelium lining of the ureter gets abraded due to which hematuria occurs. Burning micturation occurs due to the infection. Nausea and vomiting are also because of the unbearable pain and infection.

- Most of the cases in our study had calculi measuring between 5-10 mm with mean size in cases of Tadalafil and Tamsulosin group as 7.21 mm and 7.28 mm respectively because the Stone size larger than 10 mm doesn't pass through ureter thus most of the patients with ureteric calculi presented to us and in other study with colicky pain with mean stone size 7.2 mm.

- Mean expulsion time of calculi in the present study was significantly earlier in patients managed by Tadalafil as compared to Tamsulosin because Tadalafil is PDE5 inhibitor which are abundant in ureter leading to more smooth muscle relaxation than Tamsulosin whose effect are sympathetic nervous system mediated on blocking of alpha 1 A and 1 D receptors which are more in distal ureter thus less expulsion rate by Tamsulosin.

- Our study shows that complete expulsion was seen more in Tadalafil as compared to Tamsulosin as because Tadalafil is PDE5 inhibitor which are abundant in ureter leading to more smooth muscle relaxation than Tamsulosin whose effect are sympathetic nervous system mediated on blocking of alpha 1 A and 1 D receptors which are more in distal ureter thus Tamsulosin taking more time than Tadalafil.

- Our study shows that Analgesic requirement was less in the Tadalafil as compared to Tamsulosin as because of Tadalafil cause dilatation of whole of ureter thus decreases intraluminal pressure and faster expulsion and thereby this group of patients required lesser analgesic

- Our study shows that the patient with Tadalafil was have lower incidence of colicky pain as compared to Tamsulosin because Tamsulosin causes Alpha blockade, blocks C fiber mediated pain which are more concentrated in lower ureter while PDE5 mediated Tadalafil causes dilatation of whole of ureter thus decreases intraluminal pressure and faster expulsion. Hence less pain.

- In present study conclude that the patient with Tadalafil had less symptomatic hospital visit as compared to Tamsulosin because Tadalafil had early expulsion of stone with lesser colicky pain episode.

- In recent years, medical expulsive therapy (MET) has been used in the management of distal ureteric stones as a supplement to conservative treatment. In present study, we compared efficacy of Tadalafil and Tamsulosin as MET for distal ureteric stones.

- Our results showed that Tadalafil has a significantly higher ureteric stone expulsion rate. Tadalafil also provides early stone expulsion, a greater decrease in colicky pain episodes, and a greater decrease in analgesic requirement. Both drugs are safe, effective, and well tolerated with minor side effects. Thus, Tadalafil is safe, efficacious, and well tolerated as medical expulsive therapy for distal ureteric stones.

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ANNEXURE I:

LIST OF ABBREVIATIONS

MET	:	Medical Expulsive Therapy
SPSS	:	Statistical Package for Social Science
UPJ	:	Ureteropelvic Junction
UVJ	:	Ureterovesicle Junction
PDE5	:	Phosphodiesterase 5
CGMP	:	Cyclic Guanosine monophosphate
CAMP	:	Cyclic Adenosine monophosphate
ED	:	Erectile dysfunction
BPH	:	Benign Prostate Hyperplasia
ESWL	:	Extracorporeal Shock wave lithotripsy
CT	:	Computed tomography
KUB	:	Kidney ureter bladder
PAH	:	Pulmonary arterial hypertension
AUC	:	Area under the curve
CYP	:	Cytochrome P
UTI	:	Urinary tract infection
CCB	:	Calcium Channel blocker
IVP	:	Intra Venous pyelography
USG	:	Ultrasonography
HN	:	Hydronephrosis

HU : Hydroureter

SD : Standard Deviation

RS : Respiratory System

CVS : Cardio vascular system

CNS : Central Nervous system

DM : Diabetes mellitus

HT : Hypertension

CBC : Complete Blood Count

RFT : Renal Function Test

ANNEXURE II

PARTICIPANT INFORMATION SHEET

Study Title: "**Tamsulosin versus Tadalafil as medical expulsive therapy of distal ureteric stones: A comparative study**"

1. Introduction:

- Ureteric stones are common amongst population and so the no. of patients seen in hospital with ureteric stone are way too large which is due to environmental factors & Geographical locations. It can be treated with medical therapy & if large then by surgical modality. As noninvasive procedures are always preferred over invasive procedure. So here we are comparing the commonly used drugs Tamsulosin and Tadalafil for expulsion of distal ureteric stones to see the single best monotherapy that can be used.

2. What is the purpose of this study?

- To see the single best monotherapy that can be efficacious in the patient.

3. Why have I been chosen?

- Having lower ureteric stone, age>20 yrs, medical therapy is noninvasive procedure of treatment.

4. Do I have to take part?

- Yes.

5. How long will the study last?

- Until the stone expulsion or up to 3 weeks.

6. What will happen to me if I take part?

- *Screening Period: Participant will be subjected to routine investigations for lower ureteric stone.*
- *Treatment Period: For maximum of 3 weeks.*
- *Allocation of investigational product:*

  Randomly drug will be given.

- *Follow-up period: Until the expulsion of the stone or up to 3 weeks*

7. What do I have to do?

- Cooperate with the investigator & be compliant for the therapy.

8. What is the drug being tested?

- Tamsulosin and Tadalafil which are both commonly used as medical expulsive therapy.

9. What are the benefits of the study?

- Will determine efficacy of Tamsulosin versus Tadalafil, as monotherapy in medical expulsive therapy of distal ureteric stone.
- Will help in term of cost effectiveness in management of distal ureteric stone by using monotherapy.

10. What are the alternatives for treatment?

- Surgical therapy.

11. What are the side effects of the treatment received during the study?

- Tamsulosin- Headache, orthostatic hypotension, rhinitis, dizziness, arthralgia, infection.
- Tadalafil- headache, myalgia, Resp tract infections, dyspepsia, flushing.

12. What if new information becomes available?

- Even if the new information is available regarding the treatment of the expulsion of lower ureteric stone this study would not be affected because we are comparing the commonly used drug for better & single monotherapy.

13. What happens when the study stops?

- When study stops data gathered during the study will be evaluated & inference would be made accordingly. Identity of any patient will not be revealed.

14. What if something goes wrong?

- There is as such no risk to any participant because these drugs are commonly used as medical expulsive therapy and if anything happens the participant care would be immediately done as needed.

15. Will my taking part be kept confidential?

- Yes. All data collected will be kept confidential.

16. What else should I know?

- Whole study is on voluntary basis, no adverse events are expected, no extra financial burden would be levied on participant.

17. Additional Precautions:

- Compliance to the medication and procedure.

18. Who to call with questions?

- Dr. Hardik Patel , Mobile No. – 8238661817

સહભાગીદારીનું માહિતી પત્રક

વિષયનું શીર્ષક : "ટેમ્યુલોસીન વર્સીસ ટેડલફીલ એસ મેડીકલ એક્સપ્લુજીવ થેરાપી ઓફ ડીસ્ટલ યુરેટીક સ્ટોન્સ : એ તુલનાત્મક અભ્યાસ"

(૧) પ્રસ્તાવના :-

પેશાબમાં થતી પથરી એ સામાન્ય પણે ઘણા બધા લોકોમાં જોવા મળતો રોગ છે. તેથી જ દવાખાનામાં આવતા દર્દીઓમાં પેશાબમાં પથરી ધરાવતાં દર્દીઓનું પ્રમાણ વધુ જોવા મળે છે. પેશાબમાં પથરી થવાનું મુખ્ય કારણ વાતાવરણ તેમજ ભૌગોલિક પરિસ્થિતિઓ છે. આ પ્રકારની પથરીને દવાના પુરતા કોર્સ વડે અને ન મટે તો શસ્ત્રયિાનો ઉપયોગ કરવામાં આવે છે. જેમ કે, શસ્ત્રક્રિયા કરતાં દવાઓના કોર્સ વડે મટતું હોય તો પ્રાધાન્ય દવાના કોર્સને આપવામાં આવે છે. તેથી અહી સામાન્યતઃ પથરીને દૂર કરવા માટે ઉપયોગમાં લેવાતી ટેમ્યુલોસીન અને ટેડલફીલ માંથી કઇ દવા વધુ અસરકારક છે. / તેમાંથી કઇ એક દવાને ઉપયોગ વધુ અસરકારક છે. તે તપાસવાનો હેતુ છે.

(૨) આ અભ્યાસનો હેતુ શું છે ?

દર્દીને માટે કઇ દવા વધુ અસરકારક નીવડે છે. તે જોવું આ અભ્યાસનો હેતુ છે.

(૩) મારી પસંદગી શા માટે થઇ છે ?

તમને પેશાબની પથરી પેઠુના ભાગમાં છે, ઉપરાંત તમારી ઉંમર ૨૦થી વધુ છે અને આ પદ્ધતી વધુ આક્રમક નથી.

(૪) મારે ભાગ લેવાનો છે ?

હા.

(૫) અભ્યાસ કયાં સુધી આવશે ?

જ્યાં સુધી પથરી દૂર ના થાય અથવા તો ૩ અઠવાડીયા

(૬) જો હું ભાગ લઈશ તો શું થશે ?

- નિદાનનો તબક્કો : પેશાબમાં પથરીની તપાસ માટે દર્દીને જણાવવામાં આવશે.
- સારવારનો તબક્કો : વધુમાં વધુ ૦૩ અઠવાડિયા.
- અભ્યાસ અંતર્ગત જે દવાનો ઉપયોગ કરવાનો છે તે યાદચ્છિક રીતે આપવામાં આવશે.
- અનુસરણનો તબક્કોઃ પથરી નીકળે ન ત્યાં સુધી અથવા વધુમાં વધુ ૨ અઠવાડિયા.

(૭) મારે શું કરવાનું રહેશે?

સંશોધન કર્તા ને સહકાર આપવો અને જો કોઈ તકલીફ થાય તો જણાવવું.

(૮) કઈ દવાનો ઉપયોગ કરવામાં આવશે?

ટેમ્યુલોસીન અને ટેડલફીલ આ બંને દવાઓ પેશાબની પથરી માટે સામાન્યતઃ ઉપયોગ માં લેવાય છે.

(૯) અભ્યાસના ફાયદો શું છે?

બંને દવાઓમાંથી કઈ દવા દર્દીઓને વધુ અસરકારક છે. તેની જાણકારી મળશે. ઉપરોક્ત સારવારના ખર્ચ તેમજ પેશાબની પથરીનો એક જ દવા અને ઉપચાર પદ્ધતિ પ્રમાણે નીકાલ કરી શકાય તે સંદર્ભે પણ અભ્યાસ ઉપયોગી છે.

(૧૦) વૈકલ્પિક સારવાર પદ્ધતિ કઈ છે?

શરલ ક્રિયા / શલ્પ ક્રિયા

(૧૧) અભ્યાસ અંતર્ગત લેવામાં આવનાર સારવારની આડઅસરો જણાવો?

- ટેમ્યુબોસીન : માથાનો દુખાવો, ઓર્થોસ્ટેટીક હાઈપોટેન્શન, રાઈનીટીસ, ડીઝીનેસ, આર્થાલિજીઆ, ઈન્ફેક્શન
- ટેડેલફીલ :- માથાનો દુખાવો, મ્યાલજીયા, ઈન્ફેક્શન, ડિસ્પેપસીયા, ફલશીંગ.

(૧૨) નવી માહિતી ઉપલબ્ધ થાય તો શું થશે?

- જો પથરીના પેશાબ માટે નવી કોઇ જાણકારી મળશે તો પણ કોઇ અસર નહીં પડે કારણ કે આપણે આ પ્રકારની પથરી માટે સામાન્યત વપરાતી સારવાર પદ્ધતિનો ઉપયોગ કરીએ છે. તેમજ તેમાંયે કઇ દવા વધુ અસરકારક છે. તે જાણવા માટે છે.

(૧૩) અભ્યાસ બંધ થયેથી શું થશે?

- અભ્યાસ બંધ થયેથી જે માહિતી થશે તેનું મૂલ્યાંકન થશે અને તેના પરથી તારણ મેળવાશે. કોઇપણ દર્દીની ઓળખ છતી કરવામાં આવશે નહીં.

(૧૪) જો કંઇ ખોટું થાય તો શું થશે?

- કોઇપણ પ્રકારના ભયનો પ્રશ્ન ઉપસ્થિત થતો નથી કારણ કે, મોટાભાગે આજ પ્રકારની સારવાર પદ્ધતિનો ઉપયોગ કરવામાં આવે છે. અને જો કદાચ થવાકાળ આ પ્રકારનો પ્રશ્ન ઉભો થાય તો દર્દીને તરત જ જરૂર પ્રમાણેની સારવાર ઉપલબ્ધ કરાવવામાં આવશે.

(૧૫) આ અભ્યાસમાં હું ભાગ લઉં છું તે ગોપનીય રાખવામાં આવશે?

- હા, ઉપરાંત આપને લગતી તમામ માહિતી પણ ગોપનીય રહેશે.

(૧૬) માટે બીજું કંઇ જાણવાની જરૂર છે?

- સંપૂર્ણ અભ્યાસ સ્વૈચ્છિક ધોરણે થઇ રહ્યો છે. બીજી કોઇપણ પ્રકારની અનિચ્છનિય ઘટના નથી બનવાની તેમજ કોઇપણ પ્રકારનો અન્ય ખર્ચ કે વધારાનો આર્થિક બોજ આપશે નહીં.

(૧૭) વધારાની કાળજી :-

કોઇ શારીરિક તકલીફ કે ફરિયાદ થાય તો તરત જણાવવું.

(૧૮) કોઇપણ સમસ્યા કે તકલીફ હોય તો કોને સંપર્ક કરવો?

ડો. હાર્દિક પટેલ (મો) **૮૨૩૮૬૬૧૮૧૭**

अभ्यास का शीर्षक :– "टेम्युलोसीन वर्सीस टेडलफील एस मेडीकल एक्सप्लुनीव थेरापी ओफ डीस्टल युरेटीक स्टोन्स : अ रेनोमाइनड् कन्ट्रोल ट्रायल"

अभ्यासक्रमांक :– ..... *दिनांक :– .....*

(१) पस्तावना :–

युरीन में होने वाली पथरी आमतौर पर सभी लोगों में देखी जाती बीमारी है । इसी लिए अस्पतालों में आने वाले मरीजों में पथरी के मरीजों की मात्रा अधिक देखी जाती है । युरीन में पथरी होने का मुल कारण वातावरण और भौगोलिक परिस्थितिया है । इस प्रकार की पथरी को दवा से या शस्त्रक्रिया से ठीक किया जाता है । जैसे कि, शस्त्रक्रिया की जरुरत न हो, तो दवाईयों को ही प्राधान्य दिया जाता है, इसलिए यहाँ सामान्यतः पथरी को दूर करने के लिए टेम्युलोसीन और टेडलफील में से कौन सी दवाई ज्यादा उपकारक है, इस में से कौन सी दवाई की असरकारकता अधिक है, यह जानने का उदेश है ।

(२) अभ्यास का हेतु क्या है ?

मरीज के लिए कौन सी दवाई ज्यादा असरकारक है, यह देखने का आशय है ।

(३) अभ्यास में मेरी पसंदगी क्यों हुई ?

आपको युरीन की पथरी पेठु के भाग में है, साथ ही साथ आपकी उम्र २० साल से अधिक है और यह पध्धति आक्रमक नही है ।

(४) क्या मुझे इस अभ्यास में हिस्सा लेना जरूरी है ?

हा ।

(५) अभ्यास कितने समय तक चलेगा ?

जब तक पथरी दूर नहीं हो जाती या तो दो सप्ताह ।

(६) इस अभ्यास में भाग लेने के बाद मेरे साथ क्या होगा ?

निदान का समय :– युरीन में पथरी की जाँच करवाने लिए मरीज को बताया जायेगा ।

चिकित्सा का समय :– ज्यादा से ज्यादा ०३ सप्ताह ।

अभ्यास के दौरान जिस दवाई का प्रयोग किया जायेगा वह यादृच्छिक है ।

अनुसरण का समय : जब तक पथरी ना निकले तब तक या ज्यादा से ज्यादा ०३ सप्ताह ।

(७) मुझे क्या करना होगा ?

मरीज को उसकी चिकित्सा करनेवाले डोक्टर को जाँचने की अनुमति देगा और अपने बारे में संपूर्ण एवम् सच्ची जानकारी देना ।

(८) कौन सी दवाई का प्रयोग किया नायेगा ?

इस अभ्यास के दौरान टेम्युलोसीन और टेडलफील दोनों दवाई जो युरीन की पथरी के लिए सामान्यतः प्रयोग में ली जाती है ।

(९) अभ्यास से क्या लाभ होगा ?

दोनों दवाईयों में से कौन सी दवाई मरीनों पर अधिक असरकारक है, उसकी जानकारी प्राप्त होगी । उपर्युक्त चिकित्सा का खर्च एवम् युरीन की पथरी का एक ही दवाई और उपचार पध्धति के आधार पर निदान किया जा सकेगा । इस के संदर्भ में यह अभ्यास उपयोगी है ।

(१०) वैकल्पिक चिकित्सा पध्धति कौन सी है ?

शरल क्रिया / शल्य क्रिया

(११) अभ्यास के दौरान दी नाने वाली चिकित्सा की कोई विपरीत असर होगी ?

टेम्युबोसीन :– सीर दर्द, ओर्थोस्टेटीक हाइपोटेन्शन, राइनीटीस, डीझीनेस, आर्थालीजिआ, इन्फेक्शन

टेडेलफील :– सीर दर्द, म्यालजिया, इन्फेक्शन, डिस्पेपसीया, फलशींग

(१२) नई जानकारी प्राप्त होगी तो क्या होगा ?

यदि युरीन की पथरी के लिए काई नई जानकारी प्राप्त होगी, तो भी कोई नुकशान नहीं होगा, क्योंकि हम इस प्रकार की सामान्य पथरी के लिए परंपरागत चिकित्सा पध्धति का उपयोग ही करते है, और उसमें कौन सी दवाई ज्यादा उपकारक है, यह जानने के लिए उपकारक है ।

(१३) अभ्यास के अंत में क्या होगा ?

अभ्यास के अंत मे जानकारी का पृथकरण किया जायेगा और उस के उपर से किसी सामान्य निर्णय पर आयेंगे । किसी भी मरीज की पहचान प्रदर्शित नहीं की जायेगी ।

(१४) अगर कुछ गलत हुआ तो क्या होगा ?

किसी भी प्रकार का भय होने का सवाल ही पैदा नहीं होता, क्योंकि आमतौर पर इसी प्रकार की चिकित्सा पध्धति का प्रचलन है और यदी कुछ अघटित होगा तो मरीज को तुरंत ही सारवार प्रदान की जायेगी ।

(१५) अभ्यास को दौरान मेरी पहचान गोपनीय रहेगी ?

हा, साथ ही आपकी सभी जानकारी को गोपनीय रहेगी ।

(१६) मुझे ओर कुछ जानकारी प्राप्त करनी पडेगी ?

संपूर्ण अभ्यास स्वैच्छिक है, दुसरी किसी भी प्रकार की अनिच्छनीय दुर्घटना होने की कोई संभावना ही नही है, साथ ही किसी भी प्रकार का खर्च या दुसरा आर्थिक सहाय प्रदान नहीं की जायेगा ।

(१७) दुसरी हिदायत :

किसी भी प्रकार की शारीरिक तकलीफ होने पर तुरंत बता दे ।

(१८) अगर कोई भी जानकारी प्राप्त करनी हो तो किसका संपर्क करे ?

डो.हार्दिक पटेल, मोबाइल नंबर 8238661817

ANNEXURE III:

INFORMED CONSENT FORM

SUMANDEEP VIDYAPEETH UNIVERSITY

Piparia, Ta. Waghodia, Dist. Vadodara Pin: 391760

Informed Consent Form (ICF) for Participants in Research Programmes involving studies on human beings

STUDY TITLE: "**Tamsulosin versus Tadalafil as medical expulsive therapy of distal ureteric stones: A comparative study**"

Study No: SVU/SBKS/_____ /2016-_____

Participants Initials: _____ Participants Name: _____

Date of Birth: _____ Age: _____Years

1. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that the investigator of this study, others working on the investigators behalf, the Ethics committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information related to the third party or get published.
4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
5. I agree to take part in the above study.

Signature/Thumb impression of the participant _____

Legally acceptable representative _____

Signatory's Name _____ Date _____

Signature of the investigator _____ Date _____

Study Investigator's Name _____ Date _____

Signature of the impartial witness _____Date _____

Name of the witness _____

સુમનદીપવિદ્યાપીઠયુનીવર્સિટી

એસ.બી.કે.એસ. મેડિકલ ઈન્સ્ટટ્યુટ એન્ડ રીસર્ચ સેન્ટર

પીપરીયા, તા. વાઘોડીયા, જી. વડોદરા.

અભ્યાસ માં ભાગ લેવા માટે (સંશોધન)સહભાગી દ્વારા સમજી વિચારીને આપેલી પરવાનગીનુ સંમતિ પત્રક

અભ્યાસનું નામ: ધિરજ જનરલ હોસ્પિટલ, પિપરિયા ખાતે "ટેમસુર્લોસીન વર્સિસ ટેડેલાફીલ એસમેડિકલ એક્સપલસિવ થેરાપી ઑફ ડિસ્ટલયુરેટ્રિક સ્ટોન્સ ૭એ તુલનાત્મક અભ્યાસ"

અભ્યાસ ક્રમાંક :SVU/SBKS/ /૨૦૧૨-___

સહભાગીનું પુરૂ નામ:

સહભાગીનું ટુંકૂ નામ:

સહભાગીની જન્મતારીખ વર્ષ_____ / _____ **:ઉંમર /**

૧) મેંઆ અભ્યાસ(સંશોધન)સંબંધીતારીખ: / /નીમાહિતીપત્રિકાવાંચેલઅનેસમજેલછેતેમજમનેમારાડોકટર (તપાસકર્તા) નેપ્રશ્નોપુછવાનીઅનેચર્ચાકરવાનીપણતકમળીછે.

૨) મનેસમજાવેલછેકેઆઅભ્યાસ (સંશોધન)માંભાગલેવોએસંપૂર્ણમારીમરજીઉપરછેતેમજહુંગમેત્યારેકારણઆપ્યાવગરપણઆમાંથીનીકળીશકું છું, અને આમ કરવાથી મારી તબીબી સારવાર કે કાયદેસરના હક્કોને કોઇ અસર નહીં થાય.

૩) હું જાણુ છું કે આ અભ્યાસ (સંશોધન)ના તપાસકર્તા, તેમના મદદનીશો, એથિકલટીમ અને તેના ઉપર દેખરેખ રાખતા અધિકારીઓને મારા સ્વાસ્થ્યની કોઇપણ જાતની માહિતી, સદર અભ્યાસ (સંશોધન)ને લગતી કે તે સિવાયની, મેળવવા માટે મારી પરવાનગીની જરૂર રહેશે નહીં, ભલે પછી હું અભ્યાસ (સંશોધન)માંથી ખસી જાઉં. હું જાણું છું કે મારી આ પ્રકારની માહિતી અન્ય કોઇને જાણ કે પ્રસિધ્ધ નહીં કરવામાં આવે.

૪) આ અભ્યાસ (સંશોધન) દરમ્યાન, અથવા તેના અંતે પ્રાપ્ત થતી માહિતી, કોઇપણ જાતની વૈજ્ઞાનિક શોધ માટે ઉપયોગ કરવા માટે હું સ્વૈચ્છિક રીતે છુટ આપું છું

૫) હુંઆઅભ્યાસ (સંશોધન)માંભાગલેવા/ જોડાવામાટેમારીસંમતિઆપુંછું.

સહભાગીનું નામ:_____સહભાગીનીસહીઅથવાડાબાઅંગુઠાનુંનિશાન:_____

સંમતિલેનારનુંનામ:_____સંમતિલેનારનીસહી:_____

સાક્ષીનુંનામ:_____સાક્ષીનીસહીઅથવાડાબાઅંગુઠાનુંનિશાન:_____

સ્થળ:_____તારીખ:_____

सुमनदीप विद्यापीठ युनिवर्सिटी

एस.बी.के.एस. मेडिकल इन्स्टीटयुट एन्ड रिसर्च सेन्टर

पीपरिया, ता.वाघोडिया जि.वडोदरा – 391760

अभ्यास का नाम :– "टेम्युलोसीन वर्सीस टेडलफील एस मेडीकल एक्सप्लुनीव थेरापी ओफ डीस्टल युरेटीक स्टोन्स : अ रेनोमाइनड् कन्ट्रोल ट्रायल"

अभ्यासक्रमांक :– ..... *दिनांक :– .....*

(१) *मैं पूष्टि करता हूँ कि, उपरोक्त अभ्यास की (दिनांक.....) की जानकारी पढी है और ठीक से समजी है, और इस विषय में अपूर्ण जानकारी के सवाल करने के लिए मुझे मौका दिया गया था ।*

(२) *साथ ही मुझे यह भी विदित है, कि इस अभ्यास में भाग लेना वैकल्पिक है और किसी भी प्रकार की नोटिस दिये बगैर उसमें से दूर होने का मुझे अबाधित अधिकार है । ऐसा करने से मेरे चिकित्सा संबंधी अधिकारो को कोई असर नहि होगा ।*

(३) *मुझे यह भी ज्ञात है, कि अभ्यास के चिकित्सक, उसके सहयोगी, एथिकल टीम और उसके उपरी अधिकारियों को मेरे स्वास्थ्य संबंधी सभी जानकारी इस अभ्यास के संदर्भ में प्राप्त करने में मेरी रजामंदी की कोई जरूरत नहीं रहेंगी । चाहे मैं इस अभ्यास से दूर हो जाऊ, मुझे अच्छी तरह विदित है कि यह जानकारी कहीं पर भी प्रसिध्ध नहीं होगी ।*

(४) *इस अभ्यास के दौरान और उसके अंत में प्राप्त होनेवाली किसी भी जानकारी का वैज्ञानिक शोध के लिए उपयोग करने के लिए मैं पूर्ण रूप से सहमत हूँ ।*

(५) *इस अभ्यास में जूडने के लिए मैं पूर्ण होशोंहवाश में सहमति प्रदान करता हूँ ।*

प्रतिभागी के हस्ताक्षर या अंगूठे का निशान .....

कानूनी तौर पर स्वीकार्य प्रतिनिधि .....

हस्ताक्षरकर्ता का नाम ..... दिनांक .....

अन्वेषक के हस्ताक्षर ..... दिनांक .....

अन्वेषक का नाम ..... दिनांक .....

निष्पक्ष गवाह के हस्ताक्षर ..... दिनांक .....

निष्पक्ष गवाह का नाम .....

ANNEXURE IV:

PROFORMA :

1. Name:
2. Reg. No.:
3. Age/Sex:
4. Ward:
5. Address:
6. Date of Admission:
7. Date of Operation:
8. Date of Discharge:
9. Clinical History:

PRESENT COMPLAINTS

- Pain in lower abdomen
- Pain in passing urine
- Unable to pass urine

PAST HISTORY

- H/O Similar complaints / DM / HT / Trauma / Dietary Habits /prolong use of medication/ Addiction (Alcohol/ Other).

CLINICAL EXAMINATION

- Vitals
  - General Condition
  - B.P
  - Pulse
  - Temperature
  - Respiratory Rate
- Pallor / Icterus / Cyanosis / Clubbing / Edema / Lymphadenopathy

Local:

To look for

1. Phymosis
2. Meatal stenosis

- **Speculum examination for female participations**
- **Per rectal examination**

For Prostate size

- System Review
  - PER ABDOMEN
  - RS
  - CVS
  - CNS

INVESTIGATIONS

- CBC (routine)
- RFT (Se. create)
- Urine : Routine & Microscopy
- Radiological
  - X-ray KUB: Day 1 and Day 21 or post expulsion of stone.
  - ULTRA SONOGRAPHY: Stone localization and size. Day 1 and Day 21 or post expulsion of stone .
  - CT IVP: Day 1 and Day 21 or post expulsion of stone.

- **MANAGEMENT**

Drug used

Tadanfil : yes or no

Tamsulosin : yes or no

Analgesic: dose / drug and frequency

- **Outcome**
  - **Expulsion of stone : yes or no**
  - **Day of expulsion**
  - **Analgesic use**

- **FOLLOW UP**

At least 3 week

- **Remark's:**

ANNEXURE V:

MASTER CHART

KEY TO MASTER CHART

M	:	Male
F	:	Female
Y	:	Yes
N	:	No
CT-IVP	:	Computed tomography intravenous pyelography

MASTER CHART

				Presenting Complaints						USG									Adverse Reactions				
S. No	Group	Age	Sex	Abd. Pain	Burning Micturation	Hematuria	Nausea/ Vomiting	Stone Size (mm)	Opacity on X-ray	Calculi	Hydroureter	Hydronephrosis	CT-IVP	Expulsion Time	Complete Expulsion	Analgesic Use	Colicky episodes	Hospital visits	Headache	Dizziness	Backache	Hypotension	Abnormal ejection
1	Tadalafil	33	M	Y	Y	N	N	5	Y	Y	Y	N	Y	12	Y	150	0	1	N	N	N	N	N
2	Tadalafil	37	M	Y	Y	Y	N	9	Y	Y	Y	Y	Y	11	Y	150	0	1	N	Y	N	N	N
3	Tadalafil	39	M	Y	Y	N	Y	7	Y	Y	N	N	Y	10	N	100	0	1	N	N	N	N	N
4	Tadalafil	37	F	Y	N	N	N	8	Y	Y	N	N	Y	16	Y	150	0	1	N	N	N	Y	N
5	Tadalafil	38	M	Y	Y	N	N	7	Y	Y	N	N	Y	14	Y	200	1	2	Y	Y	N	N	N
6	Tadalafil	36	F	Y	N	N	N	9	Y	Y	Y	Y	Y	13	Y	150	0	1	N	N	Y	N	N
7	Tadalafil	35	M	N	Y	N	Y	3	N	Y	N	N	Y	13	Y	100	0	1	N	N	N	N	N
8	Tadalafil	39	M	Y	Y	N	N	4	N	N	N	N	Y	12	Y	150	0	1	Y	N	N	N	N
9	Tadalafil	41	F	Y	N	N	N	4	Y	Y	Y	N	Y	14	Y	250	1	2	N	N	N	N	N
10	Tadalafil	30	M	Y	Y	Y	N	10	Y	Y	Y	Y	Y	10	N	200	1	2	N	N	N	N	N
11	Tadalafil	39	F	Y	N	N	N	5	Y	Y	Y	N	Y	9	Y	250	1	2	N	N	N	N	Y
12	Tadalafil	38	F	N	Y	N	Y	6	Y	Y	Y	N	Y	11	Y	200	1	2	Y	N	N	N	N
13	Tadalafil	44	M	Y	Y	N	N	7	Y	Y	N	N	Y	10	Y	150	0	1	N	N	N	N	N
14	Tadalafil	36	M	Y	N	N	N	6	Y	Y	Y	N	Y	11	Y	200	1	2	N	N	N	N	N
15	Tadalafil	38	F	Y	Y	Y	N	10	Y	Y	Y	Y	Y	8	Y	250	1	2	N	Y	Y	N	N
16	Tadalafil	34	M	N	Y	N	Y	7	Y	Y	N	N	Y	9	Y	150	0	1	N	N	N	N	N
17	Tadalafil	40	F	Y	N	N	N	6	Y	Y	Y	N	Y	10	N	200	1	2	N	N	N	N	N
18	Tadalafil	39	M	Y	Y	N	N	7	Y	Y	N	N	Y	13	Y	250	1	2	N	N	N	N	N
19	Tadalafil	29	F	Y	Y	N	N	6	Y	Y	Y	N	Y	10	Y	150	0	1	N	N	N	Y	N
20	Tadalafil	38	M	Y	N	N	Y	7	Y	Y	N	N	Y	11	Y	200	1	2	N	N	N	N	N
21	Tadalafil	39	M	Y	Y	N	N	6	Y	Y	Y	N	Y	15	Y	150	0	1	N	N	N	N	N
22	Tadalafil	42	M	Y	N	N	N	6	Y	Y	Y	Y	Y	15	Y	100	0	1	Y	N	N	N	N
23	Tadalafil	38	F	N	Y	N	N	6	Y	Y	Y	N	Y	12	Y	150	0	1	N	N	Y	N	N
24	Tadalafil	37	M	Y	Y	N	N	6	Y	Y	Y	N	Y	14	Y	150	0	1	N	N	N	N	Y
25	Tadalafil	35	M	Y	N	N	N	5	Y	Y	Y	N	Y	11	Y	150	0	1	N	N	N	N	N
26	Tadalafil	38	M	Y	N	N	N	5	Y	Y	Y	N	Y	15	N	150	0	1	N	N	N	N	N
27	Tadalafil	51	M	Y	Y	N	Y	5	Y	Y	Y	N	Y	9	Y	200	1	2	N	N	N	N	N
28	Tadalafil	28	M	Y	Y	N	N	8	Y	Y	N	N	Y	10	Y	250	1	2	N	N	N	N	N
29	Tadalafil	39	M	Y	N	Y	N	9	Y	Y	Y	Y	Y	10	Y	150	0	1	N	N	N	N	N
30	Tadalafil	61	M	Y	Y	N	N	7	Y	Y	N	N	Y	11	Y	100	0	1	N	N	N	N	N
31	Tamsulosin	44	M	Y	Y	N	N	6	Y	Y	Y	N	Y	15	Y	250	1	2	N	N	N	N	N
32	Tamsulosin	37	M	N	N	N	N	6	Y	Y	Y	N	Y	15	Y	300	2	3	N	N	N	N	N
33	Tamsulosin	38	F	Y	Y	N	N	5	Y	Y	Y	N	Y	13	Y	350	2	3	Y	N	N	Y	N
34	Tamsulosin	24	M	Y	N	N	Y	6	Y	Y	Y	N	Y	20	N	300	2	3	N	N	N	N	N
35	Tamsulosin	51	M	Y	Y	N	N	3	N	N	N	N	Y	17	Y	250	1	2	N	Y	Y	N	N
36	Tamsulosin	50	F	Y	Y	N	N	4	Y	Y	N	N	Y	17	Y	300	2	3	N	N	N	N	Y
37	Tamsulosin	29	M	Y	N	Y	N	8	Y	Y	N	N	Y	16	N	250	1	2	N	N	N	N	N
38	Tamsulosin	37	M	Y	Y	N	N	5	Y	Y	Y	N	Y	16	Y	300	2	3	N	N	N	N	N
39	Tamsulosin	53	M	N	Y	N	N	6	Y	Y	Y	N	Y	17	N	200	1	2	N	N	N	N	N
40	Tamsulosin	43	F	Y	N	N	N	5	Y	Y	Y	N	Y	14	N	250	1	2	N	N	N	N	N
41	Tamsulosin	38	M	Y	N	N	Y	4	N	N	Y	N	Y	12	Y	300	2	3	N	N	N	N	N
42	Tamsulosin	36	M	Y	N	Y	N	10	Y	Y	Y	Y	Y	15	Y	250	1	2	Y	N	Y	N	N
43	Tamsulosin	26	M	Y	Y	N	N	5	Y	Y	Y	N	Y	13	N	300	2	3	N	N	N	N	N
44	Tamsulosin	50	F	Y	Y	N	Y	4	N	N	Y	N	Y	15	Y	350	2	3	N	N	N	N	Y
45	Tamsulosin	51	M	Y	N	N	N	3	N	N	N	N	Y	11	Y	300	2	3	N	N	N	Y	N
46	Tamsulosin	27	M	Y	Y	N	Y	4	N	N	Y	N	Y	13	N	350	2	3	N	Y	N	N	N
47	Tamsulosin	39	F	Y	N	N	N	5	Y	Y	Y	N	Y	13	Y	300	2	3	Y	N	N	N	N
48	Tamsulosin	49	M	Y	Y	N	N	5	Y	Y	Y	N	Y	17	Y	350	2	3	N	N	Y	N	N
49	Tamsulosin	44	M	Y	Y	N	N	4	Y	Y	Y	N	Y	13	N	300	2	3	N	N	N	N	N
50	Tamsulosin	36	F	N	Y	Y	N	10	Y	Y	Y	Y	Y	15	Y	250	1	2	N	N	N	N	N
51	Tamsulosin	38	M	Y	N	N	N	7	Y	Y	N	N	Y	18	Y	300	2	3	N	N	N	N	N
52	Tamsulosin	25	M	Y	N	N	N	6	Y	Y	Y	N	Y	19	N	350	2	3	N	Y	N	N	N
53	Tamsulosin	47	F	Y	Y	N	Y	8	Y	Y	N	N	Y	15	Y	250	1	2	N	N	N	N	N
54	Tamsulosin	49	M	Y	N	N	N	8	Y	Y	N	N	Y	18	Y	300	2	3	N	N	N	N	N
55	Tamsulosin	29	M	Y	Y	N	N	8	Y	Y	N	N	Y	14	N	200	1	2	N	N	N	Y	Y
56	Tamsulosin	38	M	Y	N	N	N	7	Y	Y	N	N	Y	19	Y	250	1	2	N	N	N	N	N
57	Tamsulosin	45	M	Y	Y	N	N	6	Y	Y	Y	N	Y	12	N	350	2	3	N	Y	Y	N	N
58	Tamsulosin	42	M	Y	Y	N	N	8	Y	Y	N	N	Y	14	Y	300	2	3	N	N	N	N	N
59	Tamsulosin	38	F	Y	Y	N	N	8	Y	Y	N	N	Y	13	Y	250	1	2	N	N	N	N	N
60	Tamsulosin	37	M	Y	N	N	N	8	Y	Y	N	N	Y	15	N	250	1	2	N	N	N	N	Y