"EFFICACY OF TAMSULOSIN (ALPHA 1 BLOCKER) IN THE MANAGEMENT OF SYMPTOMATIC DISTAL URETEIC CALCULUS"

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

GENERAL SURGERY

Under the Guidance of

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2015

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to be submitted to the

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA,

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ACKNOWLEDGEMENT

I am highly indebted to my guide ***Dr. K. NISCHAL,*** *Professor, Department of General Surgery, and co guide* ***Dr. KRISHNA SHETTY M.V.****, Professor , Department of Urology , Sri Devaraj Urs Medical College, Tamaka, Kolar, who guided me in bringing out this work with his thought provoking ideas and constant encouragement.*

It gives me immense pleasure to express my gratitude and sincere thanks to ***DR. MOHAN KUMAR K,*** *Professor and H.O.D., Department of General Surgery, Sri Devaraj Urs Medical College, Tamaka, Kolar, who took deep interest and gave constant support by encouraging in molding this work.*

I also acknowledge my debt to ***DR. A. BHASKARAN, DR. P. N. SREERAMULU*** *and****, DR. K KRISHNA PRASAD*** *Department of General Surgery, Sri Devaraj Urs Medical College, Tamaka, Kolar, who gave me moral support and guidance by correcting me at every step.*

I remain thankful to all my assistant professors and lecturers for their support and encouragement. I acknowledge my sincere thanks to all my co-P.G.'s for their help and support at every step throughout my study

I am much thankful to my parents ***Mr. Narasimha Reddy,*** *and* ***Mrs. Vimala*** *for their love, blessings and invaluable help.*

Last, but not the least, I thank the Almighty and ***my patients*** *for providing me the opportunity to carry out my study.*

Dr. RAKESH N

LIST OF ABBREVIATIONS

ESWL/SWL:		**Extracorporeal Shockwave Lithotripsy**
PCNL/PNL	**:**	**Percutaneous Nephrolithotomy**
URS	**:**	**Ureterorenoscopy**
UTI	**:**	**Urinary Tract Infection**
PLC	**:**	**Phospholipase C**
IP3	**:**	**Inositol Triphosphate**
DAG	**:**	**Diacylglycerol**
SS	**:**	**Supersaturation**
Ksp	**:**	**Thermodynamic solubility product**
CaOx	**:**	**Calcium Oxalate**
CaP	**:**	**Calcium Phosphate**
Kfp	**:**	**Formation product**
ULM	**:**	**Upper Limit of Metastability**
THP	**:**	**Tamm-Horsfall Protein**
RNA	**:**	**Ribonucleic Acid**
DNA	**:**	**Deoxyribonucleic Acid**
ROS	**:**	**Reactive Oxygen Species**
NC	**:**	**Nephrocalcin**
NB	**:**	**Nanobacteria**
UPJO	**:**	**Uretero-pelvic Junction Obstruction**
CD	**:**	**Calyceal Diverticulum**
AUA	**:**	**American Urology Association**
LUTS	**:**	**Lower Urinary Tract Symptoms**

ABSTRACT

BACKGROUND AND OBJECTIVES

Ureteral calculi has emerged as a global health issue. It is usually described as a loin acute pain radiating to the groin. Almost 20% of urinary stones are found in the ureters with majority (70%) being located in lower third of the ureter. The life time risk of developing urinary calculi is between 5 and 12%, affecting more men compared to women.

Various management options include- medical expulsion therapy (MET), extracorporeal shock wave lithotripsy (ESWL) and invasive therapies (ureteroscopy). Until 1980s, open surgical procedures were the mainstay of treatment of ureteric stone. In the last three decades, the management of urinary stone has undergone revolutionary change. Tamsulosin a selective alpha 1 antagonist allows the expulsion of juxtavesical ureteral stones in a decreased time, in addition, almost completely decreases painful symptoms until expulsion.

Keeping these issues, the study is aimed to evaluate the efficacy and safety of alpha blocker tamsulosin hydrochloride in the management of symptomatic distal ureter calculi compared to fluids with NSAID.

MATERIAL AND METHODS:

This is a prospective randomized study involving patients older than 18 years, presenting with unilateral , solitary distal ureteric calculus <10 mm at Sri Devraj Urs Medical College Hospital from 2012-2015.

Total number of cases studied were 60. Patients with stone size >10 mm, multiple stones, signs of UTI, severe hydronephrsis, co-morbid conditions, previous history or ureteral manipuliations and/or surgery, pregnancy were excluded.

All patients underwent renal function test and transabdominal renal ultrasonography and were divided into two groups-

Group 1 advised to take plenty of oral fluids and treated with NSAIDs (Diclofenac sodium)

Group 2 were treated with Tamsulosin (alpha blocker) 0.4mg HS for 7-10 days along with NSAIDs (Diclofenac sodium).

Patients were followed for 7 to 10 days.

RESULTS:

In the study there were 46 males [24 in Group 1 and 22 in Group 2] and 14 Females [6 in Group 1 and 8 in Group 2]. The mean age of Group 1 was 43.20 ± 13.8 and mean age of group 2 was 40.27 ± 17.7. There was no significant difference in the sex and mean age between two groups.

In the study during the follow up 32 subjects expelled the calculi within 4-5 days, of which 26 were in Tamsulosin group and 6 were in Non Tamsulosin group.

This observation was statistically significant at 0.0001. Hence it can be said that with Tamsulosin treatment expulsion of distal ureteric calculi was higher than when compared to fluids with NSAID.

INTERPRETATION AND CONCLUSION:

Tamsulosin can be used as the first line of management for uncomplicated symptomatic distal ureteric calculi. It is effective and safe. Most of the patients treated with tamsulosin expelled the calculi within short duration.

Keywords: Ureteric stones, Alpha 1 blocker, Tamsulosin, Ureteroscopy

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INTRODUCTION

Since ages Urolithiasis is a common problem among global population, affecting 1–5% of the population in Asia, Europe, North America, and Saudi Arabia[1]. Ureteral stones account for approximately 20% of urolithiasis cases; approximately 70% of ureteral stones are located in the lower third part of the ureter and are known as distal ureteral stones[2].

The highest incidence of calculi occurs between the ages of 20 to 40 years with male more common than females.[3] calculi may cause fibrosis by the damaging the Urinary tract, leading to stasis and severe infection. The transport of stones from the kidney into the bladder and their movement through the ureter is accompanied by 3 basic factors -- 1) spasm of smooth muscles 2) submucosal edema and 3) Pain

In the transport of stones, the greatest obstacle is usually the terminal part of the ureters, mainly in the intra mural 'detrusor tunnel'. Stones of size 4 mm or smaller pass spontaneously, although this is not without discomfort and expense to the patient. Ureteral calculi are often associated with renal obstruction conservative or active management should be carefully chosen to prevent irreversible damage to the kidney while choosing.

Interventional treatments comprise - medical expulsive therapy (MET), extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy, ureteroscopy and laparoscopic/open stone removal. Research to a large extent confirmed the ability of medical treatment to facilitate stone expulsion [4–7].

Relevant studies have greatly advanced our understanding of the role of MET in facilitating stone expulsion. MET also reduce medical costs and prevent unnecessary surgeries and also the risks and complications associated with surgery. Furthermore, patients in whom treatment failed may also choose minimally invasive treatments as

ancillary procedures. Due to these reasons MET for LUS has gained increasing attention in recent years.

In current practice, MET with either Nifedipine (calcium channel blocker) or Tamsulosin (alpha receptor blocker) has been demonstrated to augment the stone passage rates of moderately sized LUS[8]. Indeed, the European Association of Urology guidelines suggest these two agents as reasonable treatment choices to facilitate ureteral stone expulsion[9]

Further studies have also revealed alpha 1-adrenergic receptors in ureteral smooth muscle cells was significantly higher than other adrenergic receptors.

Alpha 1-adrenergic antagonists have also been proved to inhibit basal tone, peristaltic frequency and ureteral contractions even in the intramural tract. The study is taken up to access the possible role of combined alpha 1-antagonist Tamsulosin for facilitating spontaneous expulsion of distal ureteral stones.

OBJECTIVE OF THE STUDY

To study the efficacy of Tamsulosin (alpha 1 blocker) therapy for symptomatic distal ureteric calculi.

REVIEW OF LITERATURE

The ureters are muscular tubes whose peristaltic contractions convey urine from the kidneys to the urinary bladder. Each ureter measures around 25 to 30 cm in length and is thick-walled, narrow, and continuous superiorly with the renal pelvis which is funnel shaped. Each descends slightly medially anterior to the psoas major enters the pelvic cavity where it curves laterally, then medially, as it runs down to open into the base of the urinary bladder.

Three distinct narrowing's classically described:

a) Uretero pelvic junction, b) Crossing of the iliac vessels, and c) Ureterovesical junction.

At the ureteropelvic junction, the renal pelvis tapers into the proximal ureter. The third site of narrowing observed in the normal ureter is the ureterovesical junction. Here there is restriction of the ureter as it makes the intramural passage through the bladder wall to the ureteral orifice. The sites are clinically significant because they are common locations for urinary calculi to lodge during passage.

Unidirectional transport of urine from the kidney to the urinary bladder is one of the most important functions of the pelvi-ureter complex. Ureteral peristalsis is initiated by spontaneous activity of renal pelvis pacemaker cells; thereafter electrical and mechanical activities are conducted to inactive distal regions[10,11] . Although ureteral peristalsis is essentially regulated by the myogenic mechanisms[12,13] , neurogenic factors also play an important role in this process. Electrical activity is propagated distally from cell to cell causing a contraction wave propelling urine distally in boluses[14]. Extra- and intracellular microelectrode recordings have identified two populations of smooth muscle cells as

well as a population of renal interstitial cells that all display spontaneous electrical activity[15]. For the physiological control of ureteral peristalsis and smooth muscle tone several mechanisms have been proposed. Of note, an increase of cytoplasmic free calcium concentration is regarded to be the principal mechanism in smooth muscle contraction.

The ureter has an efferent and afferent innervation including cholinergic, adrenergic and non-adrenergic noncholinergic (NANC) components. Lower ureter has denser innervation than the upper ureter in humans.[16]

Alpha 1 -Adrenoceptors have been detected both in animal and human ureters[17,18]. Activation of alpha 1-adrenoceptors and phospholipase C (PLC), leads to ureteral contraction which in turn leads to formation of second messengers (inositol trisphosphate (IP 3) and diacylglycerol (DAG)[19]. IP 3 is involved in the mobilization of calcium from sarcoplasmic reticulum[20], whereas DAG increases calcium influx across the cell membrane via the activation of protein kinase C[21].

The density of alpha 1 -adrenoceptors (alpha 1a and alpha 1d) in the ureteral smooth muscle has been shown to be greater than other adrenoceptors[22]. Blockage of these receptors inhibits basal tone, peristaltic frequency and ureteral contractions[23].

RENAL ANATOMY

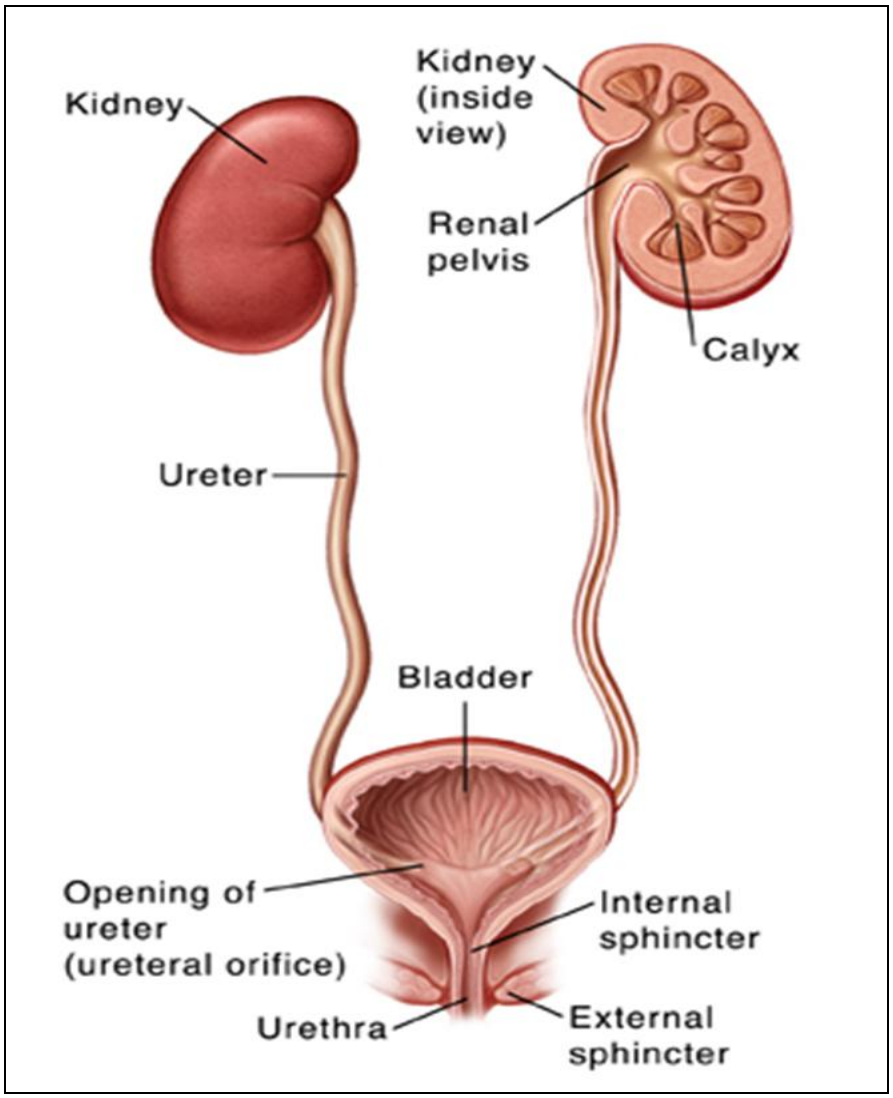


Fig 1: Renal Anatomy

KIDNEY

Kidneys are retroperitoneal organs. They extend from T12 – L4. Both the kidneys are placed obliquely with long axis parallel to psoas muscle. Normal kidney weigh around 120 to 140 mg and measure about 12x6x3 cm. Vertical slit like depression on the medial border is the hilum. The structures at the hilum are renal vein, artery and ureter from front to back. Hilum of right and left kidney lie below and above the transpyloric plane respectively.

Kidneys lie over diaphragm and quadratus lumborum muscle, with overlap medially by psoas muscle and laterally by transverse abdominis. Renal pelvis (funnel shape) communicates with the ureter. Capacity of average pelvis is less than 5 ml.

The surface of the kidney is covered by its capsule, are usually smooth and convex.

Posterior relation of both kidney are similar, comprising of diaphragm and quadratus lumborum with overlap of psoas and transverse abdominis muscle.

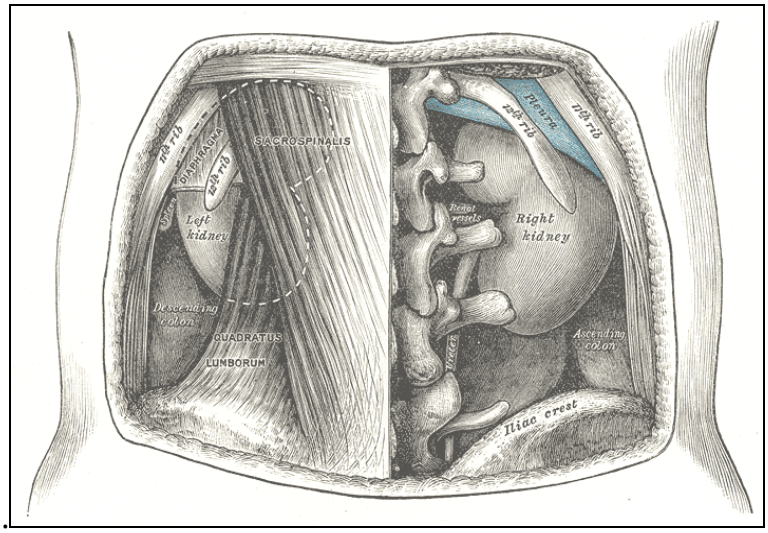


Fig 2: Relation of The Kidney

Suprarenal gland surmount the superior poles of both the kidneys.

Perinephric fat lies outsidde the renal capsule and helps in retaining the kidney in position. Renal fascia surrounds perinephric fat.

Kidneys are supplied by the renal artery which is a branch of descending aorta. Kidneys are divided into segments according to their vascular supply. Apical, upper, middle and lower are supplied by anterior renal artery. Posterior segment is supplied by posterior renal artery. Lymphatics drain to paraaortic lymph nodes. Nerve supply is by sympathetic preganglionic which lie in the spinal cord from T12 to L1.

URETERS

Ureters are tubular structure measuring around 22cm to 39 cm in length. Ureters begin from the pelviureteric junction, which lie posterior to renal artery and vein. Right ureters are crossed by right colic, iliocoloc artery and by mesentry.

Ureter is divided into 3 parts - upper, middle and lower. Upper extends from renal pelvis to upper border of sacrum, middle - upper border to lower border of sacrum and distal ureter extends from lower border of sacral to bladder.

Ureters pass down on psoas major under cover of the peritoneum and crosses in front of the genito-femoral nerve. On the right upper part is behind the third part of duodenum while lower down it is crossed anteriorly by the right colic and iliocolic vessels and the root of the mesentry.[24] On the left it is lateral to the inferior mesentric vessels and is crossed anteriorly by the left colic vessels and at the pelvic brim, by the apex of the sigmoid colon.

Blood supply of the ureter – upper end supplied by the ureteric branch of the renal artery and the lower end by the branches from the inferior and superior vesical and ureterine arteries. Middle stretch by the abdominal aorta branches.

Ureters are supplied by T10-L1 segments of the spinal cord. Preganglionic innervation arises from renal, inferior vesical, hypogastric, aortic, spermatic, inferior mesenteric and vaginal plexus and also from the celiac and upper sacral ganglia.

Visceral efferent fibers come from both sympathetic and parasympathetic sources, while afferent fibers return to T11 L2 spinal cord levels. Referred pain to cutaneous areas supplied by T11 to L2 spinal cord levels seen in ureteric pain is usually related to distension of the ureter. The areas to which pain is referred are the posterior and lateral abdominal wall below the ribs and above the iliac crest, the pubic region, the scrotum in males, the labia majora in females, and the proximal anterior aspect of the thigh.

The unique feature of the distal ureter is the presence of Autonomic ganglion cells, such cells are absent from all other regions of the ureter.

Pelvic Ureter: The anatomic relations of the pelvic ureteral differ in males and females.

Male: In the male, the vas deferens crosses the ureter in a lateral to medial direction.

At this point the vas separates the ureter from the peritoneum. At the lateral aspect of the angle formed by the vas and the seminal vesicle the ureter then continues medially to reach the seromuscular layer of bladder.

Female: In the female. The parietal division of the pelvic ureters enters the pelvis in close association with the suspensory ligament of the ovary (containing the ovarian vessels). It then descends along the posterior peritoneal surface of the broad ligament. It enters the parametrium, proceeds forward around the cervix and reaches the urinary bladder. Typically, it is separated laterally from the cervix by approximately 2 cms and is about 1 cm above the vaginal fornix at this point.

Ureter is a tube of smooth muscle lined by mucous membrane. The mucous membrane is lined by transitional epithelium.

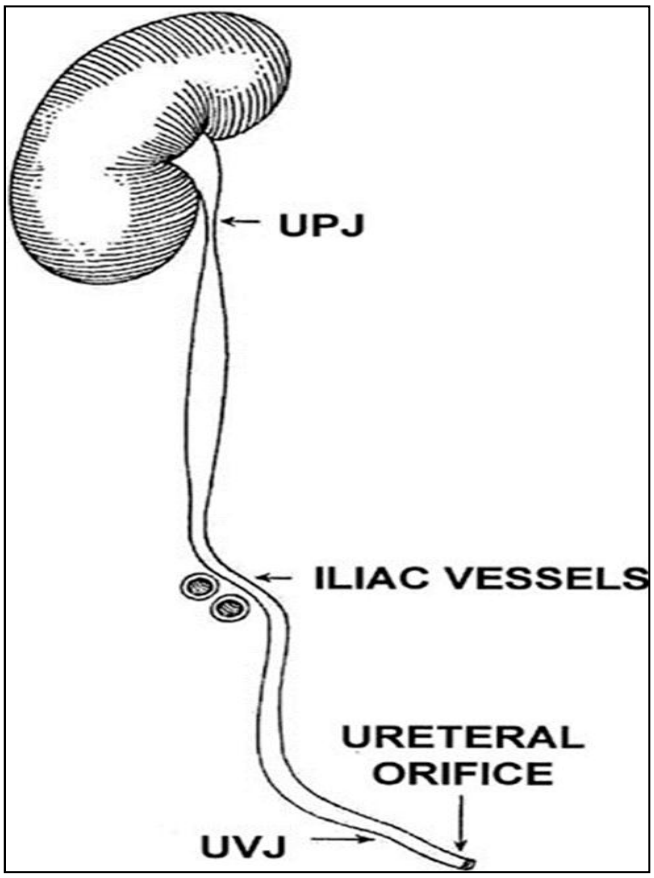


Fig 3: Anatomical Narrowing Of The Ureter

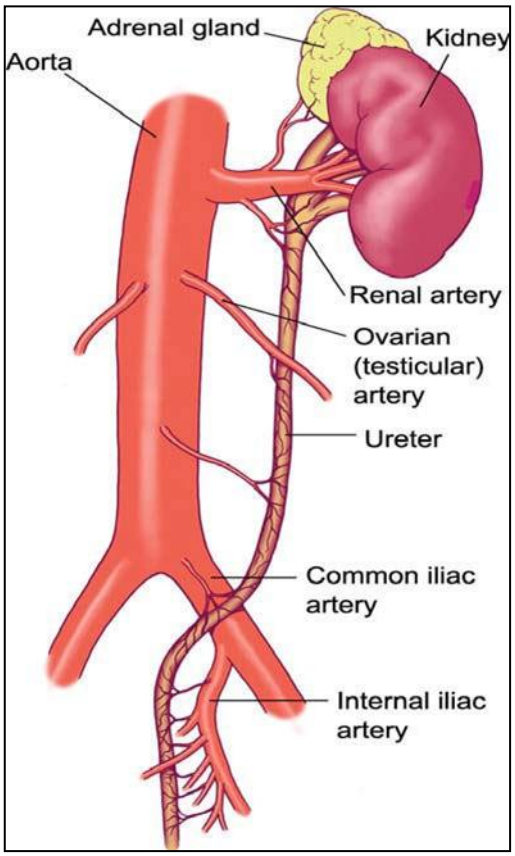


Fig 4 : Blood Supply Of The Ureter

BLADDER:

Bladder is a pyramid shaped organ present within the pelvic cavity when empty. As the bladder distends it domes up into the abdominal cavity.

It has an apex, a base, a superior surface, and two inferolateral surfaces.

Trigone is a triangular area at the base of the bladder lying between the two ureteral orifices and the internal urethral orifice. In males trigone overlies median part of the central zone of the prostate.

Blood supply is by the superior and inferior vesical arteries .Veins of the bladder form a plexsus that converge on the vesicoprostatic plexus in the groove between bladder and prostate and drain into the iliac veins.

Lymphatics is mainly to the external iliac nodes.

Nerve supply is mainly by the L1, 2 segments of the spinal cord.

Bladder is composed of interlacing network of fibers running in various directions. Both externally and internally they produce a trebaculated appearance. Contraction of these muscles help to close the ureteral orifice.

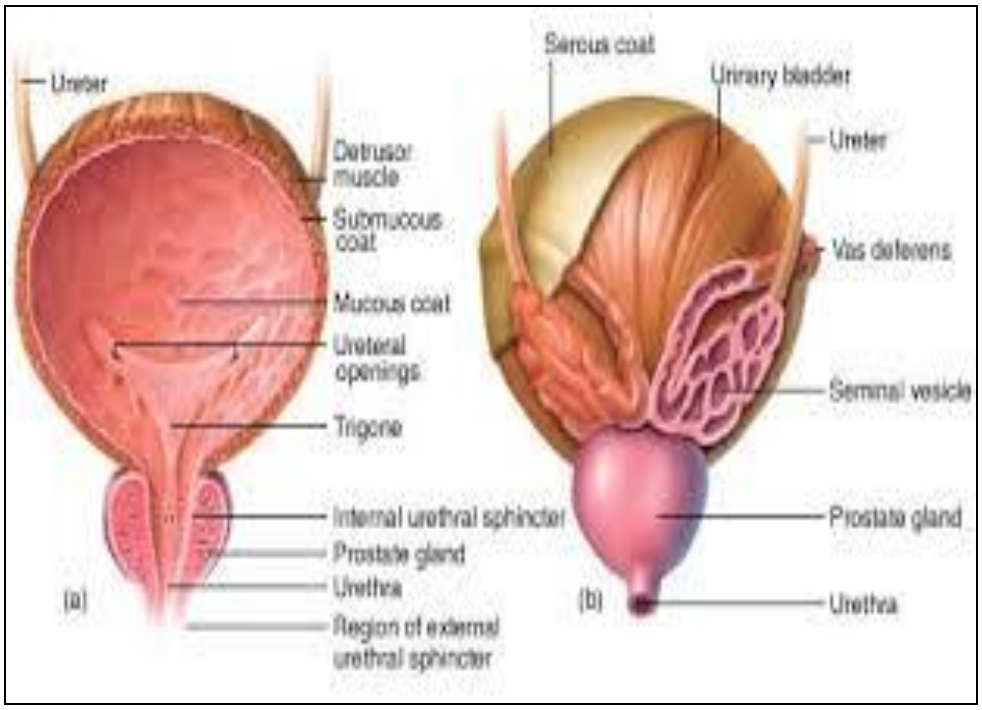


Fig 5 : Urinary Bladder Anatomy And Musculature

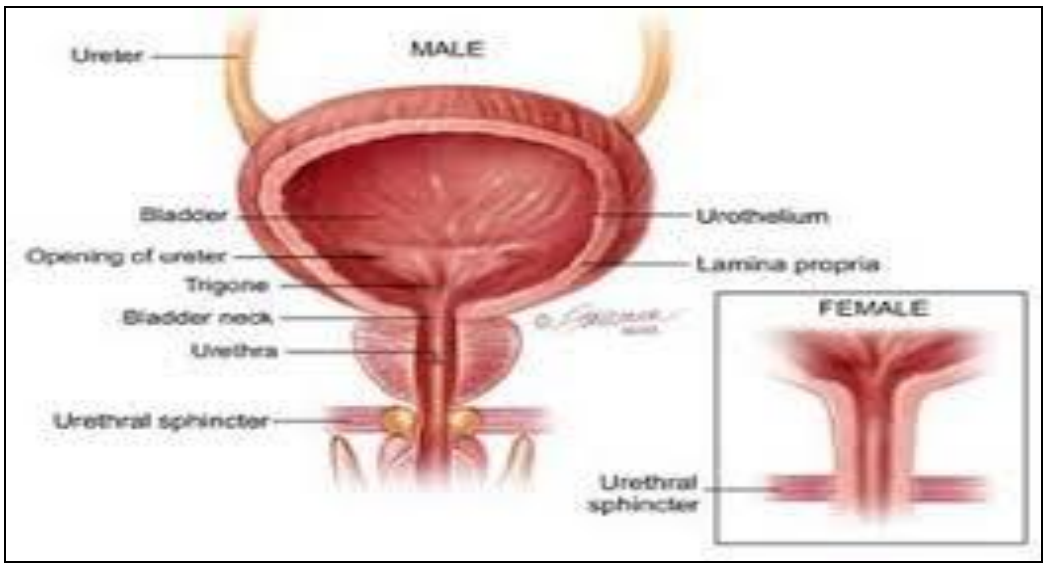


Fig 6 : Male And Female Urinary Bladder

MORPHOLOGY OF URETERIC CALCULI

Rarely the ureteric calculi develop primarily in the ureter. Usually its origin is in the kidney. To deal with this the biochemistry of the stone, mode of formation and etiological factors related to calculi need to be studied. [25]

Biochemical Studies

A urinary calculus is made up of two components.

1. Matrix or colloid
2. Crystalloid

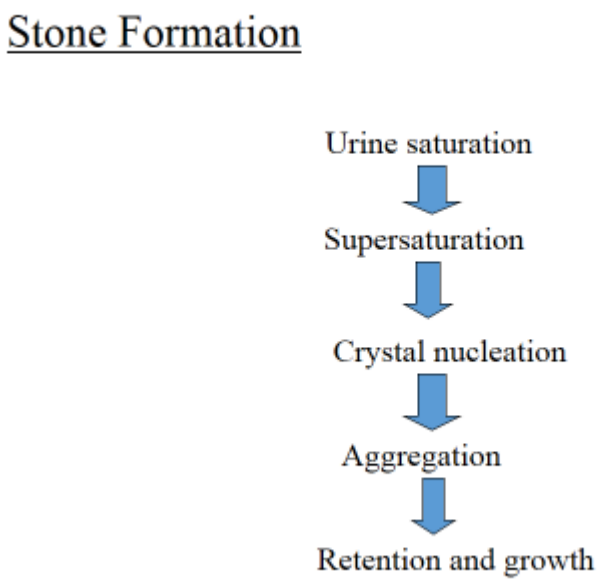
Mucoproteins and comprises about 2.5% of the matrix or colloid component of the calculus. sulphated mucopolysaccharides comes from the bones and connective tissues, while the origin of mucoproteins is not known.

98% of the calculus weight comprises of the crystalloid component comprises about. Its main bulk, is formed by calcigenous salts, the important ones being calcium oxalate, calcium phosphate and magnesium ammonium phosphate. Rest of the crystalloids portion consists of uric acid forming about 4% and cystine and xanthine about 1% which are non calcigenous.

Microscopic studies -

The crystalloids derived from the matrix are deposited in the fibrillar network. These fibrils are arranged in various ways. Arrangement varies in smooth calculi (lamellar patterns) and irregular calculi (whorls).[26]

THE PHYSICAL CHEMISTRY OF STONE FORMATION



Supersaturation and the upper limit of metastability

Urinary supersaturation (SS) is necessary for clinical stone formation. SS is the driving force for a phase change from dissolved salt to solid; that is to say that at SS values less than 1, crystals will be dissolved in solution, and at SS values greater than 1, crystals may form. 27 Thermodynamic solubility product (Ksp) is the concentration at which saturation is reached and crystallization begins. Ksp is a constant equal to the product of the concentration of the pure chemical components of the solute at saturation. 24-hr urine tests, have been shown to correlate with stone composition ,underscoring the importance of SS in stone formation.[28] Although SS is simple to caluculate in water,urine is a much more complex solution,containing substances that affect the formation calcium oxalate (CaOx) and calcium phosphate(CaP). Formation product (Kfp) referred as metastable zone is the range of SS between the solubility product and their point at which crystals. The term metastable is used because the concentration of the salt, for example CaOx, is above its solubility and precipitation is inevitable. The amount of calcium

oxalate required to produce a solid phase of CaOx or CaP is known as the upper limit of metastability (ULM). [27] ULM is lower among stone formers and varies with urinary SS which has been demonstrated in a study.[29,30]

Nucleation and crystal formation

In pure solution, nucleation will occur at a critical level of SS. The first step in crystal formation is nucleation. Which is referred to as homogenous nucleation in urine, however, crystal nuceli can form on existing surfaces, such as cell membranes, cellular debris, other crystals, red blood cells, and urinary casts, through a process known as heterogenous nucleation.[31,32] Heterogenous nucleation occurs at lower level of SS than homogenous nucleation.[33] Epitaxy is a process where one crystal similar to that of another crystal in sturcture, the second crystal may be able to nucleate and grow on the first.[34] In addition to crystal growth, crystal aggregation or agglomeration is thought to be an important mechanism in stone formation. When crystal nuclei in aqueous solution, collison between crystals caused by chemical or electrical forces can lead to crystal aggregation

Crystal retention

A volume of literature suggests that crystal retention is necessary for stone formation. Once a crystal is retained in the tubules of kidney, growth can occur in the presence of SS or aggregation of crystals. Two general mechanisms have been proposed for crystal retention: the free particle hypothesis , suggests that nucleation followed by rapid crystal growth occurs within the tubular lumen, resulting in crystal trapping at the site of the papillary collecting duct and subsequent stone formation; however, the steps necessary to produce a clinical stone event have not been elucidated.[35] Finlayson argued

against the hypothesis, stating that there was insufficient time formation of a lumen-obstructing crystal mass because of the rapid flow of ultra-filtrate through the tubule.[36] The second theory of crystal retention, the fixed particle hypothesis ,postulates the adherence of crystals to some underlying surface, such renal epithelial cells[37] based on data from cell-culture studies some investigators have proposed an integral role for crystal binding molecules, such as phosphotidyl serine [38] , sialic acid[39] ,osteopontine[40], and hyaluronan[41], in crystal retention and crystal-cell intraction.

Inhibitors and promoters of crystal growth

Urinary saturation with CaOx is common in non-stone formers, indicating the role of factors other than SS in stone formation. Urinary inhibitors of the CaOx system have been best studied. Most of the inhibitor activity resides in macromolecules such as glycoprotiens and glycosaminoglycans.[42] These inhibitors frequently contain post-transitional modifications such as phosphorylation and glycosylation.

The following urinary inhibitors have been identified:

1. Citrate- inhibitor of calcium oxalate and phosphate stone formation
2. Magnesium
3. Pyrophosphate
4. Urinary glycoprotein –

A) Nephrocalcin is an acidic amino acid which inhibit calcium oxalate crystal aggregation

B) Tamm horsfall protein ,prevents aggregation of calcium oxalate crystals

C) Osteopontin , inhibit nucleation, growth, aggregation of calcium

oxalate crystals and also reduce binding of crystals to renal epithelium

Role of protiens/matrix

Kidney stones contain a variable amount of noncrystalline organic material called matrix. Chemical analysis of the Matrix has demonstrated the presence of 65% hexosamine and 10% bound water and is believed to originate from the proximal tubule. [43]The amount of matrix present in kidney stones varies, with most solid urinary calculi having a low matrix content of 3% ; however, calculi that develop in the setting of urinary tract infection may have a matrix content[44] as much as 65%.[45]

THEORIES OF STONE FORMATION:

1. Crystal induced renal injury
2. Free particle formation in tubular lumen
3. Insufficient or abnormal urinary inhibitors
4. Nanobacteria
5. Stasis
6. Randall's plaque

1. Crystal-induced renal injury

One pathway by which crystal retention has been hypothesized to occur in the kidney is as a response to tissue injury. Hyperoxaluria triggers increased urinay excretion of enzymes associated with renal epithelial cell injury, such as N-acetyl-b-glucosaminidase, gamma-glutamyl transpeptidase, and alkaline phosphatase.[46] Oxalate is thought to induce injury through the production of reactive oxygen species (ROS) and subsequent lipid peroxidation. Crystal adherence and deposition are thought to induce renal interstitial inflammation with migration of macrophages.[47] These macrophages release tumor necrosis factor-a (TNF-a), which results in the increased expression of several matrix metalloprotienases (MMP).[48] MMP may play a role in the erosion or ulceration of sub-epithelial deposit at the renal papillary surface, creating a nidus for stone formation.

2. particle formation in tubular lumen

This theory suggests that crystal trapping at the site of the papillary collecting duct and stone formation due to nucleation followed by rapid crystal growth occurs within the tubular lumen. Fluid drag close to tubule walls, the drag effect of tubular walls on particles travelling close to the tubule walls, and the effect of gravity on particles travelling in upward-draining sections of tubule are the three new hydrodynamics factors that may lead to delay of crystal passage as suggested by Robertson[49]

3. Insufficient or abnormal urinary inhibitors

Pathogenesis of stone formation has also been proposed by the presence of more than normal concentration of urinary inhibitors. That stone formation may depend on the balance between two opposing forces: SS and urinary inhibitors was suggested by Robertson and colleagues.[50] Urinary citrate is considered an inhibitor of stone formation by binding calcium to reduce SS, and inhibiting nucleation and growth of calcium crystals. Citrate is routinely measured in the metabolic evaluation of stone formers, and

when low is considered to be a risk factor for stone formation. The inhibitor nephrocalcin (NC) has been shown to be abnormal in COM stone formers, in that the NC molecules lack gamma-carboxyglutamic acid and fail to inhibit COM crystallization normally. [51] The measurement of urinary inhibitors or the replacement of inhibitors other than citrate as therapy is not part of the routine management of kidney stone patients at present.

4. Nanobacteria

Nanobacteria (NB) are cytotoxic, sterile-filterable, gram-negative, atypical bacteria detected in bovine and human blood that have been implicated in a variety of disease states, such as atherosclerotic heart disease, peridontal disease, and renal cystic disease. [52]Recent investigations have speculated that NB may play a role in the formation of renal calculi by nucleating carbonate apatite on their surfaces.[53] In an in vitro study, Ciftcioglu and colleagues demonstrated the presence of NB in 70 of 72 kidney stones analyzed by scanning electron microscopy and immunofluoroscent staining. Presence of NB was independent of stone type; however apatite stones gave the highest immunopositivity. It has been hypothesized on these findings that NB colonization could damage renal tubular epithelial cells leading to biomineralization and subsequent stone formation.

5. Stasis

Stasis of urine as an etiologic factor has been proposed in the formation of kidney stones in patients with anatomic abnormalities of the kidney, such as ureteropelvic junction obstruction (UPJO), calyceal diverticulum (CD), horseshoe kidney, hydronephrosis, and medullary sponge.[54] Crystal retention caused by a delayed washout of crystals and risk of urinary infections; however, stasis due to distorted renal anatomy has been questioned as the sole etiologic factor. Several investigations have demonstrated that metabolic abnormalities contribute significantly to stone development in these patients.[55] The aspirated SS CaOx of urine directly from the diverticula was significantly

lower than that of the pathogenesis of calyceal diverticular calculi. A combination of metabolic abnormalities and stasis predispose these patients who have abnormalities of the kidney to stone formation.

6. Randall's plaque

Alexander Randall, over 6 decades ago, conducted a detailed examination of the papillae of more than 1000 non-selected cadaveric renal units.[56] He observed calcium salt deposits in the tip of renal papillum in19.6% of individuals studied. These deposits, which he termed plaque, were interstitial in location, composed of CaP, and not observed in the tubular lumen. Randall hypothesized that an overgrowth of CaOx to develop into a calculus the areas of plaque would be an ideal site. The data derived have demonstrated a prominent role for Randall's plaque in the pathogenesis of stone diseases.[57]

Factors relating to stone formation

- Local Factors
- Dietary Factors
- Metabolic Factors
- Climatic conditions

1) Local Factors

• Stasis: stagnation of urine due to obstruction or prolonged immobilization causes, which in turn leads to infection and concentration of salts.

• Infection: urea is split into ammonia and carbon-dioxide to form ammonium carbonate in presence of organisms like staphylococci, streptococci and proteus group

split, ammonium carbonate combines with ammonium hydrogen phosphate rendering it insoluble, which is then precipitated in alkaline urine. [58]

- pH of Urine: Solubility of certain crystalloids is affected by hydrogen iron concentration.

Oxalate, uric acid stones etc are formed in acidic urine, while alkaline pH causes their dissolution. Alkaline pH helps the deposition of ammonium magnesium phosphate, while acidity prevents their formation. [59]

2) Dietary Factors

Diets containing excess of calcium phosphate or oxalates have not been definitely proved to be the aetiolgical factors in stone formation. However, the following 3 dietary factors may directly or indirectly contribute to stone formation.

a) Vitamin Deficiency

Deficiency of Vitamin A- urinary tract epithelium, which on shedding provides nidus for crystalloid deposition due to metaplasia of urinary epithelium

Deficiency of Vitamin B6 –which get deposited in pyramids as calcium oxalate due to hyperoxaluria.

b) Protein Deficiency

Calcium gluconate binds with Glutamic Acid and Amino Acid salts and prevents stone formation. Deficiency of these amino acids may cause salt deposition.

3) Climate conditions

Hot climate predisposes to stone formation due to dehydration and excessive perspiration.

4) Miscellaneous

Calcium salts in the gastrointestinal tract combine with sodium phosphate in diet forming non- absorbable compounds, which are excreted in stools, thereby preventing hypocalcaemia.

Solubility of calcium phosphate is increased by glucoronide excretion in urine which in turn is augmented by salicylic acid.

RENAL CALCULI ARE DIVIDED INTO -

1. Calcium containing stones

- Calcium oxalate – 60%
- hydroxyapatite – 20%
- Brushite – 2%

2. Non calcium containing stones

- Uric Acid – 5- 10%
- Struvite – 7%
- Cystine – 2%

1. **CALCIUM STONES**

70 - 75% of all stones are calcium stones. The normal kidney filters approximately 270 mmol of calcium daily and reabsorbs all but 4mmol. Hypercalciuria is defined as excretion of calcium more than 4mg/kg/day or greater than 7mmol/day

Calcium Stones – Pathophysiology

- Hypercalciuria – 40 - 50%

a. Hyperparathyroidism

b. Hyperthyroidism

c. Renal tubular acidosis

d. Milk alkali Syndrome

e. Multiple myeloma

f. Metastatic malignant neoplasms

g. Drugs. Eg: prolonged steroid therapy.

- Hypocitraturia - 20 - 30%
- Hyperoxaluria – 5%
- Unclassified – 25%

2. **URIC ACID STONES**

The main determinants of uric acid stone formation are urinary pH < 5.5, hyperuricosuria and decreased urine volume. Hyperuricosuria may be due to genetic overproduction, myeloproliferative disorders and high protein diet.

3. **STRUVITE STONES**

Commonly seen in women than men. It is the most common cause of staghorn calculi. Grows rapidly, may lead to sever pyelonephritis or urosepsis and renal failure. Caused in part, by infections of organisms with urease (Proteus, Klebsiella, Pseudomonas, and Serratia). Hydrolysis of urea yields ammonia & hydroxyl ions, consumes H+ and thus increases urine pH. Increased urine pH increases saturation of struvite.

4. **CYSTINE STONES**

Hereditary disorder caused by a tubular defect in dibasic amino acid transport, autosomal recessive. Excrete excessive amounts of cystine, ornithine, lysine and arginine. Cysteine stones are hexagonal, radiopaque, greenish-yellow and often present as staghorn calculi or multiple bilateral stones.

5. **XANTHINE STONES -**

Xanthine rare stone type. Radiolucent and usually confused with uric acid stone. Inherited disorder in catabolic enzyme xanthine dehydrogenase. Xanthine dehydrogenase catalyze conversion of xanthine to uric acid. Deficiency leads to xanthine stones.

6. **MEDICATION RELATED STONES**

A) Indinavir stones it is a protease inhibitor. Incidence is 4 to 13%. Due to high urinary excretion and low solubility.

B) Triamterene stones is a potassium diuretic. It is rare seen only in 0.4%. Incorporated into existing stone or stone nidus

Clinical Manifestations:

1. Acute flank pain
2. Renal colic if passed into ureter or if obstruction
3. Urinary urgency or frequency
4. Hematuria
5. Nausea and vomiting
6. Fever and chills

Patient evaluation

1. Family history
2. Lifestyle/occupation
3. Diet: coffee, tea, proteins
4. Physical Examination

MANAGEMENT:

The goal of management of ureteric calculi is to achieve complete stone clearance with minimal morbidity to the patient. Majority of the ureteral calculi are lower one third therefore most of them do not require intervention. Most ureteral calculi are 4mm or smaller and pass spontaneously although not without discomfort and expense to the patient. Calculi measuring 4 to 8 mm can be treated conservatively with NSAIDs and Alphablockers. Renal obstruction due to ureteral calculi of any size are often associated with and care must be taken to prevent irreversible damage to the kidney whether choosing expectant or active treatment.

The management of patient with urolithiasis has shown a changing trend over time from open surgery to relative noninvasive management

1) ANALGESIA

Pain relief is usually the therapeutic step that needs to be taken most urgently in patients with an acute stone episode.

Diclofenac, Ibuprofen and Indometacin are the preferred first line drugs for pain relief. Clinical trials have shown that NSAIDs (e.g Diclofenac) provide effective relief in patients who have acute stone colic. [60-65] Moreover, the resistant index was reduced in patients with renal colic when NSAID treatment was given. [31] Alternative drugs are used if the pain persists. Hydromorphane and other opiates are associated with an increased risk of vomiting, and should not be given without simultaneous administration of atropine.

2) INVESTIGATIONS:

1. Laboratory data

a) Urinalysis

b) Urine culture

c) Blood tests

- Electrolytes, creatinine,uric acid

2. Radiology

a) Ultrasound

b) KUB

c) IVP

d) CT

ABDOMINAL ULTRASONOGRAPHY

Ultrasound is the imaging study most widely used in urology. Stones produce a bright ultrasonic reflection and cast an acoustic shadow. Stones more than 3mm can be detected by USG

Although ultrasonography is readily available, quickly performed and sensitive to renal calculi (95%), it is virtually blind to ureteral stones (sensitivity; 19%) which are far more symptomatic than renal calculi.

Hydronephrosis, which may be a manifestation of ureteral obstruction is highly sensitive to ultra sound examination. Helps in differentiating renal parenchymal pathology which may mimic renal colic.[59] The added advantage of assessing the abdominal cavity for

other pathology in the absence of an obvious renal/ureteral pathology as a cause of the symptoms.

Treatment

1. **Medical** – for stones < 10mm in size

   a) Flush therapy
   b) Steroid
   c) Calcium channel blocker
   d) Tamsulosin

2. **Surgical**

   a) Shock wave lithotripsy
   b) Intracorporeal lithotripsy
   d) Percutaneous nephrolithotomy
   e) Open ureterolithotomy

1**. WATCHFULL EXPECTANCY**

Adequate fluid intake which act as natural diuretic leading to alkalisation of urine and prevention of stone formation. Daily urine output should be more than 2 liters. Carbonated beverages increases citrate level which in turn increases the supersaturaion level. Citrus juices increase citrate and urinary pH.

2. **STEROID**

Commonly used steroid for distal ureteric calculi is Deflazocort. Deflazocort reduces the inflammation at the distal ureter where the stone is lodged. Reduces edema and helps in easy expulsion of the calculi

3. **CALCIUM CHANNEL BLOCKER**

Nifedipine is the commonly used calcium channel blocker. It causes relaxation of the smooth muscle of the distal ureter which helps in the easy expulsion of the calculi.[66]
It acts by suppressing the fast component of ureteral contraction leaving the peristaltic rhythm unchanged.

4. TAMSULOSIN:

Tamsulosin is an alpha-adrenoceptor antagonist that was specially designed for the treatment of benign prostatic hyperplasia, since it is highly selective for the urinary tract alpha-1a adrenoceptors.

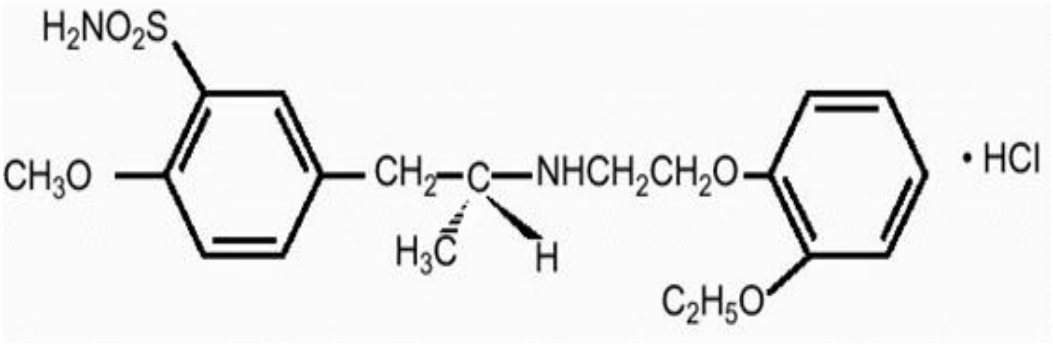


Fig 7 : structure of tamsulosin

Alpha 1 a receptors are present in the prostate and bladder whereas alpha 1 b is present in blood vessels. Tamsulosin is a smooth muscle relaxant specific to urinary tract.
Tamsulosin has 100% bioavailability and half-life of 9-13 hrs. It is extensively metabolised in liver. 76% of it is excreted in urine.

Uses:

1. BPH
2. Distal ureteric calculi
3. Acute urinary retention

Adverse effects:

1. Retrograde ejaculation
2. Dizziness
3. Fainting
4. Vertigo
5. Nasal congestion
6. Floppy iris syndrome

The primary functional anatomical unit of the ureter is the ureteral smooth muscle. Tamsulosin, that is commonly used in the treatment of bladder outflow obstruction was chosen for this study as it acts on alpha 1 A and alpha 1 D receptor subtypes in the ureter due to its alpha I receptor blocker action. It also acts on the smooth muscles of the ureter causing its relaxation and prevents spasm, and acts on the C fibers blocking pain conduction. The ureter contains excitatory alpha adrenergic and inhibitory beta adrenergic receptors. The alpha receptor binding sites are greater in ureter than any other receptor.

Tamsulosin exhibits high plasma-protein binding, largely to alpha (1)-acid glycoprotein. It is metabolized mainly by cytochrome P450 (CYP) 3A4 and CYP2D6 to compounds with low abundance, and 7-15% of an oral dose is excreted through renal as the parent compound. Age does not affect the pharmacokinetic of tamsulosin and increased concentration of alpha (1)-acid glycoprotein leads to pharmacokinetic alterations in through renal impaired patients.

Neither renal nor mild to moderate hepatic impairment necessitates dose adjustment as pharmacokinetic alterations with hepatic impairment are also only moderate. Tamsulosin exposure doubles with concomitant exposure to potent CYP3A4 inhibitors [67]

Alpha 1 adrenergic receptors have been classified into the 3 subtypes of alpha 1 A, B and D, and the distribution of these receptors in the distal ureter is alpha 1 D>A>B.[68] Alpha 1 adrenergic receptors are found in distal ureter at higher density than the middle or upper ureter.

Tamsulosin acts on the smooth muscles of the distal ureter and the bladder. Receptor blockade inhibits ureteral peristaltic amplitude and frequency and decreases intra ureteral pressure thus increasing the rate of urine transport.[69] It causes relaxation of the smooth muscle thus easy expulsion of the distal ureteric calculus.

Most studies demonstrated a favorable benefit to Tamsulosin and Alfuzosin in facilitating stone passage, increasing the rate of stone expulsion, and decreasing pain and analgesic use, with only a few studies failing to find statistically significant differences between patients using and not using these drugs.

SURGICAL TECHNIQUES

1. Intracorporeal lithotripsy

Ureteroscopy is defined as urinary tract endoscopy. It is performed most commonly with an endoscope passed through the urethra, bladder and then directly into the upper urinary tract. Ureteroscope allow easier access to stones in all parts of the kidney and ureter. Small ureteral stones can be extracted intact with baskets or grasping devices. Larger ureteral stones require lithotripsy.

Ureterorenoscopy has changed the management of the ureteral calculi from the past two decades.

The advantage of ureteroscopy is its low morbidity rate and the shorter duration of the procedure.[70,71]

The use of thin ureteroscopes has resulted in reduced dilatation (0-40%), operating time and post-operative ureteral stenting.

Ureteral access sheaths are used widely to facilitate retrograde manipulation in the proximal ureter and the kidney.

URS is, however a more invasive techniques than ESWL, and the treatment of choice for ureteral stones is therefore controversial.

The major dilemma facing the urologists today is "to blast or not to blast "i.e. To choose between the two most frequently used modalities in ureteral stone treatment- ESWL and ureteroscopy. PCNL is a less commonly used treatment option usually reserved for proximal, large ureteral stones in selected cases. Open uretero lithotomy is rarely indicated but should remain an option as a salvage procedure.[72]

The techniques available for intracorporeal lithotripsy are-

a) Electrohydraulic

b) Laser

c) Ultrasonic

d) Ballistic

Most commonly used lithotripsy are laser and ballistic.

Laser lithotripter -

Allows considerable energy to be transmitted in a highly concentrated manner. The zone of thermal injury associated with laser ablation range from 0.5 to 1.0mm. Holium laser is

the safest, most effective and most versatile. Photothermal mechanism causing stone vaporisation.

Ballistic lithotripter -

Relies on energy generated by movement of a projectile. Once the projectile is in contact with another object the ballistic energy is transferred to other object. The metal projectile in the hand piece is propelled by measured bursts of compresses air against the head of metal probe, frequency of which is 12 cycles/sec. Advantage of ballistic lithotripter is its effective means for stone fragmentation in the entire urinary tract. The major disadvantage is stone retropulsion.

Fig 8 : Ureteroscope

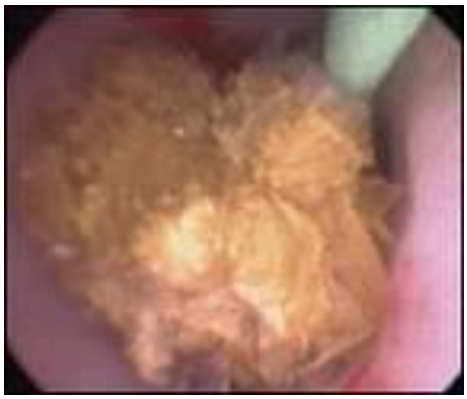


Fig 9 : Stone Seen Through Ureteroscope

2. Extracorporeal shock wave lithotripsy

Source external to the patient body generates a shockwave .Weak nonintrusive waves are generated externally and transmitted through the body. 3 types of shock wave generator are - Electrohydraulic, electromagnetic and piezoelectric. In Piezoelectric shock wave, plane shockwaves with directly converging shockfronts are produced. It is made up of mosaic of small polarized polycrystalline ceramic elements which can be induced to rapidly expand on applying high voltage. Advantage is, its anesthetic free treatment. Disadvantage is insufficient power is delivered for the breaking of stone.

Stone localization allows for the precise placement of a stone within the focal area of a shock wave generator. This requires imaging by way of radiography or ultrasonography. Patient positioning is accomplished by a remote controlled mobile at gantry or tabletop.

Mechanism of stone breakage

A) Spall Fracture - If the tensile strength of shockwave is more than the stone it produces micro cracks eventually coalase and result in stone fragmentation known as spallation.

B) Circumferential Compression – it causes stone breakage due to change in sound speed between stone and surrounding fluid traverse the stone

C) Shear Stress

D) Amplification of Stress inside the Stone Due To Geometry of the Stone

E) Cavitation – the pressure from the lithotripter causes cavitation

F) Dynamic Fracture Process

Side effects of lithotripter are cellular disruption and necrosis, Mild tubular necrosis, Intraparenchymal hemorrhage, Tubular dilatation and cast formation and damage and rupture of small arteries.

METHODOLOGY

The study was conducted on patients with distal ureteric calculi admitted at R.L. Jalappa Hospital & Research Centre attached to SDUMC, Kolar between March 2013 and September 2014.

Sampling

This is a prospective study involving patients older than 18 years of age, presenting with unilateral, solitary distal ureteric calculus <10mm at R.L.Jalappa Hospital &Research Centre attached to SDUMC, Kolar.

60 uncomplicated cases were taken up for the study

Informed consent was taken from the patients included in the study.

60 symptomatic cases of distal ureteric stones will be divided randomly by recruiting alternate cases into in a control (group 1) and a study group (group 2).

Group 1 (control) – 30 patients included in this group will be advised high fluid intake along with required dosage of analgesic (NSAID's) or smooth muscle relaxant (tab dicyclomine) as on demanded during the study period of 7 to 10 days.

Group 2(study) – 30 patients in this group will be given tab. Tamsulosin 0.4mg HS, for a period of 7 to 10 days. High fluid intake and analgesic (NSAID's) or smooth muscle relaxant (tab dicyclomine) was given on demand during the study group.

Data regarding age, gender, stone expulsion rate and time and the analgesic required will be collected and analyzed.

Inclusion criteria

Patients older than 18 years of age, presenting with symptomatic, unilateral, solitary distal ureteric calculus

Exclusion criteria

Urinary tract infection, fever, acute renal failure, history of urological surgery or endoscopic treatment, uncorrected distal obstruction, marked hydronephrosis and congenital anomalies were excluded from the study.

Follow up

Patients followed up to 7 to 10 days.

Statistical analysis:

Data was entered in to Microsoft excel data sheet and was analyzed using EPI info 7 version software. Categorical data was presented in the form of frequencies and proportions. Bar charts and pie diagrams was used to represent graphically. Chi-square test was the test of significance. Continuous data was represented in the form of Mean and Standard deviation. Independent t test was the test of significance for continuous data. p value <0.05 was considered as statistically significant.

RESULTS

60 cases of distal ureteric calculi were included in the study. 30 subjects were enrolled into Group 1 (Non Tamsulosin group) and 30 subjects were enrolled into Group 2 (Tamsulosin group) after randomization. These cases were followed up expulsion of Calculi.

Table 1: Sex distribution of subjects

		Sex		**Total**	**X^2, df, p value**
		Female	**Male**		
Groups	**Non Tamsulosin**	6	24	30	0.373,
	Tamsulosin	8	22	30	1,
Total		14	46	60	0.542

In the study there were 46 males [24 in Group 1 and 22 in Group 2] and 14 Females [6 in Group 1 and 8 in Group 2]. There was no significant difference in sex between the two groups. [This can be attributed to Randomization]

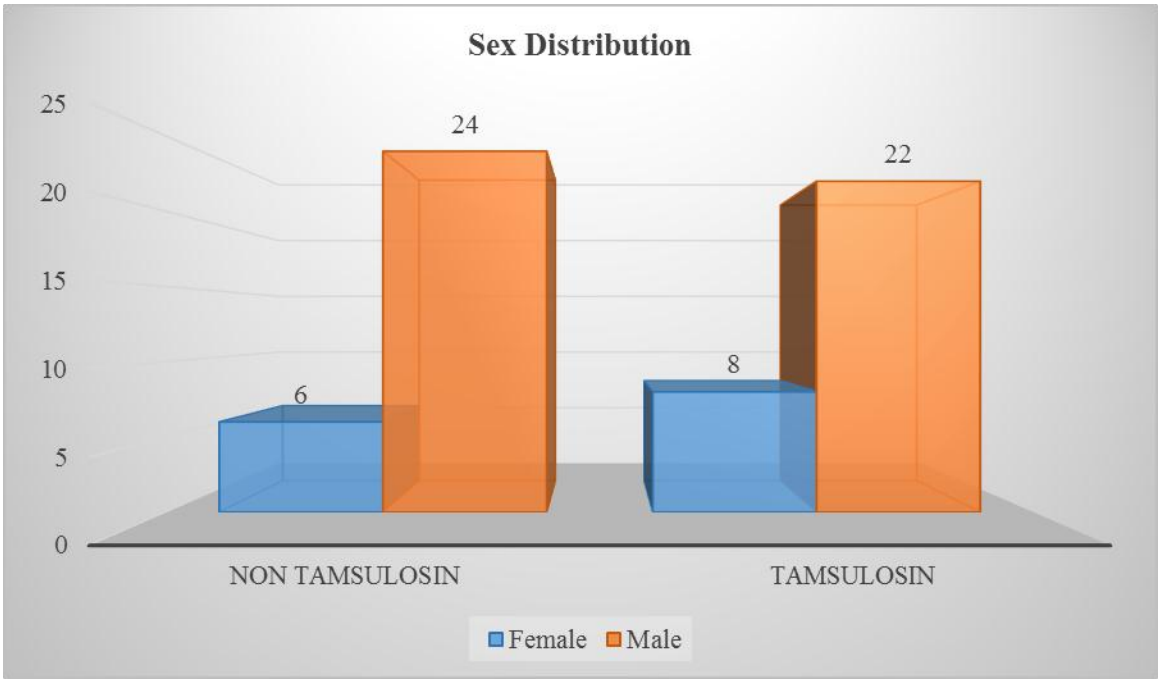


Figure 1: Bar diagram showing sex distribution of the subjects

Table 2: Age distribution of subjects

	Groups	No	Mean	Std. Deviation	t test	p value
Age	**Non Tamsulosin**	30	43.20	13.80	0.714	0.478
	Tamsulosin	30	40.27	17.76		

The mean age of Group 1 was 43.20 ± 13.8 and mean age of group 2 was 40.27 ± 17.7. There was no significant difference in the mean age between two groups. [This can be attributed to randomization]

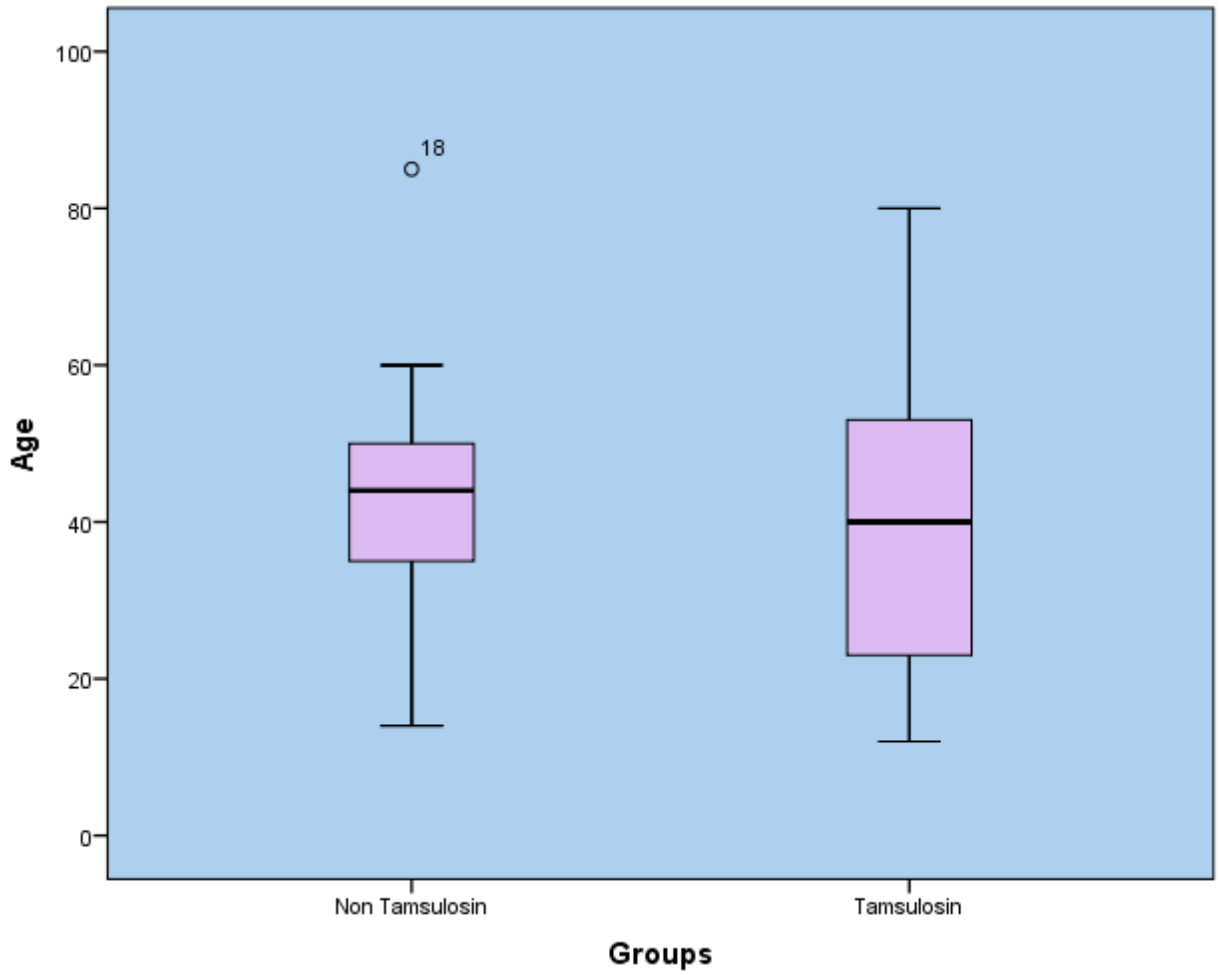


Figure 2: Box plot showing age distribution of subjects

Table 3: Size of Calculi among the subjects

	Groups	No	Mean	SD	t test	p value
Size of Calculi (mm)	**Non Tamsulosin**	30	6.87	0.77	0.714	0.478
	Tamsulosin	30	6.93	1.01		

The mean size of calculi of Group 1 was 6.87 ± 0.77 and mean age of group 2 was 6.93 ± 1.01. There was no significant difference in the mean age between two groups. [This can be attributed to randomization].

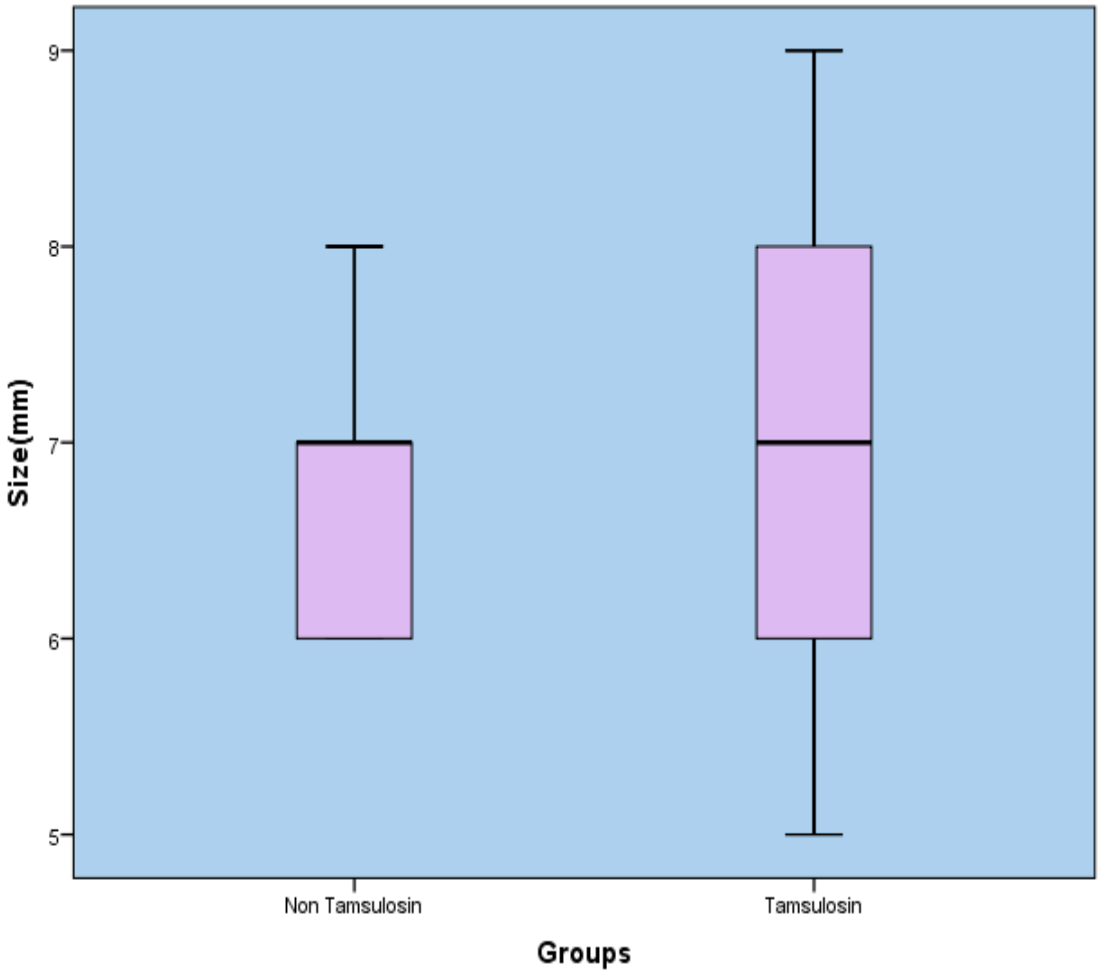


Figure 3: Box plot showing Size of calculi among the subjects

Table 4: Side of Calculi among the subjects

		Side		Total	X^2, df, p value
		Left	Right		
Groups	Non Tamsulosin	18	12	30	3.27, 1, 0.071
	Tamsulosin	11	19	30	
Total		29	31	60	

In the study among Group 1 subjects 18 had calculi on left side and 12 had calculi on right side and among Tamsulosin group 11 had calculi on left side and 19 had calculi on right. There was no significant association between two groups and side of calculi.

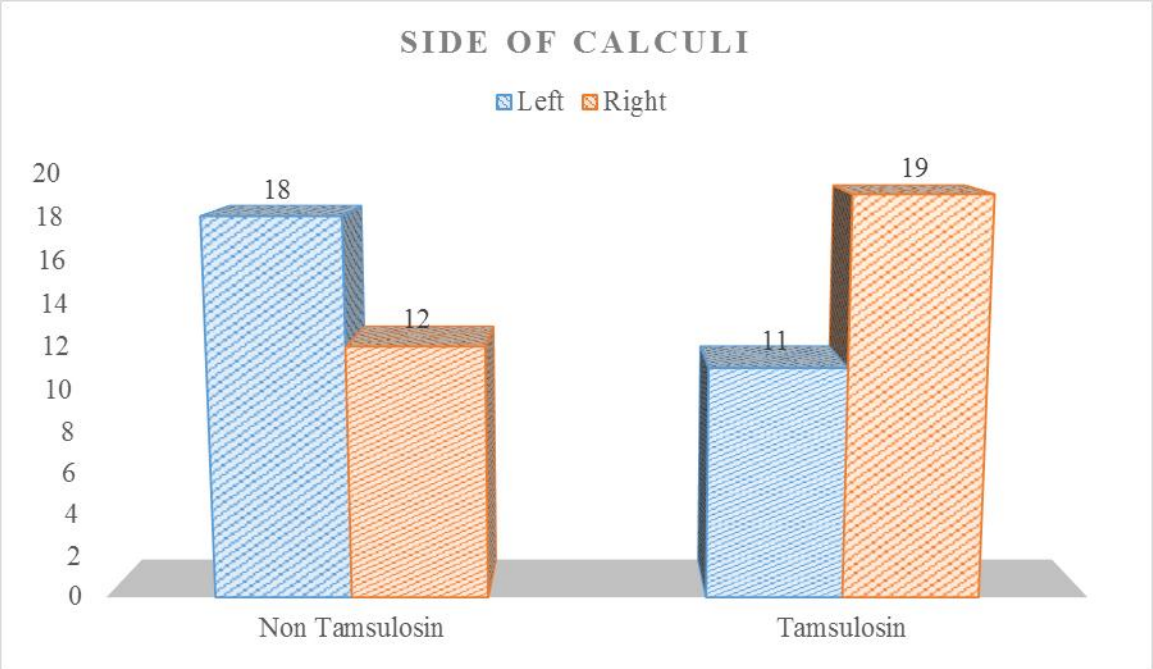


Figure 4: Bar diagram showing distribution of subjects according to side of calculi

Table 5: Expulsion of Calculi among the Groups

		Expulsion		Total	X^2, df, p value
		No	Yes		
Groups	Non Tamsulosin	24	6	30	26.786, 1, 0.0001**
	Tamsulosin	4	26	30	
Total		28	32	60	

In the study during the follow up 32 subjects expelled the calculi of which 26 was in Tamsulosin group and 6 was in Non Tamsulosin group.

This observation was statistically significant at 0.0001. Hence it can be said that with Tamsulosin treatment expulsion of distal ureteric calculi was higher than with the treatment.

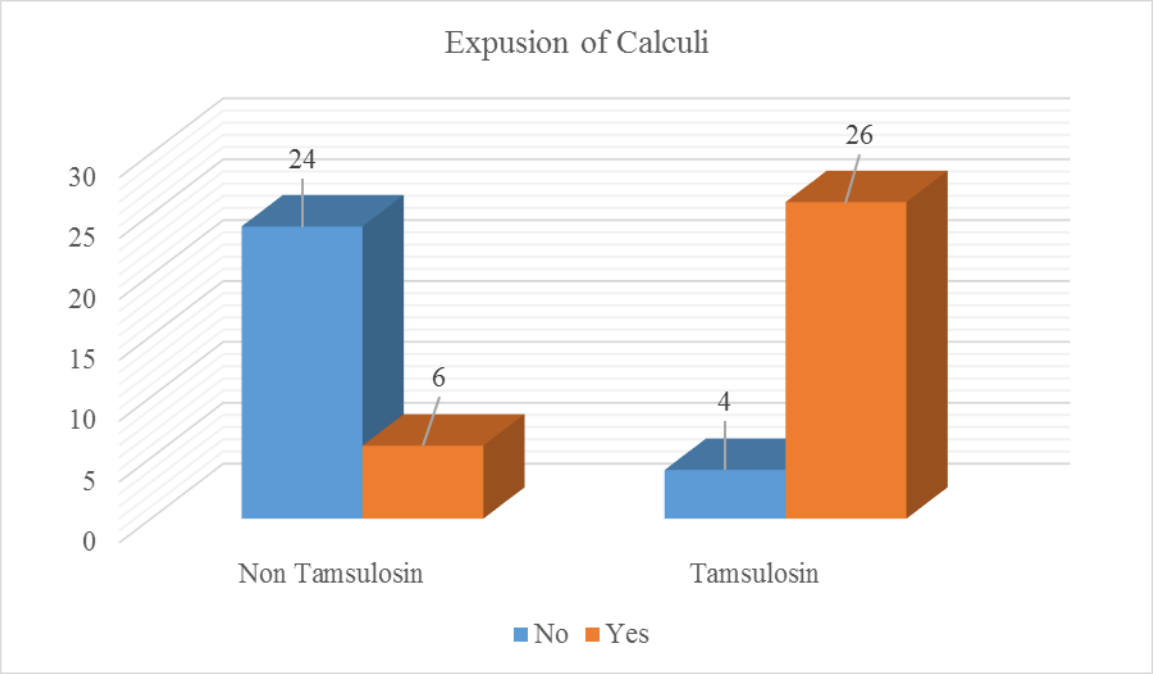


Figure 5: Bar diagram showing distribution of subjects according to expulsion of calculi

Table 6: Mean difference in age and size of calculi among Non Tamsulosin group for Expulsion of Calculi.

	Expulsion	N	Mean	Std. Deviation	t value	p value
Age	**No**	24	47.29	11.57	4.001	0.0001**
	Yes	6	26.83	9.326		
Size (mm)	**No**	24	6.83	0.816	-0.464	0.646
	Yes	6	7.00	0.632		

In the study among Non Tamsulosin group mean age was 47.29 ± 11.57 in Non expelled subjects and 26.83 ± 9.3 in Expelled subjects. This difference was statistically significant. i.e. Younger the age higher the chances of expelling calculi.

Similarly mean size of calculi was 6.83 ± 0.81 in non-expelled subjects and 7.00 ± 0.63 in Expelled subjects. There was no statistical significance.

Table 7: Mean difference in age and size of calculi among Tamsulosin group for Expulsion of Calculi.

	Expulsion	N	Mean	Std. Deviation	t value	p value
Age	**No**	4	70.25	11.75	4.821	0.0001**
	Yes	26	35.65	13.54		
Size(mm)	**No**	4	7.00	0.81	0.139	0.077
	Yes	26	6.92	1.05		

I the study among Tamsulosin group mean age was 70.25 ± 11.75 in Non-expelled subjects and 35.65 ± 13.54 in Expelled subjects. This difference was statistically significant. i.e. Younger the age higher the chances of expelling calculi.
Similarly mean size of calculi was 7.00 ± 0.81 in non-expelled subjects and 6.92 ± 1.05 in Expelled subjects. There was no statistical significance.

Table 8: Mean difference in Analgesic requirement in two groups

	Group	N	Mean	Std. Deviation	t value	p value
Analgesic (mg)	**Non Tamsulosin**	30	825.0	129.82	11.775	0.0001**
	Tamsulosin	30	413.3	140.77		

In the study mean analgesic requirement was higher among non tamsulosin group (825 ± 129.82) than in tamsulosin group (413.3 ± 140.77)

Table 9: Association between times for expulsion of calculi among the groups

		Time for Expulsion of Calculi (in days)							Total	X^2, df, p value
		3	**4**	**5**	**6**	**7**	**8**	**Not Expelled**		
Group	**1**	0	0	1	3	1	1	24	30	32.11, 6, 0.0001**
	2	4	9	7	3	2	1	4	30	
Total		4	9	8	6	3	2	28	60	

In the study it was observed that expulsion of calculi was more on 4^{th} and 5^{th} day after tamsulosin treatment. Wereas it took 6 to 8 days for expulsion of calculi among non tamsulosin group. This association was highly significant.

Table 10: Mean times for expulsion of calculi among the groups

		Time for expulsion			t value	p value
		Mean	No of Subjects	Std. Deviation		
Group	Non Tamsulosin	6.33	6	1.033	2.784	0.009**
	Tamsulosin	4.73	26	1.313		

Mean time for expulsion of calculi in Non tamsulosin group was 6.33 ± 1.033 and in Tamsulosin group was 4.73 ± 1.313. This difference in mean time was statistically significant. I.e. in tamsulosin group the mean time was less than non tamsulosin group.

DISCUSSION

Renal stones were seen in Egyptian mummies 4800 BC . It is a common condition affecting up to 12% of the population. Prevalence of renal stone varies from 2% to 3%. The life time risk of renal stone varies with sex. In Male 20% and female 5-10%. Recurrence rate is 50% at 10 years. Peak incidence is seen between fourth to sixth decades.

Adequate treatment is frequently asked to be chosen by clinicians as Ureteral stones occupy an important place in daily urological practice.

Presence of renal stones in an individual is related to alteration in the metabolic activity ie., excessive oxalate formation or formation of randall plaque.

In our study usage of hard water and extreme climate contribute to formation of renal stones. Majority of renal stones are small in size and found to be present in lower one third. Tamsulosin is known to be a potent relaxant of smooth muscles of the ureter thus aiding in expulsion of the stone.

MET of stones by flush therapy at present is not advisable as it causes hydroureteronephrosis or compensated damage of the kidney.

Watchful waiting approach can be used in a large number of cases, as demonstrated by several studies that revealed spontaneous passage rates of up to 98% for small distal ureteral stones. Moreover, even the simple watchful waiting approach can result in complications, such as infection of the urinary tract, hydronephrosis and renal function effects. Recently, use of the watchful waiting approach has been extended by using pharmacological therapy, which can reduce symptoms and facilitate stone expulsion.

Stone size and site, the internal anatomical structure of the ureter and a history of spontaneous expulsion, which are unmodifiable factors are essential for the likelihood of ureteral stone spontaneous passage. Spasm, edema and ureteral infection, which are

modifiable factors are the possible causes of stone retention. The goals of medical conservative therapy are to prevent modifiable factors and expulsion rate and time to expulsion and control painful symptoms until stone expulsion. In this study, we used Tamsulosin (selective alpha-1a blocker) to evaluate the efficacy of medical expulsive therapy in distal ureteral calculi less than or equal to 10 mm.

Tamsulosin given orally is convenient and provides good expulsion of stones upto 1cm without much complications.

In the study there were 46 males [24 in Group 1 and 22 in Group 2] and 14 Females [6 in Group 1 and 8 in Group 2]. There was no significant difference in sex between the two groups. [This can be attributed to Randomization]

The mean age of Group 1 was 43.20 ± 13.8 and mean age of group 2 was 40.27 ± 17.7. There was no significant difference in the mean age between two groups.

In the study during the follow up 32 subjects expelled the calculi of which 26 was in Tamsulosin group and 6 was in Non Tamsulosin group.

This observation was statistically significant at 0.0001. Hence it can be said that with Tamsulosin treatment expulsion of distal ureteric calculi was higher than with the treatment.

The expulsion rate in the tamsulosin group in the present study was 86% which was in concurrence with other studies[73-75].

In the study mean analgesic requirement was higher among non tamsulosin group (825 ± 129.82) than in tamsulosin group (413.3 ± 140.77). There were no significant side effects in either group which confirmed the clinical profile of tamsulosin and diclofenac as considerably safe and convenient

In the study it was observed that expulsion of calculi was more on 4^{th} and 5^{th} day after tamsulosin treatment. Whereas it took 6 to 8 days for expulsion of calculi among non tamsulosin group. This association was highly significant.

Therefore, it is possible to suggest that the effect of tamsulosin on the obstructed ureter is to induce 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.

For these reasons there would be a stronger urge to expel the stone. 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 analgesic stimulus, as in our study.

This study was conducted in SDUAHER, KOLAR. A total of 60 patients were studied with particular criteria fixed during study period were taken.

1. **Age**:

In this series, majority of the patients were in the age group of 30 - 60 years. The mean age of Group 1 was 43.20 ± 13.8 and mean age of group 2 was 40.27 ± 17.7.

Ureteric calculi are usually seen between 20 – 40 years of age.

72 , 75

2. **Sex**:

   In the study there were 46 males [24 in Group 1 and 22 in Group 2] and 14 Females [6 in Group 1 and 8 in Group 2].

Most of the studies have reported a male to female ratio between 3:1 and 2:1.

In a study in 2008 reported that in group A the number of males were 17 and females were 29, and in group B males were 23 and females were 22. [76]

Males and those with a family history of stone disease are three times more likely to be afflicted than others for urinary stone disease. Men appear to excrete more oxalate in their urine and women more citrate (thus protecting against stone formation). [77]

3. **Location of ureteric calculi**:

In our study 100 % of calculi were present in lower 1/3rd of the ureter as our study has excluded calculi at other sites.

Study of a series of 292 patients reported an incidence of 27% of calculi in the upper 1/3rd of the ureter, 12% in the middle 1/3rd of the ureter and 61% in the lower 1/3rd of the ureter. [75 , 78]

A study in 1991, reported incidence of 17% in the upper 1/3rd of the ureter, 11% in the middle 1/3rd of the ureter and 72% in the lower 1/3rd of the ureter. [75,78]

In 2002 a study reported incidence of 31% in the upper 1/3rd of the ureter, 14.9% in the middle 1/3rd of the ureter and 53.7% in the lower ureter. [75 ,78, 79]

4. **Size of calculi** :

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

In a study in 2008 by Francesco Porpiglia et al showed that the mean size of the calculus was 5.93mm in group A and 6.03mm in group B.[76]

Most of the series have reported size varying from a few millimeters to 2cms. A study in 1991 and 1997 showed that the rate of spontaneous passage in highly dependent on stone location and size of the stone. [78]

5. **Laterality** :

In the study among Group 1 subjects 18 had calculi on left side and 12 had calculi on right side and among Tamsulosin group 11 had calculi on left side and 19 had calculi on right. Most of the series found calculi with equal frequency on either side. [78]

6. **Duration of symptoms** :

In this series, 10% of patients came in the first week after appearance of symptoms, 30 % came in the second week and 60% patients came in the third and fourth week after appearance of symptoms.

It is reported that duration of symptoms vary from 3 hours to 5 years. 80% of the patients came within 1 month of onset of symptoms, 4% gave a history of one year or longer. [78]

7. **Presenting symptoms** :

In this series, 60 patients had complaints of loin pain, 6 patients had complaints of vomiting, 4 patients had hematuria and 10 patients had complaints of burning micturition. Pain, nausea/ vomiting, hematuria, burning micturition/ urgency/ frequency of micturition and oliguria were the most common symptoms.

A study in 1991 reported 87% had loin pain, 17% patients had vomiting and 3% presented with fever. [78,79]

The mean number of acute episodes of renal colic was 1.39 (1.12) in group A and 1.12 (1.04) in group B. ($P > 0.05$). [76]

Increases ureteral peristaltic frequency, smooth muscle tones and contractile force, resulting in ureteral spasm and decreased ureteral flow are due to the stimulation of alpha 1 adrenergic receptors. [80]

In this present series of 60 patients diagnosed to be having distal ureteric calculi, 30 patients were started on alpha 1 blocker drug(Tamsulosin) for 7 to 10 days. 30 patients were not given alpha 1 blocker, they were given only NSAIDS and plenty of fluids.

Out of the 30 patients who were on alpha 1 blocker (Tamsulosin) 26 patients had passed the calculi and 4 patients had no results with a success rate of 86.7%.

A study in 1980 and 1997 considered many determinants in decision making of expectant management or intervention and if intervention whether operative or endoscopic manipulation. [81]

a) Socioeconomic status and occupation: a study in 1983 advised early intervention in patients who cannot be observed expectantly due to vital loss of working hours.

In our study, most of the patients belonged to low socioeconomic status and they requested for conservative and early treatment and most of them were treated on outpatient basis.

b) Infection: Infection paralyses the ureter and kidney functions rapidly deteriorates. Infection indicated by pyrexia, leucocytosis calls for prompt surgical intervention.

c) Size and location of calculi: For the patients with stones of 5mm or less, conservative management is recommended. Intervention should be considered where the chance of spontaneous passage for larger stone diminishes considerably

A study in 1991 showed that the rate of spontaneous passage is highly dependent on stone location. Passage rates from the proximal, middle and distal ureter were 22%, 46% and 71% respectively. [78,82]

In our study, we have considered size and location of the calculi. Size <10 mm and site-lower one third of the ureter.

Degree of impaction and state of contralateral kidney: It has been observed by Hubner et al 1993, Singal and Dendtedt (1997) that if significant progress of stone passage has not occurred after approximately 1 month, intervention is required. [83,84]

The following conditions most likely call for surgical intervention. [82]

- In absence of infection or significant obstruction with the calculus more than 5 millimetres in size, which does not progress.
- Impacted ureteric calculi with associated infection and obstruction. Our study matches the same result.
- Calculi causing frequent and recurrent colic.
- Significant obstructive calculi, when the function of the contralateral
- Kidney is compromised.

Calculus less than 5 millimetre in size but fails to progress.

Most surgeons agree that an impacted obstructing, painful and possibility infected stone about 6-8mm in size lying in the lower third of the ureter with normal ureter below, calls for an attempt at endoscopic manipulation before restoring to open ureterolithotomy.

ureteroscopic management success rate of lower ureteric calculus is 95% to 100% and for calculi in middle 1/3rd and lower 1/3rd of the ureter, the success rate is 44% to 95%. In most of the reported series there remain, from 1-10 % of patients who require open removal of their calculi.[85,86]

Open ureterolithotomy remain a need for despite the range of minimally invasive alternatives now available for the treatment of ureteric calculi. [86]

Open stone surgery for ureteral stones is now indicated only as a salvage procedure. The advantage of endoscopic surgery have been well demonstrated and include less trauma, reduced post-operative discomfort, shorter hospital stay, less morbidity and shorter convalescence.

Ureteric calculi especially for calculus lodged in lower ureter has a distinct advantage with higher success rate rapid convalescence with ureteroscopic extraction with minimal post-operative morbidity and short hospital stay. Hence it is ideal for patients whose general condition does not allow surgical procedures.

For distal ureteric stone treatment, a study done on 40 patients treated by ureteroscopy to be completely stone free, compared to 90% stone free rate following ESWL. [87]

Conditions contraindicating ureteroscopic manipulations:

1) Calculus larger than 2 cms in size
2) When unsuccessful attempts have been made to remove the stone.
3) Ureteral anomalies such as uretrocele, duplication or megaureter.
4) Poorly tolerated in children and very old patients

In cases of contra-indications of URS, patients go for ESWL (extracorporeal shock wave lithotripsy) and open surgery was also considered.

Duration of hospital stay

In the present study patients were treated on inpatient and outpatient basis too. The mean duration of stay in the hospital was 7 to 10 days.

The mean duration of hospital stay was 5.16 for the patients who required endoscopic manipulations. Reid M. Morse (1991) reported a mean hospital stay of 4.7 days of endoscopic manipulation. [78]

Complications of ureteral stone management: Owing to smaller, less traumatic ureteroscopes, improved intracorporeal lithotriptors and better understanding of the principles of ureteroscopy. The number of complication arising from the management of ureteral stones has decreased. The complications include perforation, stricture, submucosal or lost stones and avulsions. The overall incidence of complications for distal stone was 7% and for proximal stone was 6.6%. A study in 1991 reported complication rate of 12.5%. [78,88,89]

Follow – up

In this series, follow up was done for 7 to 10 days. The patients were asked to pass urine in a filter and identify the passage of calculi. In our study, expulsion of calculi was more on 4th and 5th day after tamsulosin treatment. Wereas it took 6 to 8 days for expulsion of calculi among non tamsulosin group. Ultrasonography was done at the end of the study for all the patients.

CONCLUSION

Tamsulosin as a treatment for distal ureteric calculi plays an important role for conservative management as seen by the results of the study. The comparison with minimally invasive procedures in terms of cost and efficacy was useful, highlighting a predominant role of first line pharmacological treatment, which can be easily be provided in an outpatient setting and not only at large, technologically advanced, special centers.

Tamsulosin proved to be safe and effective for the rapid expulsion of the distal ureteric calculi by the reducing of the expulsion time. Majority of the ureteric calculi (70%) are situated in the distal ureter. Tamsulosin as a selective alpha antagonist can be used as the first line of management for the distal ureter calculi.

Alpha adrenergic receptors have been detected in the human ureter with a predominance of alpha 1A and alpha 1D receptor subtypes in the lower ureter. Alpha 1 adrenergic inhibition reduces the frequency and intensity of peristalsis of the ureter with an increase in the flow of urine.

Tamsulosin, an alpha I receptor blocker that is commonly used in the treatment of bladder outflow obstruction was chosen for this study as it acts on alpha 1 A and alpha 1 D receptor subtypes in the ureter. It also prevents spasm by relaxing the smooth muscle of the ureter and acts on the C fibers blocking pain conduction. The common side effects of tamsulosin are headache, abnormal ejaculation, dizziness and diarrhea.

Tamsulosin considerably decreases the need for analgesic dosage thereby reducing the need for additional drug for the pain relief and serves as an effective bridge between watch-and-wait management and surgical intervention.

SUMMARY

Ureteric calculus is one of the major disorders of the urinary system. The highest numbers of patients affected were males and the commonest age group was 20-40 years. All the patients presented with Pain abdomen.

Ultrasonography is a reliable and safe investigation of choice for the diagnosis of ureteric calculi which is more sensitive and specific than conventional X-rays.

Tamsulosin (alpha 1 blocker) drug caused spontaneous passage of stones with a success rate of 73.8%. It is a safe drug with minimal complications like dizziness, headache.

There was no statistical significant difference in age and calculus size distribution in the two groups.

The expulsion time was significantly less in the tamsulosin group.

The analgesic dose used by patient in the tamsulosin group was significantly lower

Ureterorenoscopy (URS) is a safe and effective minimally invasive surgery as complications are minimal.

REFERENCES

1. Ramello, A., Vitale, C. & Marangella, M. Epidemiology of nephrolithiasis. J Nephrol 13 Suppl 3, S45–50 (2000).
2. Erturhan, S. et al. Comparative of efficacy of use of tamsulosin and/or tolterodine for medical treatment of distal ureteral stones. Memorial Hospital, Istanbul, Turkey. Urology 69, 633–636 (2007).
3. Morse RM, Resnick MI. Ureteral calculi: Natural history and treatment in the era of advanced technology. J Urol 1991; 145:263-5, and Glowacki LS, Beecroft ML, Cook RJ, Pahl D, Churchill DN. The natural history of asymptomatic urolithiasis. J Urol 1992; 147:319-21
4. Picozzi, S. C. M. et al. Management of ureteral calculi and medical expulsive therapy in emergency departments. J Emerg Trauma Shock 4, 70–76 (2011).
5. Hollingsworth, J. M. et al. Medical therapy to facilitate urinary stone passage: a metaanalysis. Lancet 368, 1171–1179 (2006).
6. Fan, B. et al. Can tamsulosin facilitate expulsion of ureteral stones? A metaanalysis of randomized controlled trials. Int J Urol 20, 818–830 (2013).
7. Gravas, S. et al. The use of tamsulosin as adjunctive treatment after ESWL in patients with distal ureteral stone: Do we really need it? Results from a randomized study. Urol Res 35, 231–235 (2007).
8. Singh, A., Alter, H. J. & Littlepage, A. A systematic review of medical therapy to facilitate passage of ureteral calculi. Ann Emerg Med 50, 552–563 (2007).
9. Preminger, G. M. et al. Guideline for the management of ureteral calculi. J Urol 178, 2418–2434 (2007).

10. Lang RJ, Exintaris B, Teele ME, Harvey J, Klemm MF: Electrical basis of peristalsis in the mammalian upper urinary tract. Clin Exp Pharmacol Physiol 1998; 25: 310–321.
11. Santicioli P, Maggi CA: Myogenic and neurogenic factors in the control of pyeloureteral motility and ureteral peristalsis. Pharmacol Rev 1998; 50: 683–721.
12. Bozler E: The activity of the pacemaker previous to the discharge of a muscular impulse. Am J Physiol 1942a; 136: 543–552.
13. Burnstock G, Prosser CL: Responses of smooth muscles to quick stretch: relation of stretch to conduction. Am J Physiol 1960; 198: 921–925.
14. Woodburne RT, Lapides J: The ureteral lumen during peristalsis. Am J Anat 1972; 133: 255–258.
15. Lang RJ, Davidson ME, Exintaris B: Pyeloureteral motility and ureteral peristalsis: essential role of sensory nerves and endogenous prostaglandins. Exp Physiol 2002; 87: 129–146.
16. Edyvane KA, Trussell DC, Jonavicius J, Henwood A, Marshall VR: Presence and regional variations in peptide-containing nerves in the human ureter. J Auton Nerv Syst 1992; 39: 127–138.
17. Morita T, Ando M, Kihara K, Oshima H: Function and distribution of autonomic receptors in canine ureteral smooth muscle. Neurourol Urodyn 1994; 13: 315–321.
18. Scofield MA, Liu F, Abel PW, Jeffries WB: Quantification of steady state expression of mRNA for _ 1 -adrenergic receptor subtypes using reverse transcription and a competitive polymerase chain reaction. J Pharmacol Exp Ther 1995; 275: 1035–1042.
19. Berridge MJ: Inositol triphosphate and diacylglycerol as second messengers. Biochem J 1984; 220: 345–360.

20. Streb H, Irvine RF, Berridge MJ, Schulz I: Release of Ca 2+ from a non-mitochondrial store in pancreatic acinar cell by inositol 1, 4,5triphosphate. Nature 1983; 306: 67–69.

21. Nishizuka Y: The role of protein kinase C in cell surface signal transduction and tumor production. Nature 1984; 308: 693–698.

22. Sigala S, Dellabella M, Milanese G, Fornari S, Faccoli S, Palazzolo F, Peroni A, Mirabella G, Cunico SC, Spano P, Muzzonigro G: Evidence for the presence of _ 1 –adrenoceptor subtypes in the human ureter. Neurourol Urodyn 2005; 24: 142-148.

23. Richardson CD, Donatucci CF, Page SO, Wilson KH, Schwinn DA:Pharmacology of tamsulosin: saturation-binding isotherms and competition analysis using cloned _ 1 –adrenergic subtypes. Prostate 1997;33: 55–59.

24. John N Kabalin. Surgical anatomy of the retroperitoneum, Kidneys and Ureters in Campbell's urology, 8th edition, vol 1, Patrick C Walsh, Alan B, Retik E. Darracott Vaaughan, et al. Published by WB Saunders Company, Philadelphia 2002; 3-40.

25. Mani Menon, Martin I Resnith. Urinary Lithiasis: Etiology, Diagnosis and Medical management in Campbell's urology. 8th edition, vol. 4, Patrick C. Walsh, Alan B et al, Published by WB Saunders company, Philadelphia 2002:3229-3305.

26. Elliot JS. Structure and composition of Urinary Calculi. J Urol 1973; 109: 82-83.

27. Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest 2005;115(10):2598–608.

28. Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. Kidney Int 1997;51(3):894–900.

29. Asplin JR, Parks JH, Nakagawa Y, et al. Reduced crystallization inhibition by urine from women with nephrolithiasis. Kidney Int 2002;61(5):1821–9

30. Asplin JR, Parks JH, Coe FL. Dependence of upper limit of metastability on supersaturation in nephrolithiasis. Kidney Int 1997;52(6):1602–8.

31. Brown C, Purich D. Physical chemical processes in kidney stone formation. In: Coe FL, Favus MJ, editors. Disorders of bone and mineral metabolism. New York: Raven Press; 1992. p. 613–24.

32. Khan SR. Calcium phosphate/calcium oxalate crystal association in urinary stones: implications for heterogeneous nucleation of calcium oxalate. J Urol 1997;157(1):376–83.

33. Garside J. Nucleation. In: Nancollas GH, editor. Biological mineralization and demineralization. New York: Springer-Verlag; 1982. p. 23–5.

34. Jenkins AD. Calculous formation. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. 4th edition Adult and pediatric urology, vol. 1. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 356–92.

35. Vermeulen CW, Lyon ES. Mechanisms of genesis and growth of calculi. Am J Med 1968;45(5): 684–92.

36. Finlayson B, Reid F. The expectation of free and fixed particles in urinary stone disease. Invest Urol 1978;15(6):442–8.

37. Khan SR. Calcium oxalate crystal interaction with renal tubular epithelium, mechanism of crystal adhesion and its impact on stone development. Urol Res 1995;23(2):71–9.

38. Bigelow MW, Wiessner JH, Kleinman JG, et al. Surface exposure of phosphatidylserine increases calcium oxalate crystal attachment to IMCD cells. Am J Physiol 1997;272(1 Pt 2):F55–62.

39. Verkoelen CF, van der Boom BG, Kok DJ, et al. Sialic acid and crystal binding. Kidney Int 2000; 57(3):1072–82.

40. Yamate T, Kohri K, Umekawa T, et al. Interaction between osteopontin on madin darby canine kidney cell membrane and calcium oxalate crystal. Urol Int 1999;62(2):81–6.

41. Verkoelen CF, Van Der Boom BG, Romijn JC. Identification of hyaluronan as a crystal-binding molecule at the surface of migrating and proliferating MDCK cells. Kidney Int 2000;58(3):1045–54.

42. Worcester EM. Inhibitors of stone formation. Semin Nephrol 1996;16(5):474–86.

43. Malek RS, Boyce WH. Intranephronic calculosis: its significance and relationship to matrix in nephrolithiasis. J Urol 1973;109(4):551–5.

44. Williams JC Jr, Zarse CA, Jackson ME, et al. Variability of protein content in calcium oxalate monohydrate stones. J Endourol 2006;20(8):560–4.

45. Allen TD, Spence HM.Matrix stones. J Urol 1966; 95(3):284–90.

46. Khan SR, Shevock PN, Hackett RL. Urinary enzymes and calcium oxalate urolithiasis. J Urol 1989;142(3):846–9.

47. Khan SR. Crystal-induced inflammation of the kidneys: results from human studies, animal models, and tissue-culture studies. Clin Exp Nephrol 2004;8(2):75–88.

48. de Water R, Leenen PJ, Noordermeer C, et al. Cytokine production induced by binding and processing of calcium oxalate crystals in cultured macrophages. Am J Kidney Dis 2001;38(2):331–8.

49. Robertson WG. Kidney models of calcium oxalate stone formation. Nephron Physiol 2004;98(2): 21–30.

50. Robertson WG, Peacock M, Marshall RW, et al. Saturation-inhibition index as a measure of the risk of calcium oxalate stone formation in the urinary tract. N Engl J Med 1976;294(5):249–52.

51. Coe FL, Nakagawa Y, Asplin J, et al. Role of nephrocalcin in inhibition of calcium oxalate crystallization and nephrolithiasis. Miner Electrolyte Metab 1994;20(6):378–84.

52. Ciftcioglu N, Bjorklund M, Kuorikoski K, et al. Nanobacteria: an infectious cause for kidney stone formation. Kidney Int 1999;56(5):1893–8.

53. Kajander EO, Ciftcioglu N. Nanobacteria: an alternative mechanism for pathogenic intra- and extracellular calcification and stone formation. Proc Natl Acad Sci U S A 1998;95(14):8274–9.

54. Liatsikos EN, Bernardo NO, Dinlenc CZ, et al. Caliceal diverticular calculi: is there a role for metabolic evaluation? J Urol 2000;164(1):18–20.

55. Matin SF, Streem SB. Metabolic risk factors in patients with ureteropelvic junction obstruction and renal calculi. J Urol 2000;163(6):1676–8.

56. Randall A. Papillary pathology as a precursor of primary renal calculus. J Urol 1940;44:580.

57. Evan AP, Coe FL, Lingeman JE, et al. Insights on the pathology of kidney stone formation. Urol Res 2005; 33(5):383–9.

58. Mani Menon, Martin I Resnith. Urinary Lithiasis: Etiology, Diagnosis and Medical management in Campbell's urology. 8th edition, vol. 4, Patrick C. Walsh, Alan B et al, Published by WB Saunders Company, Philadelphia 2002:3229-3305.

59. King JS. Etiological factors involved in Urolithiasis: A review of recent research, J Urol 1967; 97: 583-591.

60. Holmlund D, Sjödin J-G. Treatment of ureteral colic with indomethacin. J Urol 1978;120(6):676-7.

61. Lundstam SO, Leissner KH, Wåhlander LA, Kral JG. Prostaglandinsynthetase inhibition of diclofenac sodium in the treatment of renal colic: comparison with use of a narcotic analgesic. Lancet 1982;1(8281):1096-7

62. Lundstam SO, Wåhlander LA, Kral LG. Treatment of ureteral colic by prostaglandin-synthetase inhibition with diclofenac sodium. Curr Ther Res 1980;28:355-8.

63. Walden M, Lahtinen J, Elvander E. Analgesic effect and tolerance of ketoprofen and diclofenac in acute ureteral colic. Scand J Urol Nephrol 1993;27(3):323-5.

64. Cohen E, Hafner R, Rotenberg Z, Fadilla M, Garty M. Comparison of ketorolac and diclofenac in the treatment of renal colic. Eur J Clin Pharmacol 1998;54(6):455-8.

65. Pricop C, Novac C, et al. Can selective alpha blockers help the spontaneous passage of the stones located in the uretero- bladder junction.Rev Med Chir Soc Med Nat Lasi 2004 Jan-Mar; 108(1): 128-33.

66. EU guidelines: Guidelines on Urolithiasis; H-G. Tiselius, P. Alken, C. Buck, M. Gallucci, T. Knoll, K. Sarica, Chr. Türk: Update Mar 2008.

67. Clin Pharmacokinet.2010 Mar 1; 49(3): 177-88.

68. Itoh Y, Kojima Y et al. Examination of alpha 1 adrenoreceptor subtypes in the human ureter. Int J Urol 2007;14: 749.

69. Della Bella M, Milanese g et al. Efficacy of Tamsulosin in the medical management of juxtavesical ureteral stones. J Urol 2003; 170: 2202.

70. Monga M. Accessory instrumentation for ureteroscopy. Curr Opin Urol 2004; 14(2):107-9.

71. Portis AJ, Rygwall R, Holtz C, Pshon N, Laliberte M. Ureteroscopic laser lithotripsy for upper urinary tract calculi with active fragment extraction and computerized tomography followup. J Urol 2006; 175(6):2129-33.

72. James E Lingeman , David A. Lifshitz, Andrew P Ewan. Surgical management of urinary lithiasis in Campbell's urology 8th edition vol 4, Published by WB Saunders Company, Philadelphia 2002:3361-3451.

73. Cervenakov I, Fillo J, Mardiak J, Kopecný M, Smirala J, Lepies P. Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker--Tamsulosin. Int Urol Nephrol. 2002; 34:25–9

74. Dellabella M, Milanese G, Muzzonigro G: Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. J Urol 2003, 170:2202–2205.

75. SAH Rizvi et al. The management of stone disease. Br Jr Urol 2002;89:62.

76. Francesco Porpiglia, Cristian Fiori et al. A second cycle of tamsulosin in patients with distal ureteric stones: a prospective randomized trial. BJUI 2009 Jun; 103(12) :1700-3.

77. David J, Galvin et al. The contemporary management of renal and ureteric calculi. BJUI 2006; 98: 1283-1288.

78. Reid M Morse and Martin I Resnick. Jr Urol 1991; 145: 263-265.

79. Puppo P et al. Primary Endoscopic treatment of ureteric calculi: A review of 378 cases. Euro Urol 1999; 36(1) :48-52.

80. Xizhao Sun, Lei He, Weihong Ge and Jianlin Lv. Efficacy of selective alpha 1D blocker Naftopidil as Medical Expulsive therapy for distal ureteral stones. J Urol 2009; 181: 1716-1720.

81. Eskelinen M et al. Usefulness of history taking, physical examination and diagnostic scoring in acute renal colic. Eur Urology 1998; 34: 467-473.

82. Mathew T Gettmen et al. Management of ureteric stones: issues and controversies. Br J Urol 2005; 95 (2): 85-93.

83. Hubner WA et al. Natural history and current concepts for the treatment of small ureteral calculi. Eur Urol 1993;24: 172-176.

84. Singal RK, Denstedt JD. Contemporary management of ureteral stones. Urol Clin North Am 1997; 24 :59-70.

85. Tawfiek ER and Bagley DH. Management of upper urinary tract calculi with ureteroscopic technique. Urology 1999; 53: 25-31.

86. Harewood LM, Cleave LK. The visual endo urological removal of ureteric calculi. Med J Aust 1986; 145: 574-9.

87. Steven J. Sowter and David A. Tolley. The management of ureteric colic. Curr Opin Urol 2006; 16: 71-76.

88. Theirry Flam, Michael Maline, Robert Roth. Complications of ureteroscopy, urological clinics of North Am. 1988; 15: 167.

89. Carter S, Cox R, Wickham JA. Complications associated with urteroscopy. Br J Urol 1986; 58: 625-628.

ANNEXURE -1

CASE PROFORMA

EFFICACY OF TAMSULOSIN (ALPHA-1 BLOCKER) IN THE MANAGEMENT OF SYMPTOMATIC DISTAL URETERIC CALCULUS

Name :

Age:

Sex:

Occupation:

Address:

IP/OP NO:

Chief complaints:

History of present illness Lumbar pain:

Vomiting:

Burning micturition:

Colicky Pain:

Radiation of pain:

Haematuria:

Past History:

Diabetes Mellitus

Hypertension

Asthma

others

Personal History:

Diet

Appetite

Sleep

Alcohol

Smoker

General Examination

Pallor

Icterus

Cyanosis

Clubbing

Lymphadenopathy

Edema

Abdominal Examination:

Site of tenderness

Renal angle

External genitalia

Respiratory System:

Normal vesicular breath sounds

Wheeze

Rhonchi

CVS:

S1S2

Murmur

Investigations:

1)Hematological

Hb%

Total count

Platelet count

ESR

PCV

2) Biochemical

Blood Urea

Serum Creatinine

RBS/FBS/PPBS

3) Urine Microscopy

pH

colour

WBC

RBC

Albumin

Sugar

Casts

Abdominal ultrasonography: renal

Site:

Side:

Size:

Hydroureteronephrosis:

Management:

1. Analgesic (inj diclofenac in mg)

2. Anti-spasmodic (inj mefenamic acid in mg)

3. Tamsulosin 0.4mg (number of days)

ANNEXURE II

INFORMED CONSENT

EFFICACY OF TAMSULOSIN (ALPHA-1 BLOCKER) IN THE MANAGEMENT OF SYMPTOMATIC DISTAL URETERIC CALCULUS

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. This study has been reviewed by the institution ethical committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ Provide thumb impression only if you voluntarily agree to participate in this study

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understand the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation. Contact no 9880447187.

Subject name: DATE:

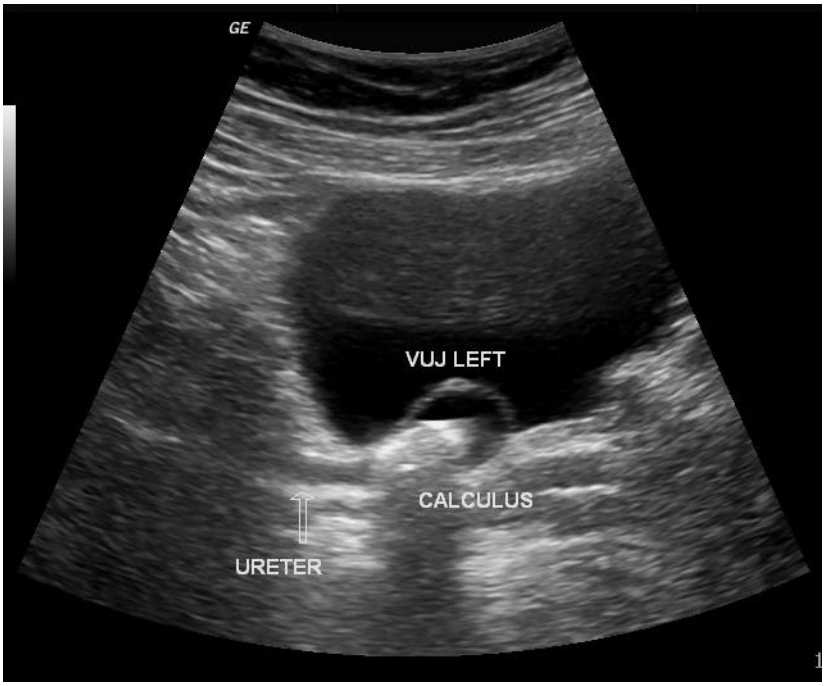
Signature/ thumb print:

Parents/ guardians name: DATE:

Signature/ thumb print:

Signature of person taking consent: DATE:

ANNEXURE III



Photograph 1: LEFT VUJ CALCULI

ANEXURE IV

Photograph 2 : DICLOFENAC SODIUM INJECTION

ANNEXURE V

Photograph 3 : TAMSULOSIN TABLET 0.4MG

KEY TO MASTER CHART

HOSP NO.	:	Hospital Number
EXPL	:	Expulsion
ANLG	:	Analgesic Dose
M	:	Male
F	:	Female
L	:	Left
R	:	Right
NA	:	Not Applicable