

"ASSESSMENT OF PLASMA HOMOCYSTEINE AS A
MARKER OF ACUTE RENAL INJURY IN PATIENTS
UNDERGOING EXTRACORPOREAL SHOCK WAVE
LITHOTRIPSY (ESWL) FOR RENAL STONE DISEASE –
ONE YEAR CROSS SECTIONAL STUDY"

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“ASSESSMENT OF PLASMA HOMOCYSTEINE AS A
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LITHOTRIPSY (ESWL) FOR RENAL STONE DISEASE – ONE
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LIST OF ABBREVIATIONS USED

μmol/L	-	Micromole per litre
1,25(OH) ₂ D	-	1,25-dihydroxyvitamin D
ADCY10	-	Adenylyl cyclase
AKI	-	Acute kidney injury
AKIN	-	Acute Kidney Injury Network
ARF	-	Acute renal failure
ARI	-	Acute renal injury
B2M	-	b-2-microglobulin
BC	-	Before Christ
BGAL	-	b-galactosidase
BMI	-	Body mass index
BUN	-	Blood urea nitrogen
cAMP	-	Cyclic adenosine-3',5'-monophosphate
CaOx	-	Calcium oxalate
CaP	-	Calcium phosphate
CASR	-	Calcium sensor receptor
CLDN14	-	Claudin 14
cm	-	Centimeter
CO ₂	-	Carbon dioxide
Cr	-	Creatinine
CT	-	Computed tomography
dRTA	-	Distal renal tubular acidosis
DTPA	-	Diethylenetriaminepentacetate
ECG	-	Electrocardiogram

EMLA	-	Eutectic mixture of local anesthetics
ESWL	-	Extracorporeal shock wave lithotripsy
g/d	-	grams per day
GFR	-	Glomerular filtration rate
HBsAg	-	Hepatitis B surface antigen
HFJV	-	High-frequency jet ventilation
HIV	-	Human immunodeficiency virus
hs CRP	-	High sensitivity C Reactive Protein
HU	-	Hounsfield units
i.e	-	That is
J	-	Joules
KDIGO	-	Kidney Disease Improving Global Outcomes
KUB	-	Kidney Ureter Bladder
kV	-	Kilovolts
L	-	Liter
MAG3	-	Mercaptoacetyltriglycine
mEq/d	-	Milliequivalents per day
mg/d	-	Milligrams per day
mg/dL	-	Milligrams per deciliter
mm	-	Millimeters
mmol/L	-	Millimole per litre
MRI	-	Magnetic resonance imaging
MS	-	Metabolic syndrome
n	-	Total number
NAG	-	N-Acetyl-b-D-glucosaminidase

NCCT	-	Noncontrast computed tomography
NCT	-	Nonrandomized controlled trial
NNT	-	Nonrandomized, non-placebo controlled trial
NSAID's	-	Non steroidal anti-inflammatory drugs
O ₂	-	Oxygen
p value	-	Probability value
PDI	-	Percussion, diuresis, and inversion
PTH	-	Parathyroid hormone
R	-	Retrospective
RCT	-	Randomized controlled trial
RIFLE	-	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RSSR	-	Dithio acid
S.creatinine	-	Serum creatinine
SD	-	Standard deviation
-SH	-	Sulfhydryl group
SSD	-	Skin-to-stone distance
SW/min	-	Shock waves per minutes
SWL	-	Shock wave lithotripsy
SWs	-	Sound waves
tHcy	-	Total homocysteine
U.S.	-	United States
UA	-	Uric acid
USA	-	United States of America
USG	-	Ultrasound

vs	-	versus
W	-	Watt
yr	-	Year
ZNF365	-	Zinc finger protein 365

ABSTRACT

Background and Objectives

Extracorporeal Shock wave lithotripsy (ESWL) commonly used procedure for treating upper urinary tract stones may result in complications of acute renal failure. The present study was aimed to assess plasma homocysteine (HCy) as a marker of acute renal injury in patients undergoing ESWL for renal stone disease and compare the same with other markers i.e. serum creatinine and serum high sensitive C reactive protein (hs-CRP).

Methodology

This one year cross-sectional study was done in the Department of General Surgery and Department of Urology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2015 to December 2015. 64 patients undergoing ESWL were investigated for plasma tHCy, serum creatinine and hs-CRP 24 hours before and after ESWL procedure.

Results

Majority of the patients were males (71.88%). The male to female ratio was 2.55:1. Most of the patients were aged between 31 to 40 years and 41 to 50 years (31.25% each) and mean age was 40.88 ± 10.46 years. Most of the patients presented with pain (96.87%). Left renal calculus was noted in 53.13% of the patients while right renal calculus was noted in 46.88% of the patients. Post ESWL, AKI developed in 56.25% of the patients. Post ESWL mean plasma tHCy levels were significantly high in patients with AKI (21.01 ± 7.67 vs 16.93 ± 7.44 $\mu\text{mol/L}$; $p=0.036$) compared to those who did not develop AKI. The mean change

in plasma HCy levels in patients with AKI was significantly high (10.90 ± 4.87 vs 6.85 ± 6.06 $\mu\text{mol/L}$; $p=0.004$). The post ESWL mean serum creatinine levels were significantly high in patients with AKI (1.59 ± 0.44 vs 1.32 ± 0.29 mg/dL ; $p=0.006$). The mean change in serum creatinine levels in patients with AKI was significantly high (0.90 ± 0.25 vs 0.28 ± 0.24 mg/dL ; $p<0.001$). The post ESWL mean hs-CRP levels were comparable in patients with AKI and those who did not develop AKI ($p=0.120$). 72.22% of the patients with AKI has significant rise of s.hs-CRP (2 fold of baseline) level after ESWL which is the only insult on kidney in 24 hours.

Conclusion and interpretation

Plasma total homocystine, serum hs-CRP and serum creatinine can be used as renal injury markers following ESWL in patients with renal stone disease.

Keywords

Acute kidney Injury (AKI); Extracorporeal shock wave lithotripsy (ESWL); Plasma total homocysteine, Renal stone disease; Serum creatinine; Serum high sensitivity C reactive protein (hs-CRP);

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INTRODUCTION

The increased prevalence of renal stone disease is pandemic^{1,2} with a lifetime risk of kidney stones currently at 6–12% in the general U.S. population.^{1,3} Nephrolithiasis has been considered as a systemic disorder^{1,4} that is associated with chronic kidney disease, renal calculi-induced bone disease,⁵ increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and the metabolic syndrome (MS).⁶ Nephrolithiasis is a chronic illness with a recurrence rate greater than 50% over 10 yr without medical treatment.⁷ Given that the economic and social burden of nephrolithiasis is immense with the annual expenditure in the United States exceeding \$5 billion.⁸

The prevalence of renal stone disease in the United States has doubled over the past three decades. Such increase in prevalence has also been noted in most European countries and Southeast Asia.^{1,2} There are racial and ethnic differences seen in kidney stone disease which occurs primarily in Caucasian males and least in young African-American females. Its occurrence in Hispanic and Asian ethnicities is intermediate.^{1,2}

The incidence of kidney stones is highest in Caucasian males,^{1,3} where its incidence rises after age 20, peaks between 40 and 60 yr of age (at approximately 3 per 1000 per year), and then declines.⁹ In females, the incidence rate is highest in the late 20s, decreases by age 50, and remains relatively constant thereafter.^{3,9}

Approximately 80% of calcium kidney stones are made of calcium oxalate (CaOx), with a small percentage (15%) of calcium phosphate (CaP) stones. The

various pathophysiological mechanisms for calcium kidney stone formation are complex and diverse and include low urine volume, hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, and abnormalities in urine pH.¹

Management of renal stones is either by conservative, percutaneous or surgical approaches.

Conservative management includes increase in fluid intake to get a daily urine output of 2 L, carbonated beverages, citric juices, dietary modifications with decreased protein, sodium, calcium and oxalate consumption.

Ultrasonography and Fluoroscopy are most commonly used for percutaneous approaches. Depending on the location, size and type of the stone the treatment approaches varies. Various modalities includes percutaneous nephrolithotomy, open nephrolithotomy, ureteroscopic removal, intracorporeal lithotripters and extracorporeal short wave lithotripsy. At present, the great advancement in minimally invasive techniques has led to the reduction in open surgery.

Shock wave lithotripsy is a commonly used procedure for treating upper urinary tract stones in patients who require treatment. Various methods have been proposed to improve the results of this procedure, including proper patient selection, technique modification, additional adjunctive therapy to ease elimination of fragments and changes in design of the lithotripter.¹⁰

Extracorporeal shock wave lithotripsy (ESWL) has been introduced as an alternative approach which fragments stones in the kidney and upper urinary tract with the use of sound waves. Dornier HM3 lithotripter was first lithotripter to be introduced.¹¹ Since its introduction in early 1980s, Extracorporeal Shockwave

Lithotripsy (ESWL) is accepted as the first line treatment modality for renal and upper ureteric stones. It is a noninvasive procedure which is simple, safe and effective and can be performed with and without anaesthesia on outpatient basis. There are three main types of shock wave generators – electrohydraulic, electromagnetic and piezoelectric.^{11,12}

ESWL continues to be the treatment of choice for uncomplicated kidney stones of < 2 cm in diameter, 25 years after its introduction into the USA. ESWL is noninvasive which is well tolerated by patients and has a low morbidity and high success rate.¹² However, it has been known since 1985 that a clinical dose of sound waves (SWs) induces acute renal injury that extends from the papilla to the outer cortex, with a change in renal function in most, if not all patients.¹⁴ This focal and predictable injury has two components; a traumatic vascular injury thought to be induced by the physical forces of the shock wave, and an ischaemic/hypoxic response linked to the severely damaged renal vessels. In addition, an inflammatory response, termed ‘lithotripsy nephritis’ quickly ensues at the sites of endothelial injury.¹⁴

In spite of ESWL being the commonest and safest modality for treatment of renal stones there are some risks and complications associated with it like acute renal injury (Oxidative stress), pain, hematuria, hypertension, steinstrasse, subcapsular, perirenal and suburothelial haemorrhages, severe urinary tract infections (such as pyeloureteritis, pyelonephritis, renal abscesses and pyonephrosis), ureteral injuries, delayed strictures and cyst formation.

ESWL uses shock waves that cause oxidant stress renal injury followed by release of markers. The impact of ESWL on renal function has been evaluated in many studies. Many indicators have been used for this purpose such as DTPA scan, ultrasonography and MAG3 scan.¹⁵

Recently it is suggested that, plasma homocysteine levels increase in patients with renal dysfunction. Numerous studies have demonstrated that kidney function is one of the most important determinants of plasma total homocysteine (tHcy) concentration.¹⁵

Homocysteine is a sulphur containing amino acid with a reactive sulfhydryl group (-SH) and like most thiols (RSH) can undergo oxidation to disulfide (RSSR) at physiological pH in the presence of O₂. It is formed by demethylation of methionine and can be reversibly converted back to methionine and irreversibly to cysteine. These reactions are catalyzed by transition metals, vitamin B₆, B₁₂ and folic acid. Homocysteine can cyclize to give homocysteine thiolactone, a five membered heterocycle. Because of this “self looping” reaction, homocysteine – containing peptides tend to cleave themselves by reactions generating oxidative stress. Homocysteine is cleared from the body by renal and extrarenal metabolism. Renal metabolism includes urinary excretion after glomerular filtration just like creatinine. Elevated total homocysteine (tHcy) levels have been associated with atherothrombotic vascular disease and numerous other diseases including Alzheimers disease, osteoporosis, deep vein thrombosis and pulmonary embolism in general population.^{16,17}

Since tHcy levels are markedly elevated in patients with chronic renal failure, it has been presented as a potential factor contributing to the high risk of cardiovascular disease in these patients.¹⁵ Association of Homocysteine is well documented in diseases like atherosclerosis, stroke etc.^{16,17}

Furthermore, serum creatinine is raised in any kidney disease either acute or chronic. It is excreted by glomerular filtration and is one of the well known renal injury marker. Serum high sensitivity C Reactive Protein (hs-CRP) is a non specific marker of any injury and inflammatory process.

This prompted us to assess plasma homocysteine as a marker of acute renal injury in patients undergoing extracorporeal shock wave lithotripsy (ESWL) for renal stone disease and compare the same with other markers i.e., serum creatinine and serum hs-CRP.

OBJECTIVES

The objectives of this study were

Primary

To assess plasma total homocysteine as a marker of Acute Renal Injury in patients undergoing extracorporeal shock wave lithotripsy (ESWL) for renal stone disease

Secondary

To compare plasma total homocysteine, serum creatinine and serum high sensitivity C-Reactive Protein (hs-CRP) as renal injury markers.

REVIEW OF LITERATURE

Nephrolithiasis remains a major burden on economics and health worldwide. It is considered a systemic disorder which is associated with chronic kidney disease, loss of bone and fractures, higher risk of coronary artery disease, the metabolic syndrome, diabetes mellitus type 2 and hypertension. It is necessary to further study the pathophysiological link between kidney stones and these systemic disorders for the development of new therapeutic options.¹

Renal calculus is from the Latin word *renis* meaning kidneys and *calculus* meaning pebble. Lithiasis meaning stone formation in the kidneys is called as nephrolithiasis from *nephro* (kidney) + *-lith* (stone) + *-iasis* (disorder).^{18,19}

The occurrence of kidney stones was first recorded thousands of years ago, and one of the earliest known surgical procedures for the removal of stones is lithotomy. In 1901, a stone discovered in an ancient Egyptian mummy was dated to 4,800 BC. There is a mention about calculous disease in medical texts from ancient Mesopotamia, China, India, Greece, Persia and Rome. The Roman medical treatise i.e *De Medicina* by Aulus Cornelius Celsus has a description of lithotomy, and this work provided the basis for this procedure till the 18th century.^{19,20}

Famous people who were formers of kidney stone include Napoleon I, Epicurus, Peter the Great, Napoleon III, George IV, Louis XIV, Oliver Cromwell, Lyndon B. Johnson, Michel de Montaigne, Benjamin Franklin, Francis Bacon, Isaac Newton, William Harvey, Samuel Pepys, Herman Boerhaave, and Antonio Scarpa.²¹

From 1520 new techniques in lithotomy began to emerge, but the operation remained risky. There was a drop in the mortality rate from about 24% to 2.4% after Henry Jacob Bigelow popularized the technique of litholapaxy in 1878.²² But there was high level of mortality using other treatment techniques, especially among inexperienced urologists. Since the introduction of extracorporeal shock wave lithotripsy by Dornier MedTech in 1980 for breaking up stones via acoustical pulses, this technique has come into widespread use.²³

Epidemiology

The increased prevalence of nephrolithiasis is pandemic.^{1,2} In the general U.S. population the lifetime risk of nephrolithiasis is currently at 6–12%.³ Kidney stone is a chronic type of illness with a recurrence rate that is greater than 50% over 10 yr without medical treatment. The economic and social burden of nephrolithiasis is immense with the annual expenditure in the United States exceeding \$5 billion.⁸

The prevalence of renal stone disease in the United States has doubled over the past three decades. There is similar increase noted in most European countries and Southeast Asia.² There are racial and ethnic differences seen in kidney stone disease, which occurs primarily in Caucasian males. It is least prevalent in young African-American females. The prevalence is intermediate in Asian and Hispanic ethnicities.^{1,2}

The incidence of renal calculi is highest in Caucasian males,^{1,3} where the incidence rises after age 20. It peaks between 40 and 60 yr of age at approximately 3 per 1000 per year and then declines.⁹ Whereas in females, the incidence rate is

highest in the late 20s, decreases by age 50, and thereafter it remains relatively constant.^{1,3,9}

Pathophysiological Mechanism(s) of Calcium Stones

Majority of calcium kidney stones are calcium oxalate (CaOx) about 80%, followed by calcium phosphate (CaP) stones about 15%^{1,24}. The pathophysiological mechanisms for calcium nephrolithiasis are complex and include low urine volume, increased calcium, uric acid and oxalate excretion in urine, hypocitraturia, and abnormalities in urine pH.¹

Hypercalciuria

Hypercalciuria is the most common abnormality in calcium kidney stone formers which is detected in 30–60% of adults with nephrolithiasis.²⁵ In 1939, the link between hypercalciuria and nephrolithiasis was initially described by Flocks.²⁶ In 1958, Albright²⁷ and Henneman²⁸ used the term “idiopathic hypercalciuria.” The mechanisms for hypercalciuria involves increased intestinal calcium absorption, decreased calcium reabsorption from kidneys and increased calcium mobilization from bone.^{1,5} However, increased intestinal calcium absorption is the most common abnormality. Nevertheless, all the above mentioned physiological defects may coexist in individual patients, which may lead to decreased mineral density of bone and also bone fracture.^{1,5}

Hypercalciuria is a heterogeneous disorder in which increased intestinal calcium absorption may be either dependent or independent of 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Hypercalciuria is usually classified into two different groups. The severe most type is characterized by normocalcemia, intestinal

hyperabsorption of calcium, hypercalciuria, and either normal or suppressed serum PTH level and/or urinary cAMP level. However, a less severe form has many of the same biochemical characteristics, but hypercalciuria comes to normal after a restricted calcium diet (<400 mg/d).²⁹

1,25(OH)₂D-dependent hypercalciuria

There was increased serum concentration of 1,25(OH)₂D noted in the majority of renal stone formers with hypercalciuria as noted in the following two studies. Insogna *et al*³⁰ demonstrated increased 1,25(OH)₂D production rather than reduced clearance in patients with hypercalciuria. However The underlying mechanism(s) of enhanced 1,25(OH)₂D production have yet to be found out. But in the majority of these cases, the main regulators of 1,25(OH)₂D production i.e. serum PTH, serum phosphorus and maximum tubular renal phosphorus reabsorption, were all comparable to those of normal non-stone-forming subjects.³¹ An association between renal tubular phosphorus abnormalities and serum 1,25(OH)₂D levels is also suggested. It is also shown that excessive urinary calcium excretion in normal subjects who were given a large dose of 1,25(OH)₂D.¹ However, the origin of hypercalciuria is not clear with a disagreement between studies in which one study supports the intestinal origin of hypercalciuria³² and the other study suggests calcium mobilization from the bone.³³

1,25(OH)₂D-independent hypercalciuria

Despite the presence of many reports of high circulating 1,25(OH)₂D in hypercalciuric stone formers,^{30,32} several studies have shown that increased absorption of calcium is not dependent on vitamin D, with more than two thirds of

idiopathic hypercalciuric patients having increased intestinal calcium absorption with normal prevailing serum 1,25(OH)₂D concentration. To prove this possibility, short-term administration of ketoconazole, an antifungal agent known to decrease serum 1,25(OH)₂D, which showed significant reduction in serum 1,25(OH)₂D concentration without a significant alteration in calcium absorption from intestine in hypercalciuric subjects. Similar findings were noted with thiazide, glucocorticoids, and phosphate treatment suggesting that calcitriol has a limited pathophysiological causative role in hypercalciuria.¹

Renal leak hypercalciuria

Renal leak hypercalciuria is less common variety of hypercalciuria where there is defective renal tubular calcium reabsorption which is associated with enhanced PTH, calcitriol and net intestinal absorption of calcium.³⁴

Resorptive hypercalciuria

Primary hyperparathyroidism is the most common cause of resorptive hypercalciuria.. However, due to the early diagnosis of primary hyperparathyroidism, the prevalence of kidney stones in this condition is decreased to approximately 2–8%.³⁵

Hyperuricosuria

Hyperuricosuria is one of the cause for nephrolithiasis and is detected as an isolated abnormality in 10% of calcium stone formers. However, it may be present in 40% of the population in combination with other metabolic abnormalities.³⁶ The cause for this is attributed to a high purine diet.³⁷ But in approximately one third of

patients, overproduction of endogenous uric acid (UA) is the cause where dietary restriction does not significantly alter urinary uric acid excretion.³⁸

Hypocitraturia

Citrate is an endogenous inhibitor of calcium renal stone formation. Low urine citrate excretion (hypocitraturia) is found in approximately 20–60% of calcium kidney stones.³⁹ The major determinant of urinary citrate excretion is maintenance of acid-base balance.⁴⁰

Hyperoxaluria

Raised urinary oxalate and calcium excretion are equally important in forming urinary CaOx stones.⁶ Hyperoxaluria is present in 10–50% of calcium stone formers.⁶ The mechanisms of hyperoxaluria can be divided into: 1) Oxalate overproduction due to an inborn error in metabolism;¹ 2) increased intake in diet and its bioavailability;⁴¹ and 3) Intestinal oxalate overabsorption.¹

Urinary pH disturbances

Highly acidic urine (pH < 5.5) and highly alkaline urine (pH > 6.7) both predispose patients to calcium nephrolithiasis. With acidic pH, urine becomes supersaturated with undissociated UA which increases CaOx crystallization in urine.⁴² Significantly alkaline urine raises monohydrogen phosphate [dissociation constant (pKa) ~ 6.7], which, along with calcium, forms thermodynamically unstable brushite (CaHPO₄·2H₂O) and finally to hydroxyapatite [Ca₁₀(PO₄)₆(OH)₂]. In practice, conditions associated with CaP stone formation are dRTA, primary hyperparathyroidism and with carbonic anhydrase inhibitors.¹

Histopathological mechanisms of calcium kidney stone formation

Urinary supersaturation of stone-forming salts is one of the mechanism for the formation of calcium stones, which forms a homogeneous nucleus in the lumen of the nephron which is followed by crystal growth and consequent obstruction in the distal nephron.⁶ CaOx grow from Randall's plaque which is an interstitial apatite plaque which covers the renal papillary surface.⁴³ The decreased proximal tubular reabsorption of calcium with increased renal tubular calcium reabsorption in the thick ascending limb have been proposed as the potential mechanism for interstitial plaque formation. Whereas in CaP stone formers the apatite crystal is deposited in the inner medullary collecting duct, which produces plugs associated with interstitial scarring.⁴³

Genetic basis of calcium calculi formation

A higher percentage of renal stones has been reported in first-degree relatives and family members with nephrolithiasis.⁴⁴ The genetic link is found associated with polymorphisms in the putative *soluble adenylyl cyclase* (ADCY10) gene located on chromosome 1q23.4–1q24, polymorphisms in sequence variants in the *Claudin 14* (CLDN14) gene and *calcium sensor receptor* (CASR) gene polymorphism. But the functional significance of these polymorphisms is not yet established.¹

Uric acid stone formation and its link to the Metabolic Syndrome

The etiological causes of UA stone formation may be either genetic, acquired or a combination of both. Metabolic syndrome (MS) has been considered as the most prevalent cause of uric acid stone formation. The underlying mechanisms

responsible include 1) low urine volume; 2) hyperuricosuria; and 3) unduly acidic urine.¹

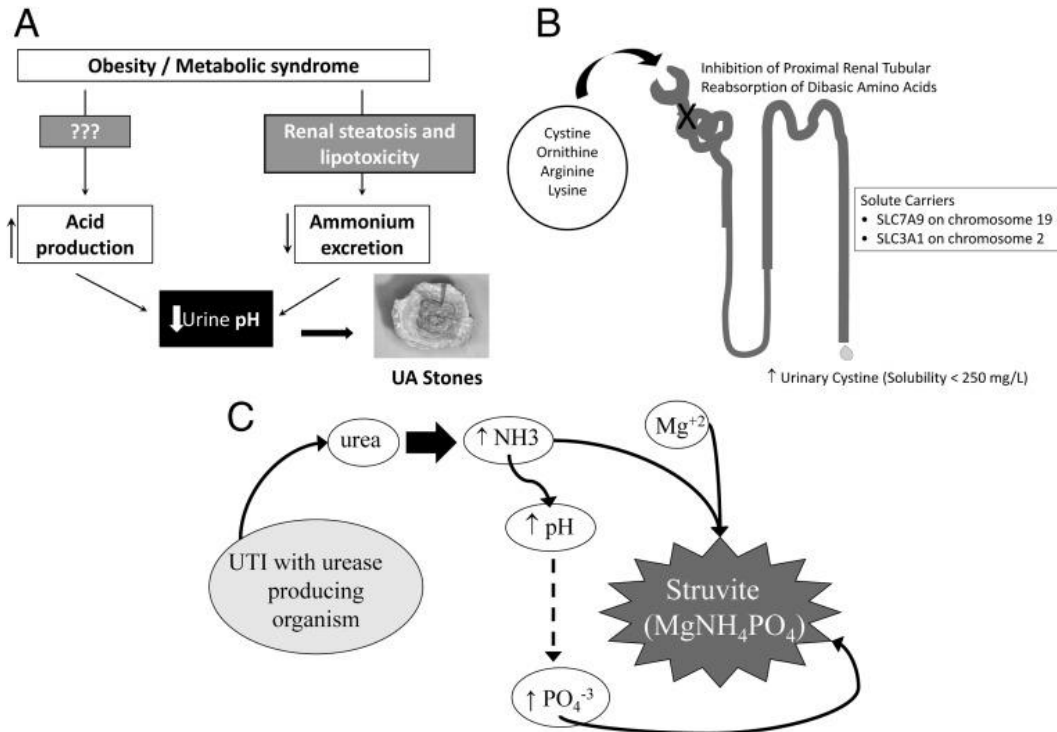


Figure 1. Causes of non-calcium kidney stone formation. A - UA stones; B - cystine stones; C - infectious stones.¹

Genetic basis of UA calculi formation

In one of the study, genetic analysis found a locus on chromosome 10q21-22 associated with increased tendency to UA nephrolithiasis. Another study identified the putative gene as *zinc finger protein 365* (ZNF365). But, the functional importance of this gene and the role of the protein encoded have not been fully established.¹

Cystinuria

It is more prevalent among children and adolescents with renal stones but comprises only a small fraction in adults.⁴⁵ Cystinuria is either autosomal recessive i.e. obligate heterozygotes who have normal urinary cystine excretion or autosomal dominant with incomplete penetrance i.e. obligate heterozygotes who have increased urinary cystine excretion but typically not enough to cause cystine stones. It is associated with an inherited defect in renal cystine reabsorption expressed as b⁰⁺ (*SLC3A1* and *SLC7A9*). In a recent genetic classification, cystinuria is classified as type A if mutations are found in both *SLC3A1* alleles, type B if mutations are found in both *SLC7A9* alleles and type AB if one mutation is found in each one of the gene.⁴⁶

Infection and rare stones

The utmost important factor for the formation of infectious stones is presence of highly alkaline urine pH (>7.2) with the presence of urease-producing organisms and supersaturation of urine with respect to magnesium, ammonium and phosphate ions.⁴⁷ Rare forms of kidney stones such as dihydroxyadanine, ammonium urate and stones resulting from protease inhibitor drugs may also occur.¹

Diagnosis

Medical history

In the diagnosis of patients with nephrolithiasis, systemic and environmental influences must be carefully identified. Systemic abnormalities include intestinal disease, disorders of calcium homeostasis such as primary hyperparathyroidism,

conditions accompanied by extra renal 1,25(OH)₂D production such as granulomatous diseases, obesity, type II diabetes, recurrent urinary tract infection, bariatric surgery, medullary sponge kidney and various drug treatments.¹

Diet plays a crucial role in the formation of kidney stones. The two most common dietary aberrations that increase the risk of kidney stones are high dietary salt and protein consumption). Epidemiological studies have shown an association between a higher risk of nephrolithiasis and lower dietary calcium intake. Although the exact pathophysiological mechanism has not been established, it has been suggested to be due to lowered urinary oxalate excretion or possibly a rise in urinary antilithogenic factors with a high-calcium diet. In contrast, increased calcium and vitamin D intake is also accompanied by a higher risk of nephrolithiasis. Aside from dietary risk factors, it has been suggested that risk of nephrolithiasis increases in hot climates, with frequent and/or intense exercise, largely due to extra renal fluid loss as a result of perspiration, resulting in a significant decrease in urine volume. Certain professions associated with decreased fluid intake and/or increased perspiration are also at high risk for nephrolithiasis.¹

Although hypercalciuric nephrolithiasis is typically a polygenetic complex trait but in rare instances it may be a monogenetic disorder. Dent's disease is an x-linked recessive disorder associated with the occurrence of hypercalciuric nephrolithiasis among male subjects accompanied by renal impairment and low-molecular-weight proteinuria.⁴⁸ Lowe syndrome is the occurrence of kidney stones and nephrocalcinosis in male subjects with early cataracts, glaucoma, and neurological deficit.⁴⁹ In patients with dRTA aggressive nephrolithiasis,

nephrocalcinosis, retarded growth, and deafness can be present which can be both autosomal dominant and autosomal recessive inheritance.⁵⁰

Laboratory diagnosis

Laboratory diagnosis includes the following - stone analysis, imaging studies, blood profiles, and a urine metabolic evaluation. Stone analysis plays an important role in the diagnosis of kidney stone patients, specifically in infrequently encountered kidney stones such as UA, cystine, infection-induced, drug-induced, and NH_4^+ urate stones. Imaging studies are valuable in the diagnosis of nephrolithiasis. Despite presence of numerous imaging methodologies like USG KUB, X-RAY KUB etc computed tomography is the most sensitive and specific mode of diagnosis.⁵¹ In blood investigation high fasting blood calcium, low phosphorus and elevated PTH are suggestive of primary hyperparathyroidism. In these case, the patients must be considered for a noninvasive localization study followed by parathyroidectomy. If there is normal serum calcium, low serum phosphorus, elevated $1,25(\text{OH})_2\text{D}$ and normal PTH then it is suggestive of renal phosphorus leak. If there is low serum potassium and low CO_2 it is suggestive of dRTA. Hyperuricemia and high serum triglycerides are encountered in patients with UA stones.¹

Treatment

Conservative management

High oral fluid intake must be considered in all renal stone formers. A prospective controlled study has shown that increasing water intake with a urinary volume of approximately 2.5 liters/d was associated with decreased urinary

supersaturation with CaOx and a significant reduction in renal stone occurrence and recurrence.⁵² Another study suggests that intake of fruit juice, specifically orange juice, is also effective in decreasing urinary CaOx saturation and increasing urinary citrate excretion.⁵³ This same effectiveness is not seen with apple juice, grapefruit juice, cola, and some sport drinks because of their elevated oxalate and fructose content.⁵³⁻⁵⁵ According to one study in Italian men with hypercalciuria, great emphasis has been placed on low dietary sodium intake (<100 mEq/d) and animal protein consumption (50–60 g/d) as well as normal calcium intake (1200 mg/d) which helps in the reduction of calcium stone recurrence.⁵⁶ However in another study where only a low-fiber, low-protein diet cohort in the United States did not show decreased stone recurrence.⁵⁷ Decreased dietary oxalate consumption (<100 mg/d) is also useful in lowering urinary oxalate excretion. Foods which are known to cause increased urinary oxalate excretion include fruits such as raspberries, figs and plums; vegetables such as spinach, rhubarb and beets; and most nuts, tea, wheat bran, chocolate and high amounts of vitamin C.^{58,59} There is no specific report suggesting the amount of vitamin D intake for these subjects. However, 800 IU/d is generally recommended.¹

Pharmacological treatment

This treatment is required in most patients with recurrent calcium kidney stone and also in specific type of calculus such as uric acid, cystine and infection-induced stones due to unavailability and/or consensus on the effectiveness of dietary restrictions.^{56,57}

Clinical trials based on pharmacotherapy of calcium and non-calcium nephrolithiasis.¹

First author (Ref.)	Treatment	No. of patients	Design	Outcome
Thiazide diuretics				
Laerum ⁶⁰	Hydrochlorothiazide vs. placebo	50	RCT	Decreased new stone formation and also prolonged stone-free interval
Ettinger ⁶¹	Chlorthalidone vs. Mg hydroxide vs. placebo	124	RCT	Chlorthalidone more effective than Mg hydroxide or placebo in decreasing stone calculi formation
Ohkawa ⁶²	Trichlormethiazide vs. no treatment	175	RCT	Decreased calciuria and calculi formation in rat
Alkali treatment				
Pak ⁶³	Potassium citrate vs. pretreatment in calcium and uric acid stone formers	89	NNT	Decreased calculus events
Soygür ⁶⁴	Potassium citrate vs. no treatment after shock wave lithotripsy	110	RCT	Decreased calculus recurrence
Allopurinol treatment				
Ettinger ⁶⁵	Allopurinol vs. placebo	60	RCT	Decreased calculus events

First author (Ref.)	Treatment	No. of patients	Design	Outcome
Coe ⁶⁶	Thiazide vs. allopurinol vs. both	202	RCT	Decreased calculus events
Other treatment				
Dahlberg ⁶⁷	d-Penicillamine	89	R	Decreased calculus event and dissolution of calculus
Pak ⁶⁸	d-Penicillamine or - mercaptopropionylglycine vs. conservative Rx	66	R	Both drugs are equally effective in decreasing calculus events
Griffith ⁶⁹	Acetohydroxemic acid vs. placebo	210	RCT	Decreased calculus growth

R, Retrospective; RCT, randomized controlled trial; NCT, nonrandomized controlled trial; NNT, nonrandomized, non-placebo controlled trial.

Thiazide diuretic treatment

These diuretics are commonly used medical treatments which decreases calcium excretion in recurrent calcium renal stone formers.⁷⁰ In several RCTs, the effectiveness of thiazide diuretics in significantly reducing renal calculi recurrence was demonstrated.^{60,61} There were similar results consistent with a number of open studies showing reduced renal calculi formation with thiazides.¹ The optimal effect of thiazides is achieved by a low-salt diet that attenuate urinary calcium excretion and also with sufficient potassium supplementation to avoid hypocitraturia.⁷¹ Potassium citrate usage is better than potassium chloride.⁷²

Alkali treatment

Potassium citrate is used either alone or with thiazide diuretics in recurrent calcium or uric acid stone formers. In four RCTs, three NNCT studies, and one NRCT, this treatment was shown to reduce the risk of renal calculus events. Alkali

treatment is useful in decreasing urinary calcium excretion, increasing urinary citrate, and decreasing urinary CaOx, CaP, and undissociated uric acid supersaturation.¹

Allopurinol treatment

In a RCT in hyperuricosuric calcium renal stone formers, treatment with allopurinol was shown to decrease urinary UA excretion and stone recurrence.⁶⁵ Because of the reason of multiple metabolic abnormalities which may coexist in hyperuricosuric patients, one study has shown that combined treatment with thiazide and allopurinol is more effective in reducing renal stone occurrence when compared with the usage of either treatment alone.⁶⁶

Other drug treatment for prevention of renal calculi

Although cystine solubility in urine is pH dependent, alkali treatment alone has a limited role in the management of cystine stone formers. The main treatments used in severe cystinuria (>500 mg/d) are thiol-derivatives that split cystine molecules into two cysteine which produces a highly soluble disulfide compound.⁷³ Two drugs with these mechanisms are d-penicillamine and -mercaptpropionylglycine. In four retrospective, NNCT, both drugs were shown to decrease formation of cysteine stones. Despite both drugs share many side effects, -mercaptpropionylglycine have lower incidence of adverse effects when compared with d-penicillamine.^{1,73}

Acetohydroxamic acid is the only drug chosen for the treatment of infectious renal stones which is used only if surgical removal of an infectious stone with eradication of infection with antibiotics is ineffective. It causes an irreversible

inhibition of the enzyme urease attenuating the rise in both urinary pH and NH_4^+ . Three randomized controlled studies have found decreased stone growth with this treatment.⁷⁴⁻⁷⁶ However, compliance is not satisfactory due to severe side effects.¹

Clinical Follow-Up

Follow-up treatment is achieved by an annual clinical visit which includes medical history, physical examination and also laboratory tests for full serum chemistries and urine profiles.¹

Extracorporeal Shockwave Lithotripsy (ESWL)

Evolution of shockwave lithotriptors

The Dornier HM3 which was originally designed to test parts of supersonic aircraft, was the first discovered shockwave lithotripter introduced in the United States. In spite of being somewhat dated, it is still one of the most effective and standard lithotripters to which other devices are been compared. The designing of the HM3 is based on an electrohydraulic shockwave generator where the shock waves are focused via an ellipsoid metal water-filled tub in which both the patient and the generator are submerged. Biplanar fluoroscopy is used for localization which allows placement of the calculi to be fragmented in the target zone.⁷⁷

Second-generation lithotriptors typically use piezoelectric or electromagnetic generators as the energy source. These shockwave generators commonly have a smaller focal zone when coupled with the appropriate focusing device. The smaller focal zone may minimize damage to the surrounding tissue, but during respiratory excursion, the stone may move in and out of the focal zone which may compromise

fragmentation rates. The coupling device in these lithotripter is a silicone-encased water cushion that coacts to the patient. This design greatly simplifies the positioning of patients.⁷⁷

The newest-generation lithotripters offers greater portability and adaptability. These systems often provide imaging including both fluoroscopy and ultrasonography. The ability of these newer systems to use either of the imaging modalities helps the urologist to compensate for the disadvantages of either system.⁷⁷

Most newer lithotripters have an electromagnetic generator. Electromagnetic generators and their focusing units deliver shock waves that are similar in intensity to those of the HM3, but to a smaller focal zone. This has an advantage of minimizing damage to surrounding soft tissue. But because of the smaller focal zone, the stone may move out of the target zone during respiration. Although better localization techniques and anesthesia be used to cover this, the shock waves applied when the calculi are out of the target zone do not cause fragmentation. Thus, some second and third generation machines have higher failure rates, incomplete treatment and the need for retreatment.⁷⁷

In patients who require treatment shock wave lithotripsy is a commonly used procedure for fragmenting upper urinary tract calculi. Various methods have been proposed to improve the results of this procedure, which includes proper patient selection, technique modifications, additional adjunctive therapy to ease elimination of fragments and changes in the design of the lithotripter.

Stone Size

It is well documented that, as stone size goes on increasing, SWL success rates decrease. Investigators have demonstrated that patients with renal stones > 2 cm are less likely to be rendered stone free.⁷⁸ Abdel-Khalek and associates⁷⁹ performed an analysis on 2954 patients with single or multiple radio-opaque renal stones < 30 mm who underwent SWL utilizing a Dornier MedTech MFL-5000 lithotripter. Stone size significantly impacted success of treatment. A multivariate analysis showed that, at a stone size of < 15 mm, the probability of being rendered free of stone was 1.94 times greater than for stones > 15 mm. Many other studies have clearly demonstrated that stones > 2 cm are less likely to be cleared after SWL⁸⁰

Skin-to-Stone Distance and Body Mass Index

Body mass index (BMI) and skin-to-stone distance (SSD), have been demonstrated to influence stone-free status after SWL. Pareek and associates⁸¹ performed the first study which assessed BMI as an independent predictor of outcomes of SWL. In this study, 100 patients of SWL with renal or upper ureteral stones of 5- to 10-mm who had pretreatment noncontrast computed tomography (NCCT) imaging were analyzed using binary logistic regression. A Medstone electrohydraulic lithotripter (Aliso Viejo, CA) was used, and patients were divided into stone-free or residual fragment groups. Results revealed that BMI was a significant predictor of stone-free status. The mean BMI with failed SWL was 30.8, as compared with 26.9 in those with successful treatment outcomes. Nakada and colleagues⁸² were the first to use SSD to predict success rate with SWL when they

studied 64 patients with 5- to 15-mm lower pole kidney stones treated with a Doli S lithotripter (Dornier MedTech). The investigators then measured the length from the skin to the center of the stone at 0°, 45°, and 90°; and used the average of these values as the SSD. The results illustrated that an SSD > 10 cm was a strong predictor of failure of SWL treatment. Others have demonstrated similar findings. In a multivariate analysis of 111 SWL patients with 5- to 20-mm renal stones, Perks and colleagues⁸³ illustrated that if SSD > 9 cm then it predicted failure.

Hounsfield Unit Attenuation Values and Stone Composition

NCCT measures stone attenuation which been demonstrated to impact on the results of SWL which is quantified as Hounsfield units (HU). Pareek and associates⁸¹ assessed HU attenuation values as an independent predictor of outcomes of SWL. In this study, 100 SWL patients with renal or upper ureteral 5- to 10-mm stone had pretreatment NCCT imaging and were analyzed using binary logistic regression. Here an Medstone electrohydraulic lithotripter was utilized, and later patients were categorized as stone free or having residual fragments. Stone attenuation was demonstrated as a significant discriminator with a mean HU of 910.4 in those with residual fragments and 577.9 HU in those rendered stone free. Perks and colleagues⁸³ performed a multivariate analysis including 111 patients with 5- to 20-mm renal calculi who underwent SWL with a Philips LithoTron Ultra. Stone attenuation was again shown to predict success (stone free or < 5 mm fragments); the mean value for the failure group was 1092 HU and the mean value was 837 HU for the successful treatment group. Another multivariate analysis by Wang and colleagues⁸⁴ assessed 80 adult patients with renal calculi < 25-mm who

were treated via a Philips LithoTron electrohydraulic lithotripter. Success (stone free or fragments < 4 mm) was associated with calculi HU values < 900.⁷⁸

It is clear that stone attenuation influences results with SWL. The cutpoint is not clearly defined, but a liberal estimate of 1000 HU is allowed before predicting failure. A more conservative estimate would utilize an HU value of 750. These thresholds may be impacted by the type of lithotripter used, the lithotripsy techniques employed and stone internal architecture.⁷⁸

Reducing the Rate of Shock Wave Delivery

There is in vitro, in vivo, and clinical evidence that reducing the rate of shock wave delivery enhances stone fragmentation leading to stone clearance. Vallancien and associates⁸⁵ performed in vitro studies assessing fragmentation of stones using various delivery rates of SWL of 75 to 600 shock waves per minute (SW/min) using EDAP LT-01 piezoelectric device was used. Slower shock wave delivery caused more efficient fragmentation. In another study, Weir and colleagues⁸⁶ delivered shock waves at artificial plaster stones at rates of 60, 80, and 117 SW/min using an electrohydraulic Dornier MFL-5000 in which fragmentation took significantly longer at the highest rate.

In vivo studies were conducted that again demonstrated that better fragmentation was achieved at a slower rate. Paterson and colleagues⁸⁷ implanted gypsum stones into the lower pole of swine kidney using a percutaneous approach. Later shock waves were delivered at these stones using an electrohydraulic Dornier HM3 device at rates of either 30 or 120 SW/min, a kilovoltage of 20, and total shocks of 400 shock waves were used for both rates. Fragmentation was expressed

as a percent increase in stone fragment surface area which was significantly higher at 30 SW/min ($327\% \pm 63\%$ vs $135\% \pm 136\%$).

Several clinical trials have assessed the impact of shock wave delivery rates on the outcomes of SWL. The first was reported by Robert and associates⁸⁸ in a trial where 114 patients with ureteral stones were treated with a piezoelectric EDAP LT-02 lithotripter at shock wave frequencies of 60 or 240 SW/min. The stone free rates of lower ureteral stones were greater utilizing the more rapid sequence. Madbouly and associates⁸⁹ performed a trial including 156 patients having renal or ureteral stones and participants were randomized to receive either 60 or 120 SW/min. Successful treatment was defined as stone free or fragments < 2 mm. Their data analysis showed a success rate that was 8.7% higher in the slow wave shock group, as well as a decreased total number of shock waves required for success, at the cost of a longer treatment time—all of these results were statistically significant. Other two additional trials in the following year also produced similar results. In a study with 349-patient study with two shock wave groups each receiving 70 to 80 or 120 SW/min, respectively, resulted in a 19% greater stone-free rate in the slow wave group.⁹⁰ Similarly, in another study with 134-patients, success was defined as stone free or fragments < 4 mm and revealed effective fragmentation of 65.2% in the slow group (60 SW/min) as compared with 47.1% in the fast group (120 SW/min).⁹¹ Similar to the results of Robert and associates,⁸⁸ Davenport and colleagues⁹² reported a study of 100 patients with kidney stones who underwent randomization to be treated at 60 or 120 SW/min using an electromagnetic Dornier Lithotripter S. They did not demonstrate differences in success rates as defined by a combination of stone-free status or fragments < 4 mm.⁹² However, patients in this study rather had

small single kidney stones with a mean stone area of 60 mm². Pace and associates⁹³ also found no significant difference in treatment success which was defined as fragments < 5 mm or stone-free status-using these two rates for smaller stones (< 1 cm), but success rate was 14% higher for patients with larger stones (> 1 cm) treated at a rate of 60 SW/min. Yilmaz and colleagues⁹⁴ randomized 170 patients with kidney stones to be treated with an electrohydraulic Stonelith Lithotripter (PCK Medical Systems, Ankara, Turkey) at rates of 60, 90, and 120 SW/min. Success was significantly higher (stone free or < 3 mm fragments) for those being treated at rates of 60 and 90 minutes; there was no significant difference between these latter rates of shock waves. Kimura and associates⁹⁵ included 1291 patients with either renal or ureteral stones and treated at rates of 90 or 120 SW/min using a Siemens Lithostar Multiline electromagnetic device. A significant increase in the stone-free rate at 3 months was demonstrated at the end of 3 months in those with ureteral stones treated at the slower rate, but there were no differences for those with renal stones. Semins and associates⁹⁶ performed a meta-analysis of four randomized, controlled clinical trials who utilized a fixed-effect model and found that patients who were treated with rates of 60 SW/min had a 10.2% (95% confidence interval, 3.7–16.8) high likelihood of a successful treatment outcome, which was highly significant. The limitations of this analysis included lack of uniformity among the four trials with respect to variation in stone size criteria, location of calculi, type of lithotripter, anesthesia techniques and definitions of successful treatment.

Mechanism of stone fragmentation

The mechanism behind stone fragmentation using shock waves is not entirely clear. According to the leading theories reduced shock rate improves bubble

dynamics due to reduced water and gas content surrounding the stone, decreases acoustic impedance mismatch, or optimizes the production of cavitation bubbles on the surface of stones. As early as 1989, it was shown that SWL causes the development of cavitation bubbles on the surface of stones.⁹⁷ More cavitation bubbles accumulate at the surface of the stone with increasing shock wave delivery rates and are thought to attenuate the impact of subsequent shock waves. In addition microbubbles generated with collapse of the cavitation bubbles serve as cavitation nuclei. The latter can lead to “cavitation debris or bubble clouds” which further reduce the delivery of shock wave energy.⁷⁸ Pishchalnikov and colleagues⁹⁸ supported this theory when they illustrated in in vitro studies that bubble clouds are increased with increasing shock wave delivery rates. The presence of such bubble cloud has also been demonstrated by Bailey and colleagues in a porcine model.⁹⁹ The cloud was shown to reflect shock waves and limit the collapse of cavitation bubbles.

A reduction in the shock wave delivery rate may also decrease renal damage that can occur when this energy is delivered to the renal parenchyma. In a study by Evan and associates¹⁰⁰ in a porcine model in which 2000 shock waves at 24 kV were delivered at rates of 30 or 120 SW/min using a Dornier HM3 lithotripter, hemorrhagic renal lesions involving 4.7% of the functional renal volume were present in the 120 SW/min group, whereas they occurred in just 0.08% in the 30 SW/min group. The reasons for this reduced injury with a slower rate have not been fully elucidated, but the above mentioned research group has proposed two mechanisms. The first is that a slower rate allows cavitation nuclei to be more effectively cleared from the vascular space hence thus limiting the impact of

cavitation bubble collapse and vessel rupture. The other hypothesis is that stress within the renal parenchyma can accumulate if the rate of shock wave delivery is faster than the displacement relaxation time of this tissue. The latter mechanism is possible at this increased rate and could lead to vascular damage.

The above mentioned results strongly suggest that stone fragmentation is enhanced at slower shock wave delivery rates. Therefore, a practical approach is to use rates of 60 to 90 SW/min, as this should result in improved fragmentation as compared with a more rapid delivery. Furthermore, it has the theoretical advantage of limiting renal injury.⁷⁸

Ramping Up Voltage

A strategy of ramping up shock wave energy to improve fragmentation of stone and its clearance and limit renal damage has been proposed. In vitro and in vivo studies suggest that this may be beneficial, whereas clinical results have been discordant.⁷⁸

An in vitro study demonstrated that better fragmentation of stone occurred with a ramping up sequence. Zhou and colleagues¹⁰¹ performed a study where 1500 shocks were delivered to spherical Bego stone phantoms (Bego USA, Smithfield, RI) at 60 SW/min by using an unmodified electrohydraulic Dornier HM3 lithotripter. Three different treatment strategies were utilized: increasing output voltage from 18 to 20 to 22 kilovolts (kV) every 500 shocks, decreasing output voltage from 22 to 20 to 18 kV every 500 shocks, or maintaining a constant output voltage of 20 kV. The ramping up voltage sequence resulted in the best final comminution efficiency.

In vivo studies have assessed both the impact of energy sequences on stone fragmentation and also the renal injury. Maloney and colleagues¹⁰² implanted Bego stone phantoms into the renal pelvis of 11 swine and later divided into the three following groups for treatment with a Dornier HM3 lithotripter: group 1 was subjected to 600, 600, and 800 shocks at 18, 20, and 22 kV; group 2 received 800, 600, and 600 shocks at 22, 20, and 18 kV; and group 3 received 2000 shocks all at 20 kV. The rate was maintained at 60 SW/min for all groups. The ramping up strategy used in group 1 resulted in significantly higher mean comminution efficiency, determined by percentage of stone fragments < 2 mm post treatment. Connors and associates¹⁰³ treated 19 porcine kidneys with shock waves with a Dornier HM3 electrohydraulic lithotripter at a rate of 120 SW/min using distinct protocols for three groups. Group 1 received 2000 24-kV shock waves, group 2 received 100 shock waves at 18 kV followed by 2000 shock waves at 24 kV, and group 3 was treated with 100 shock waves at 24 kV followed by 2000 shock waves at 24 kV; both pretreatment cohorts included a 3- to 4-minute protective pause. The mean hemorrhagic lesion size expressed as a percentage of renal volume was significantly smaller in both pretreatment groups compared with the group without pretreatment, whereas there was no much difference in mean lesion size between the respective pretreatment groups. The authors concluded that, although voltage ramping helps in reducing renal injury, the initial pretreatment voltage does not significantly affect the size of the renal lesion.

Demirci and colleagues¹⁰⁴ conducted the first clinical trial that studied voltage ramping in a cohort of 50 patients with kidney or ureteral stones < 20mm. Patients were randomized to receive either a constant treatment energy of 13 kV or

increasing output voltage every 500 shocks at 11, 12, and 13 kV, respectively. The rate of shock wave delivery rate was not reported by these investigators. All SWL was performed using a Dornier Compact Delta electromagnetic lithotripter and were treated with a total of 3000 shock waves per patient in each group. The stone-free rate was found to be significantly higher in the stepwise treatment group (96% vs 72%). A drawback of this study was that a significant number of subjects in both groups underwent multiple treatment sessions of SWL. In addition, secondary stone removing procedures were performed more routinely in the stepwise treatment group. Lambert and colleagues¹⁰⁵ prospectively randomized 45 patients with renal calculi to receive SWL for renal stones (median size 8 mm) with an escalating strategy of 500 shocks at 14 kV, 1000 at 16 kV, and 1000 at 18 kV, or a conventional strategy of 2500 shocks at 18 kV. A Dornier Doli 50 electromagnetic lithotripter was utilized. The shock wave delivery rate of both groups was 60 to 80 per minute. A significantly higher stone-free rate at 1 month was noted in the escalating voltage group (81% vs 48%). In addition to this, urinary microalbumin and 2-microglobulin levels, indices of renal injury, were significantly decreased 1 week postoperatively in the escalating voltage group, suggesting a renoprotective effect with voltage ramping.

Explanations have been proposed regarding as to why a ramping-up strategy may optimize fragmentation and limit renal injury. If there is a high energy delivered to the stone initially, fragmentation is quite efficient leading to formation of several small stone fragments that accumulate in front of the remaining stone mass, potentially attenuating the ensuing shock waves. This barrier can be overcome by increasing energy output at the end of treatment as with a ramping-up sequence.

A gradual increase in energy may enhance cavitation and its synergistic interaction with stress waves. The renoprotective effects of pretreatment is due to an increase in the renal vascular resistive index which is thought to be induced by constriction of renal blood vessels.⁷⁸

With a ramping-up strategy there may be stone fragmentation benefits, but the strength of evidence for this is less than that for slower shock wave delivery rates. Further there is a need for better-designed studies to determine if this is a beneficial strategy. A practical approach to such strategies is suggested. There is little downside to delivering a pretreatment dose, delaying further shock wave delivery for 3 minutes, and proceeding with shock wave delivery, as this strategy may be renoprotective. Many patients who undergo SWL under intravenous (IV) sedation are currently being treated using a dose escalation strategy, and this should not be altered.⁷⁸

Anesthesia

It has been suggested that modality of anesthesia used may influence SWL outcomes. Eichel and associates¹⁰⁶ assessed a population of 370 patients with renal or ureteral stones treated in a span of 6-month span with a Dornier Doli U50 electromagnetic lithotripter; 49% of patients in group 1 received IV sedation, whereas all patients in group 2 received either general or regional anesthesia. On comparison of success rate of SWL which is defined as stone free or fragments < 3 mm, it revealed a significantly higher success rate in group 2 (78% vs 51%). Similarly, Sorensen and colleagues¹⁰⁷ reported a study of 295 patients with renal or upper ureteral stones < 2 cm. They were treated with a Dornier Doli U50

electromagnetic lithotripter. The patients either underwent IV sedation (92 patients) or general anesthesia (203 patients). At 3 months, the stone-free rates after SWL were significantly higher in the general anesthesia group (87% vs 55%).⁷⁸

It is possible that some of the differences between IV sedation and general anesthesia can be explained by a greater variability in patient response to IV sedation. Specifically, it is possible that IV sedation could provide insufficient analgesia which results in decreased patient cooperation, erratic breathing, and further inaccurate stone localization. Several studies have been performed, therefore, to provide strategies for optimizing IV sedation during SWL, with variable techniques and results. But utilizing these techniques, however stone fragmentation outcomes have not been reported.⁷⁸

Studies have demonstrated that a stone during respiration may move up to 50 mm which may impact SWL efficacy. An in vitro model mimicking respiratory stone motion showed a significant reduction in stone comminution with movement of stone as small as 10 mm; in fact, stone motion can result in up to 75% of shock waves missing the stone entirely.⁷⁸ Sorensen and colleagues¹⁰⁸ conducted an analysis of 10 patients who underwent SWL for treatment of 13 renal stones with a mean size of 10.5 mm (range, 5–18 mm) which used either a Healthtronics LithoTron electrohydraulic lithotripter (Healthtronics, Atlanta, GA) or a Dornier Compact Delta II electromagnetic lithotripter. Diagnostic ultrasonography was used to record images of the stone during treatment. Two independent observers reviewed ultrasound videos and determined shock wave accuracy which was defined as the proportion of shock waves that resulted in stone motion and also respiratory stone motion. It was found that $60\% \pm 15\%$ of delivered shock waves were accurately

delivered to the stone and the average respiratory stone motion was 1.5 ± 0.3 cm. Image-based renal stone tracking software which automatically adjusts lithotripter targeting during shock wave treatment has been developed, but this technology has not been adapted or promoted.¹⁰⁹ There are modifications of general anesthesia that have also been utilized in an attempt to limit respiratory stone motion. Mucksavage and coworkers¹¹⁰ studied a cohort of 112 patients who underwent SWL with conventional anesthesia or high-frequency jet ventilation (HFJV) and was found that the HFJV group needed significantly fewer shocks and total energy to achieve comminution.

It was believed that the utilization of general anesthesia during SWL may promote better targeting and efficient fragmentation when a third-generation lithotripter is used. Increased respiratory motion hampers shock wave delivery, and strategies such as tracking software and HFJV are being assessed to solve these concerns. It is hoped the further development of the newer stone tracking technology will improve SWL outcomes which can be implemented into clinical practice.⁷⁸

Coupling Techniques

Numerous studies have documented that first-generation Dornier HM3 may be more effective as compared to second- and third-generation lithotripters. Several of these studies explain this discrepancy by the fact that first-generation lithotripters were run by immersing both the patient and the head of the lithotripter in a water bath, which provides an excellent medium for the transmission of acoustic energy. Comparatively, although the newer lithotripters are smaller, more transportable devices but they utilize a dry shock wave delivery head which is not immersed in

water. There is evidence that lithotripter shock waves essentially do not propagate through air. In fact, more than 99% of a shock wave is reflected by an air pocket. For this reason there is a necessity to eliminate air between the head of the lithotripter and the patient using a coupling agent, ultimately providing a medium for shock wave transmission to the targeted calculus.⁷⁸

Due to these facts, when the second- and third-generation lithotripters were first used, various coupling mediums were utilized, including creams, petroleum jelly, castor oil, ultrasonography gel and other water-soluble lubricating jellies. Studies in the late 1990s mentioned the use of several types of media which were used as both coupling agents and topical anesthetics.⁷⁸ Cartledge and coworkers¹¹¹ performed an in vitro study which compared five different contact media to determine if coupling agents affected the number of shock waves required for stone fragmentation. According to their results a commercial water-soluble lubricating jelly required the least number of shock waves to achieve fragmentation to particles < 2 mm. EMLA (eutectic mixture of local anesthetics) cream and petroleum jelly needed a significantly greater number of shock waves compared with the other media utilized.

Subsequent studies on SWL coupling demonstrated that air pockets trapped within the coupling media can significantly reduce the transmission of acoustic energy, thus providing a mechanism for the divergence in outcomes between coupling agents. Pishchalnikov and coworkers¹¹² demonstrated this effect when they observed and photographed air pockets trapped at the coupling interface between a Dornier Doli U50 electromagnetic lithotripter and a test tank covered by a polyester membrane. Throughout their experiment, a commercial coupling gel (LithoClear;

NEXT Medical Products, Bellingham, WA) was used. The authors demonstrated that the coupling produced air pockets ranging from 1.5% to 19% of the coupling surface area, causing approximately 20% mean decrease in amplitude of shock waves. Also, air pockets covering about 2% of the coupling area decreased stone fragmentation by 20% to 40%. The process of decoupling and recoupling, simulating patient repositioning, reduced transmission of acoustic energy by 57%. Similarly, Jain and Shah¹¹³ used high-resolution photographs to demonstrate that decreased bubble contents of gel increased depth and volume of stone craters significantly in vitro ($p < 0.001$). The implications of these studies is that inferior acoustic coupling results in ineffective stone fragmentation, which places the patients at increased risk for renal injury if they received higher shock wave dosages.⁷⁸

In light of the above mentioned conclusions, it can be taken that the technique of applying coupling gel may impact fragmentation. Neucks and associates¹¹⁴ used digital imaging to find out coupling defects to determine the best methods for gel application, when they found that the best technique was to use a large amount of gel directly from a stock jug onto the lithotripter water cushion, as opposed to gel application by hand. Then the gel was allowed to spread during inflation of the lithotripter water cushion. The above mentioned techniques resulted in significantly fewer coupling defects compared with application of gel by hand, but clinical application of these techniques could prove difficult. They also found that the coupling interactions at the central portion of the water cushion are the most important.¹¹⁵

A surveillance mechanism could help in finding out followed by elimination of air pockets, thereby helping in optimizing coupling during SWL treatment. Bohris and associates¹¹⁶ showed the usefulness of this strategy who used a video camera integrated into a Dornier Doli SII lithotripter to find air pockets in coupling gels during SWL. They used three different coupling gels including LithoClear, Sonogel (Sonogel Vertriebs GmbH, Bad Camberg, Germany) and a low viscosity custom-made gel. Air ratios in the coupling area were measured in each coupling gel and lithotripter fragmentation was assessed at varying air ratios. They showed that the mean total number of shock waves required for effective stone fragmentation increases with increasing air ratios. Furthermore, when the custom-made low viscosity gel was used less air was produced within the coupling medium. These findings suggest that usage of surveillance mechanisms monitoring for defects in coupling gels and refinements of such products may improve the results of SWL.⁷⁸

Facilitating Fragment Passage

α_1 -Antagonists

Medical therapy with α_1 -blockers may help in clearance of fragments after SWL. K peli and colleagues¹¹⁷ performed a trial including 48 patients with distal ureteric calculi 5- to 16-mm in size who were randomized to undergo SWL without or with adjuvant tamsulosin for 15 days after treatment. The stone-free rate was significantly higher in the second group i.e. those receiving tamsulosin—70.8% versus 33.3%, respectively. Gravina and colleagues¹¹⁸ studied a cohort of 130-patient with renal stones 4- to 20-mm in diameter who had a single SWL session. Patients were randomized to receive methylprednisolone 75 mg and diclofenac or

the same agents combined with tamsulosin for a maximum of 12 weeks. Patients with stone-free rates i.e. fragments < 3 mm was significantly higher in the tamsulosin group (78.5% vs 60%).⁷⁸

The aforementioned studies suggest that α -blocker therapy is useful adjunct for patients who undergo SWL. Potential benefits of this include bolstering stone-free rates, quicker expulsion, and lowering of analgesic requirements.⁷⁸

Percussion, Diuresis, and Inversion

The stone fragments in the lower pole are thought to clear less effectively after SWL. The technique of percussion, diuresis, and inversion (PDI) is been used for the clearance of lower pole stone fragments following SWL. D'a Honey and colleagues¹¹⁹ conducted a study of 12 patients with residual lower pole stone fragments \leq 2 mm at a mean of 37 days following SWL. PDI was performed with the following methods: patients were given 20 mg of furosemide and then placed in the prone Trendelenburg position on a pivoting stretcher. Later they were given 10 minutes of percussion over the flank using a mechanical chest physiotherapy device. Five patients who underwent this were rendered stone free after a single PDI treatment. Later the same authors subsequently performed an expanded cohort trial employing a crossover design which consisted of 69 patients with lower calyceal fragments \leq 4 mm at 3 months following SWL. The 69 patients were randomized to receive PDI using the above mentioned technique weekly for 1 month or until rendered stone free versus observation. A significantly higher stone-free rate was demonstrated in the PDI group (40% stone-free vs 3%). The control patients with

remaining stones were then subjected to the same PDI treatment, which resulted in a similar stone fragment clearance rate.⁷⁸

The aforementioned results suggest that PDI may facilitate clearance of stone fragments which remains in the lower pole after SWL. Therefore, it may be proposed to such patients and theoretically could be supplemented with α -blocker therapy.⁷⁸

Focal Zone Width

One of the many differences between the second- and third-generation lithotripters and the Dornier HM3 is that many of the newer devices have a narrower acoustic energy focal zone, which results in more focused and often higher pressure shock waves. A number of experimental studies, including mechanistic assessments in vivo and randomized controlled trials, have been performed to know the potential effects of focal zone variation on stone fragmentation and renal injury.⁷⁸

The generation of shear waves external to the stone from the shock wave as it passes through fluid is thought to play an important role in stone breakage. Cleveland and Sapozhnikov¹²⁰ and Sapozhnikov and colleagues¹²¹ used mathematical modeling to demonstrate this phenomenon. They demonstrated that these shear waves were significantly more powerful than the spall effect. As the focal zone of the lithotripter reduces, the intensity of these shear waves decreases. Subsequent investigations by this group using a Dornier HM3 lithotripter and artificial stones demonstrated that these shear waves generate the greatest stress on the stone.⁷⁸

Renal injury as demonstrated in the animal experiments is more prominent with narrow focal zone devices. Connors and associates assessed renal parenchymal hemorrhage after the delivery of shock waves to the porcine kidney using either a Dornier HM3 or Modulith SLX device (Karl Storz Lithotripsy-America, Kennesaw, GA). The latter lithotripter caused more intense renal injury which focused mainly in the cortex and medullary areas.⁷⁸ Evan and colleagues¹²² compared a new device, the XX-Es lithotripter (Suzhou XiXin Medical Instruments, Jiangsu, China) (wide-focus, lowpressure, electromagnetic), with the Dornier HM3 in a porcine model where gypsum stones were implanted into the lower pole. The results between the two groups were similar with regard to renal injury and hemodynamic function. Fewer shock waves were needed to comminute the stone using the XX-Es device. This illustrates that this new device may yield similar results to those achieved with the gold standard wide focal zone lithotripter, the Dornier HM3.

Clinical studies of wide and narrow focal zone lithotripters demonstrate that the former devices appear to yield better results. Eisenmenger and associates¹²³ conducted a study assessing the effectiveness of a novel wide-focus, low-pressure lithotripter in which a total of 297 patients were treated with this device and 86% were stone free at 3 months; no other additional procedures for stone clearance were performed. In addition to this, the patients did not require general or regional anesthesia and only three were administered IV sedation or analgesia. Gerber and associates¹²⁴ conducted a study in which patients with kidney stones were either treated with a Dornier HM3 device (largest focal zone), Siemens Lithostar Plus (intermediate focal zone) or Modulith SLX (smallest focal zone). Although there were no differences in ultimate stone-free rates between these three devices at 3

months, the HM3 device was associated with the lowest retreatment rate and the Modulith SLX with the highest. Dhar and associates,¹²⁵ conducted a study in which 4.1% of patients treated with a narrow focal zone lithotripter, Modulith SLX, had a subcapsular or perinephric hematoma, suggesting that these devices may cause more renal injury compared to wider focal zone devices in which significantly lower rates have been reported.

The aforementioned findings suggest that wider focal zone lithotripters may be more effective and produce less tissue injury than narrow focal zone/high energy devices. There is a need for prospective randomized studies to determine if this is truly the case.⁷⁸

Dual-Heal Lithotripters

Dual-pulse lithotripters have been developed to improve the effectiveness of stone comminution and to reduce renal damage. The majority of work has been done in vitro and in vivo and a limited number of clinical studies have been reported.

In 2001, Sokolov and colleagues¹²⁶ designed a dual-pulse lithotripter which was compared with a conventional single-head lithotripter in an attempt to localize and intensify cavitation damage in vitro using twin lithotripter pulses. They used a high-speed digital video camera which recorded the cavitation fields produced in water on aluminum foil. The dual-pulse lithotripter was set up such that the two shock wave sources faced each other and were triggered simultaneously to create a confocal 4 cm × 5 cm cylindrical cloud of cavitation bubbles. Here a focused hydrophone was used which measured bubble growth and collapse. The authors observed that compared to the conventional lithotripter synchronous arrival of twin

pulses increased bubble growth and increased foil pit depth (a measure of cavitation). A commercially developed dual-headed, Duet lithotripter (Direx Medical Systems, Petach Tikva, Israel), was developed. Greenstein and colleagues¹²⁷ assessed the ability of this device to fragment gypsum stones using single-pulse and dual-pulse modes in which they demonstrated a decreased number of shocks required for complete fragmentation in the dual-pulse mode.

In vivo porcine studies have been conducted to assess the impact of tissue damage with these devices. Sheir and associates¹²⁸ used a Twinheads dual-pulse lithotripter (FMD, Lorton, VA) to treat 20 porcine kidneys operating in single- or dual-pulse modes where they found that the kidneys receiving dual-pulse treatments had minimal histologic damage, whereas injury was substantially more with the single-pulse group. In another study in a porcine model by Handa and colleagues¹²⁹ to assess renal injury generated by the Duet and Dornier HM3 devices, histologic injury and renal functional responses were similar. The same group also employed the Duet lithotripter to treat U30 gypsum stones implanted into porcine kidneys using a synchronous or asynchronous mode and where they found that fragmentation and renal functional responses were similar.⁷⁸

Sheir and associates¹³⁰ presented the results of the first clinical study on synchronous dual pulse SWL utilizing the Twinheads lithotripter in a group of 50 patients with renal or upper ureteral stones (mean stone size = 12.3 mm); in this treatment, 74% of patients were stone free or had residual stones of 5 mm. A total of 26% of subjects underwent a repeat treatment after 14 days following which the stone-free rate was 100% at 1 month. The same group then compared both the Twinheads lithotripter with the Dornier Lithotripter S (single generator) in 240

patients with solitary renal stones < 25 mm. Patients were evaluated with MRI and urinary enzyme studies pre and post treatment. They found stone-free rates were similar in both groups whereas renal hematomas were only present in the single-generator group. Urinary enzyme (markers of renal injury) levels were increased in both groups but earlier normalization was seen in those treated with the Twinheads device. Thus, although some of the aforementioned studies suggest that twin-pulse lithotripsy may have some benefits, more studies are needed to demonstrate the efficacy of this technology.⁷⁸

There are many ways to improve results with SWL. Patient selection is very important and factors to be considered include stone size, BMI, stone attenuation measured by NCCT, and SSD for renal stone cases. Also by modifying lithotripsy technique success rate can be increased. There is strong evidence that performing SWL at a low delivery rate improves results of SWL, whereas the benefits of a ramping-up strategy are less clear. Anesthetic technique may impact results like general anesthesia may result in better targeting and fragmentation. Real-time monitoring of stone position is technically possible and feasible and it has increased scope in the future. If this technology is introduced as a component in future devices, targeting and fragmentation will also improve. Measures to assure proper coupling may also be beneficial. A technical modification that should be considered for rebirth is to use lithotripters with wide shock wave focal zones. Although dual-head lithotripsy offers some theoretical benefits, more clinical trials are needed to assess their real utility. Finally, other adjunctive measures should be considered, such as α -blocker therapy, to promote expulsion of renal and ureteral stone fragments and also physiotherapy to assist passage of lower pole stone fragments.

The implementation of these strategies in appropriate patients should facilitate more effective stone comminution and fragment expulsion, thereby optimizing shock wave therapy.⁷⁸

- Stone size, skin-to-stone distance (SSD), and body mass index all play a vital role on patients stone-free status after shock wave lithotripsy (SWL). Patients with stones > 2 cm are less likely to be rendered stone free. Results also illustrated that an SSD > 10 cm was a strong predictor of failure of SWL treatment.
- There is in vitro, in vivo and clinical evidence that decreasing the rate of shock wave delivery enhances fragmentation and thus ease stone clearance. A reduction in the shock wave delivery rate may also reduce renal damage that can occur when this energy is delivered to the renal parenchyma. A practical approach is to use rates of 60 to 90 SW/min.
- Utilization of general anesthesia during SWL may promote better targeting of stones and efficient fragmentation when a third-generation lithotripter is used; increased respiratory motion compromises shock wave delivery.
- -Blocker therapy may be a useful adjunct for patients undergoing SWL. Its usage have benefits including bolstering stone-free rates, quicker expulsion, and lowering of analgesic requirements.
- Animal experiments have demonstrated that renal injury is more prominent with narrow focal zone devices. Wider focal zone lithotripters may be more

effective and produce less tissue injury than narrow focal zone/high-energy devices.

Complications of ESWL¹³¹

Complications after ESWL for urinary stones¹³¹

Immediate	Delayed
Related to stone fragments	Renal functions?
Infectious	Hypertension?
Tissue effects	Fertility?
<ul style="list-style-type: none"> • Renal (haematoma, haemorrhage) • Cardiovascular • Gastrointestinal • Genital system • Foetus 	

Complications of ESWL related to stone fragments¹³¹

Possible predisposing factors	Possible prevention measures
Hard stones	Alternative therapy for hard and large stones (PCNL, sandwich therapy)
Large stones	Stenting when treating large Stones
Lower pole stones Increase number of stones Impaired renal anatomy Increased shock wave rate Decreased shock wave energy	Improve ESWL efficacy

Renal complications

Renal complications is divided into early complications that effects the kidney anatomy leading to haematuria and haematoma formation, and late complications affecting kidney function and cause systemic hypertension.¹³¹

Possible renal effects of ESWL¹³¹

Effect	Possible predisposing factor	Possible prevention measures
Acute Damaged to vascular endothelium Damage to nephron, renal tubules, and interstitium Loss of corticomedullary demarcation Increased excretion in urine of metabolites indicating renal damage Haematuria Haematoma Decreased in GFR Decreased in effective RPF	Pre-existed hypertension Pre-existed renal disease Increased shock wave number, rate and energy Increased patient age	Use of different types of lithotripter Decrease shock wave number , rate, and energy Use of two shock-waves tubes Delivery of tow shock-waves at carefully timed close intervals
Chronic New onset of hypertension? Perirenal Fibrosis Loss of renal function	Increased shock wave number, rate and energy Increased patient age	Decrease shock wave number , rate, and energy

Immediately following ESWL histopathological examination of the kidneys (human and animal) demonstrated endothelial cell damage of midsized arteries,

veins and glomerular capillaries. Thin-walled arcuate veins present in the corticomedullary junction are especially vulnerable to shock wave exposure which leads to haematuria and haematoma formation. The lesion is usually a focal process and most of the renal parenchyma remains unaffected.¹³¹

ESWL-induced acute renal damage may cause severe injury to the nephron microvasculature alongwith the surrounding interstitium. Renal tubules and vessels are more vulnerable compared to the renal blood flow to the discharged energy. These injuries may be responsible for long-term effects of ESWL on renal function.¹³¹

4.2. Effects on renal anatomy

Gross haematuria is the most common clinical manifestation of renal trauma that resolves in few days. Symptomatic intrarenal, subcapsular or perirenal fluid collections and haematomas are rare which occur in <1% of patients who undergo ESWL. But, when computerized tomography or magnetic resonance imaging is performed post ESWL, the haematoma rate may increase to 20%–25%.¹³¹

The percentage of haemorrhage and haematomas differ with the type of lithotripter used. The HM3, which utilizes electrohydraulic energy, delivers more energy per shock wave leading to more renal trauma than the Lithostar Plus machine which uses an electromagnetic source. The Lithostar is apparently thought to exert a greater pressure on the renal capsule, which may result in the greater incidence of subcapsular hematoma in comparision to EDAP LT-01 piezoelectric machine. Important risk factors for higher chances of hematoma formation are bleeding diathesis, the use of anti platelet drugs, hypertension, obesity, diabetes mellitus and

the number/intensity of shock waves. In case of electro hydraulic lithotripsy none of the above factors have been consistently proved to be a risk, but hypertension remains a plausible factor. The probability of hematoma formation increased significantly as patients age increased during electromagnetic lithotripsy, but it was not associated with increasing mean arterial pressure or any other factor. Hematomas are treated conservatively in most cases and the most likely outcome of conservative management is spontaneous radiographic resolution of the hematoma in a span of two years without clinically evident adverse effects either on blood pressure or renal function. However, a reduction in renal blood flow has been reported which is associated with acute renal failure and hypertension when there is involvement of both the kidneys or in patients with a single kidney. These high-risk patients should have regular followup.¹³¹

Renal function after ESWL

Immediately after ESWL biochemical evidence of renal injury is apparent. Blood and urine markers such as renin, creatinine, N-Acetyl-b-D-glucosaminidase (NAG), b-2-microglobulin (B2M), b-galactosidase (BGAL) and proteinuria return to near normal levels in a span of few days. Urinary studies on animals and humans show a reduction of glomerular filtration rate (GFR) and renal plasma flow immediately following ESWL, especially when there is coexisting pyelonephritis. However, post ESWL GFR is not affected over the long-term and immediate effects appears to resolve over few days to few months. Renal function is not affected when ESWL is applied to specific clinical situations. Definitive treatment for calculi after relieving the obstruction in patients having renal insufficiency further improves renal function. In the literature, there are several conflicts about the possibility of the

adverse effect of shock waves on growing kidneys of children. Significant alterations of growth in children's kidney after ESWL were shown in a long-term study, although the authors could not determine whether these alterations in the kidney were secondary to the ESWL treatment or due to some underlying conditions that were present intrinsic to pediatric kidneys with renal calculi.¹³¹

Shock wave energy induces transient functional damage to tubular function in children. The vasoconstriction in the renal vessels induced by ESWL is greater in small kidneys than in bigger ones. On the other hand, on assessment of long-term effects of ESWL on GFR in children using renal scintigraphy showed no significant reduction in mean ipsilateral and total GFR. Some other long-term follow-up studies could not show any parenchymal damage in children following ESWL. These studies supports the concern about potential damage to epiphyseal growth centres in children but no long-term skeletal deformities to date having been reported.¹³¹

There is proof that shock wave lithotripsy injury to the kidney is reduced by suppressing the cavitation. By decreasing the voltage and number of shocks the deleterious effect can be minimised.¹³¹

Acute renal injury (ARI) is one of the problem after ESWL. Early recognition could help clinical management, but recent indices lack sufficient predictive value for ARI. Therefore, there is need for biomarkers which detects renal and/or dysfunction at an early stage before glomerular filtration rate declines as noted by raised serum creatinine.¹³¹

Acute kidney injury (AKI), is commonly defined as an abrupt decline in renal function, clinically manifesting as a reversible acute increase in nitrogen waste

products measured by blood urea nitrogen (BUN) and serum creatinine levels over the course of hours to weeks. Several classification systems have been developed to define AKI.¹³² These include

RIFLE classification - Risk, Injury, Failure; Loss; and End-stage kidney disease.¹³³

Acute Kidney Injury Network (AKIN)¹³⁴

Kidney Disease Improving Global Outcomes (KDIGO)¹³⁵

Since its appearance at the beginning of the 1980s, extracorporeal shock wave lithotripsy (ESWL) is considered as the least invasive and the most widely used treatment of renal and ureteral stones and also in acute conditions. Naturally, as like in any other treatment, ESWL is indeed accompanied by some side effects and complications along with its efficacy. Despite being generally mild in nature, it requires a proper evaluation and implementation of measures to prevent them. For example is the flank pain during the procedure, which is actually not to be considered as a complication, but as an undesired side effect for which the patient may ask for the interruption of the treatment. The protocol of the procedure to include an analgesic prophylaxis and therapy with opioids anagesics or NSAID's drugs were both evaluated.¹³⁶

ESWL in essence, is not altogether benign, but rather it may cause lesions to kidneys and/or its neighbouring organs. Also, even a technically successful lithotripsy may cause subsequent morbidity due to related fragmented products. So a few contraindications do actually exist. These are (i)pregnancy; (ii)uncontrolled urinary tract infections; (iii)Deranged coagulation profile; (iv)aortic or renal artery aneurysm; (v)serious skeletal malformations; (vi)serious obesity.¹³⁶

The primary aim of an SWL is the breakage of stones and asymptomatic elimination of fragments. Due to incomplete fragmentation this procedure may not always be completely successful, with residual fragments of a significant size causing ureteral blockage by fragments (Steinstrasse) which results in obstruction to the urinary flow.¹³⁶

To illustrate this, the formation of fragments post ESWL of <4 mm is present in up to 59% of the cases, with a risk of a symptomatic episode, requirement of operation or even both, equal to 43%.¹³⁶

Factors responsible for the success of lithotripsy and therefore real risk factors leading to SWL failure are the composition, volume, site, number of stones and the frequency/strength of the shock wave.¹³⁶

The stones made of Struvite, uric acid and dehydrated calcium oxalate tend to break into tiny parts that may be easily passed. Whereas on other hand, dehydrated calcium phosphate stones (brushite) and monohydrate calcium oxalate stones usually produces larger fragments which are much difficult to pass. Cystine stones are particularly difficult to treat which, like any organic compound, has acoustic features matching to the surrounding tissues.¹³⁶

The success rate of SWL treatment is related to the volume of the stones being treated. For stones <2 cm, the percentage of success achieved which is considered as “stone free rate,” is in the range of 66–99%, which drops to 45–70% for calculi of 2-3 cm and even further again for staghorn calculi.¹³⁶

Moreover, stones >2 cm almost always require multiple treatments and have a tendency to shatter incompletely with a greater risk of complication with incidence

of partial obstruction between 19–50%. In some cases, it is size alone which determines treatment success like after an SWL, cystine stones <15 mm shatter in 71% of cases; if the size of the stone is >20 mm, the success rate drops to 40%.¹³⁶

For this reason, for cystine stones >15 mm SWL as a monotherapy is currently not recommended.¹³⁶

The most evident finding of kidney trauma is haematuria which generally resolves in a few days.¹³⁶

Symptomatic perirenal, subcapsular, or intrarenal hematomas are meagre and occurs in less than 1% of patients but if patients have systematically undergone a CT scan or MRI then incidence of hematoma rises to 25%. Other lesions as shown in X-rays in most patients is an increase in the volume in the kidney, loss of corticomedullary demarcations and a reduction in the signal in the perirenal fat. These signs mark the presence of lesions such as hemorrhages, generally focal and oedema in and around the kidney. Perirenal collections usually disappear in few days, whereas subcapsular ones takes between 6 weeks and 6 months. It is rare to see lesions later for any longer than that.¹³⁶

A microscopic examination shows up characteristic lesions: hemorrhagic lesions are usually present in the corticomedullary joint, probably due to changes in the density of the tissue at that level and also signs of damage are immediately visible from the thin vascular walls and the glomeruli. Hemorrhage leads to tissue hypoxia, which can play a role in the development of apoptosis, but it has been experimentally shown that shock waves administration does not affect the apoptosis index in normal rats if >2000 and 4000 shock waves are used and after 1-2 weeks

signs of reorganisation may be noticed, while after 1 month signs of glomerular atrophy and sclerosis are noticeable in tiny areas of fibrosis. However, most of the parenchyma appears normal, which means that damage due to SWL is a focal process that leaves most of the parenchyma intact. A short pretreatment with 10–20 shockwaves could further on reduce the risk of renal tissue damage, probably due to a reflex local vasoconstriction.¹³⁶

A MEDLINE/PubMed search was performed, including all articles about biomarkers for ARI. All publication types, human and animal studies, or subsets were searched in English language. An extraction of relevant articles was made for the purpose of this narrative review. These biomarkers include tubular enzymes (alpha- and pi-glutathione S-transferase, N-acetyl-glucosaminidase, alkaline phosphatase, gamma-glutamyl transpeptidase, Ala-(Leu-Gly)-aminopeptidase, and fructose-1,6-biphosphatase), low-molecular weight urinary proteins (alpha1- and beta2-microglobulin, retinol-binding protein, adenosine deaminase-binding protein, and cystatin C), Na⁺/H⁺ exchanger, neutrophil gelatinase-associated lipocalin, cysteine-rich protein 61, kidney injury molecule 1, urinary interleukins/adhesion molecules and markers of glomerular filtration such as proatrial natriuretic peptide (1-98) and cystatin C. These biomarkers are either detected in urine or serum shortly after tubular injury and have been suggested to contribute to prediction of ARI. However, excretion of these biomarkers may also increase after reversible and mild dysfunction. It may not always necessarily be associated with persistent or irreversible damage. Large prospective studies in human are needed to demonstrate an improved outcome of biomarker-driven management of the patient at risk for ARI.¹³⁷

In a study done by Demir, E. et al.¹⁵ immediate and long term high levels of plasma homocysteine after extracorporeal short wave lithotripsy in patients with renal stone disease, after first-time ESWL, the increase in serum levels of creatinine and tHcy due to renal injury, such as ischemia/reperfusion injury, may be severe and continue for a long period, such as 3 months. According to baseline levels, the increase in homocysteine levels as an indicator of oxidant stress was more severe than the creatinine levels after ESWL for renal stones. Patients were first-time ESWL patients in this study; however, in patients who undergo EWSL more than once long-term high tHcy levels should also be considered as renal.¹⁶

In a study done by Arnadottir M et al.¹³⁸ A dramatic decrease in glomerular filtration rate (GFR) was reported during the first few hours after ESWL for renal stones. It was also found that plasma tHcy levels were negatively correlated with GFR. Infact ,impaired renal function may be the most important determinant of tHcy concentration in plasma.(3)

In a study done by Al-Marhoon MS et al.¹³⁹ Siemens Modularis Vario lithotripter is a safe and effective tool for treating renal and ureteric stones.

METHODOLOGY

The present study was conducted in the Department of General Surgery and Department of Urology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015.

Study design and duration

The one year study design was a cross-sectional study.

Study period

This study was done from January 2015 to December 2015.

Place

The present study was carried out in the Department of General Surgery and Department of Urology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi a tertiary care teaching hospital attached to KLE University's Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Patients undergoing ESWL for renal stones were included in the study.

Sample size

The study sample was comprised of 64 patients undergoing ESWL.

Sampling procedure

Patients fulfilling the selection criteria undergoing ESWL during the study period were advised to participate in the study over a period of one year. The sample size for the study was determined by following formula

$$n = 4pq/d^2$$

Where, n is sample size

p is prevalence (50)

q is 100 – p (100-50 =50)

d is absolute error (12.5%)

$$n = 4 \times 50 \times 50 / 12.5 \times 12.5 = 64$$

Hence a minimum sample size of 64 was considered for the study.

Selection criteria

Inclusion

- Patients aged between 24 to 61 years.
- Patients undergoing ESWL in first sitting and was used as only modality of treatment.

Exclusion

- Pregnant patients.
- Patients with baseline renal impairment who developed post ESWL complications such as ureteric obstruction or sepsis that required further intervention.

- Stone or calculi >2 cm.
- Patients with chronic kidney disease and ARF.
- Patients with blood coagulation disorders.

Ethical clearance

Prior to the commencement, the Ethical Clearance was obtained from the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

Patients fulfilling selection criteria were briefed about the nature of study and a written informed consent was obtained (Annexure I).

Method of collection of data

The demographic data such as age and sex, presenting complaints were noted. The patients were subjected to clinical examination and vitals were noted. The systemic examination was done. These findings were recorded on a predesigned proforma (Annexure II).

Investigations

Patients were subjected to the following routine investigations pre ESWL.

- Complete blood count
- Mini renal test
- Liver function test

- Urine routine and microscopy
- HIV and HBsAg
- ECG
- Chest X-ray

Patients were subjected to the following investigations pre and post ESWL i.e 24 hours before and 24 hours after ESWL and fasting samples were collected.

1. Plasma Total Homocysteine (tHcy)

EDTA anticoagulated blood is used for measuring Plasma total homocysteine. Plasma total homocysteine levels were estimated by Automated Architect Immunoassay Analyser. Plasma total homocysteine levels between 5.9 to 16 micromol/L was regarded as normal.¹⁴⁰

2. Serum High Sensitivity C Reactive Protein (hs-CRP)

hs-CRP levels were estimated on Automated DADE Dimension RXL Analyser. hs-CRP levels between 0 to 3 mg/dL was regarded as normal.¹⁴¹

3. Serum creatinine

Serum creatinine levels were estimated on Automated DADE Dimension RXL Analyser. Serum creatinine levels between 0.5 to 1.4 mg/dL was regarded as normal.¹⁴²



Photograph 3. X-ray KUB showing left renal calculus in the lower pole



Photograph 4. USG KUB showing a calculus in the renal pelvis of right kidney

Plain blood is used for s.creatinine and s.hs-CRP measurement. The above three markers are measured 24 hrs before (i.e. baseline values) and 24 hrs after ESWL and noted for rise in the level.

The stone diameter was measured by either X-ray KUB, USG KUB or plain CT KUB.

ESWL

Patients were hydrated thoroughly before, during and after ESWL. All the ESWL were carried out using Siemen's modularis lithotripter either under local anaesthesia using gel or under IV sedation (Fentanyl/propofol/Morphine/Ketamine).

The procedure was done under supine position. In most cases a combination of USG and fluoroscopy was used to target the calculi. According to the Department's protocol, therapy was commenced at low power and gradually increased during lithotripsy based on the stone fragmentation. The shock rate was set at 60 /minute. Maximum shocks delivered was adjusted to 3000 per sitting. Total number of shocks used per sitting was adjusted to achieve satisfactory fragmentation of calculus. The procedure was terminated if maximum shocks delivered reached 3000 without satisfactory fragmentation.

Outcome variables

Patients were monitored for the development of acute renal injury which was considered based on RIFLE criteria as two fold rise in serum creatinine from the baseline value after ESWL and risk was considered as 1.5 fold rise in serum creatinine from the baseline value after ESWL.

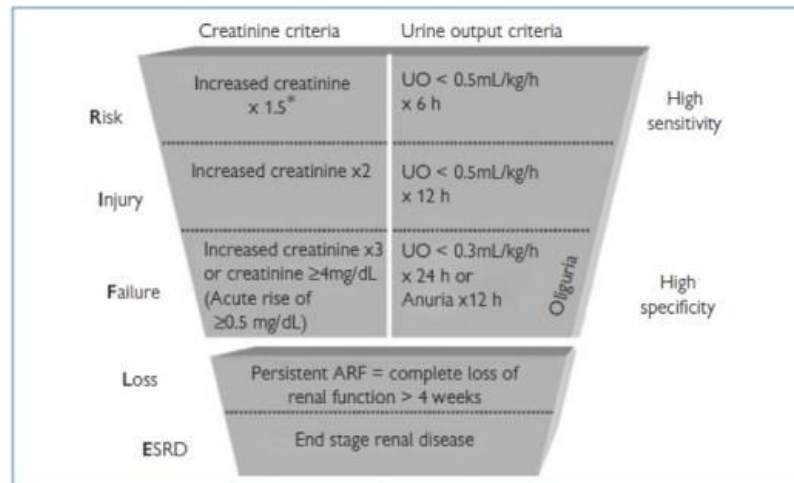


Figure 2. RIFLE criteria¹³³

Statistical analysis

The data was entered into the Microsoft Excel Spreadsheet (Annexure III). The data was analyzed using SPSS statistical software version 20.0. The categorical data was expressed as rates, ratios and percentages and continuous data was expressed as mean \pm standard deviation and for non-normal distributed data Mann-Whitney *U* test is used. A probability ('p' value) of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

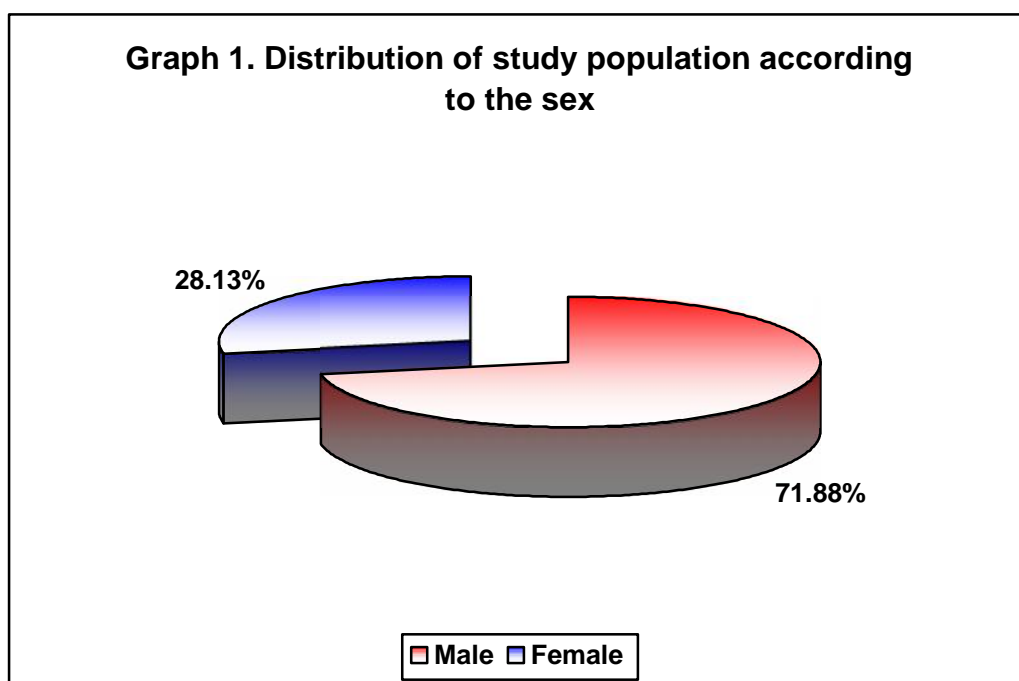
RESULTS

The present one year cross-sectional study was done in the Department of General Surgery and Department of Urology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 64 patients undergoing ESWL were studied.

The data obtained was analysed and the final results were tabulated as below.

Table 1. Distribution of study population according to the sex

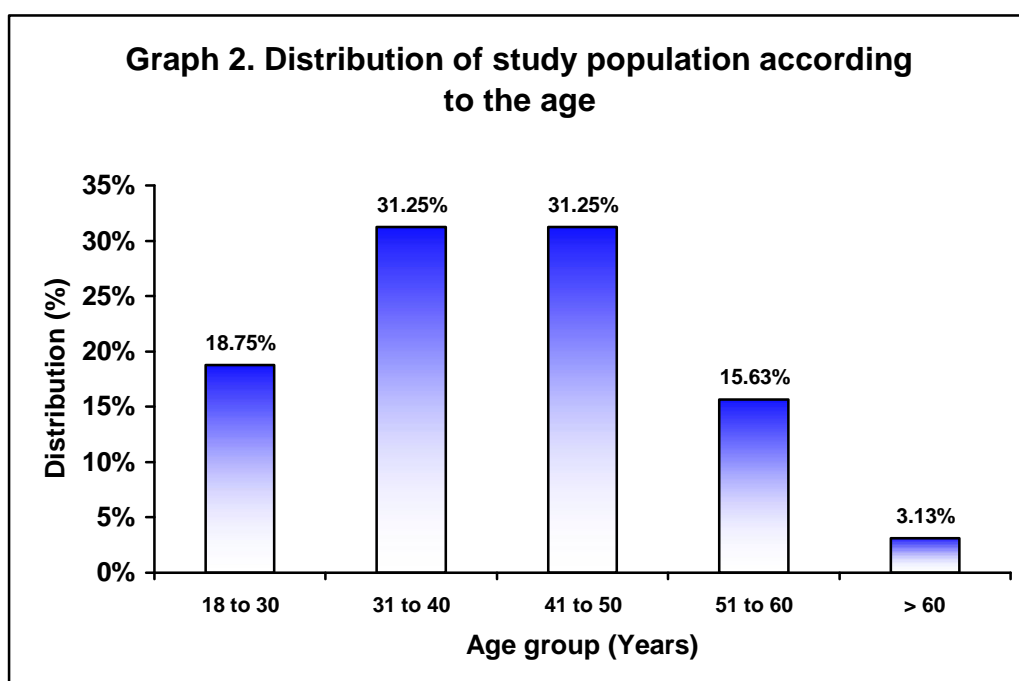
Sex	Distribution (n=64)	
	Number	Percentage
Male	46	71.88
Female	18	28.13
Total	64	100.00



In the present study, majority of the patients were males (71.88%). The male to female ratio was 2.55:1.

Table 2. Distribution of study population according to the age

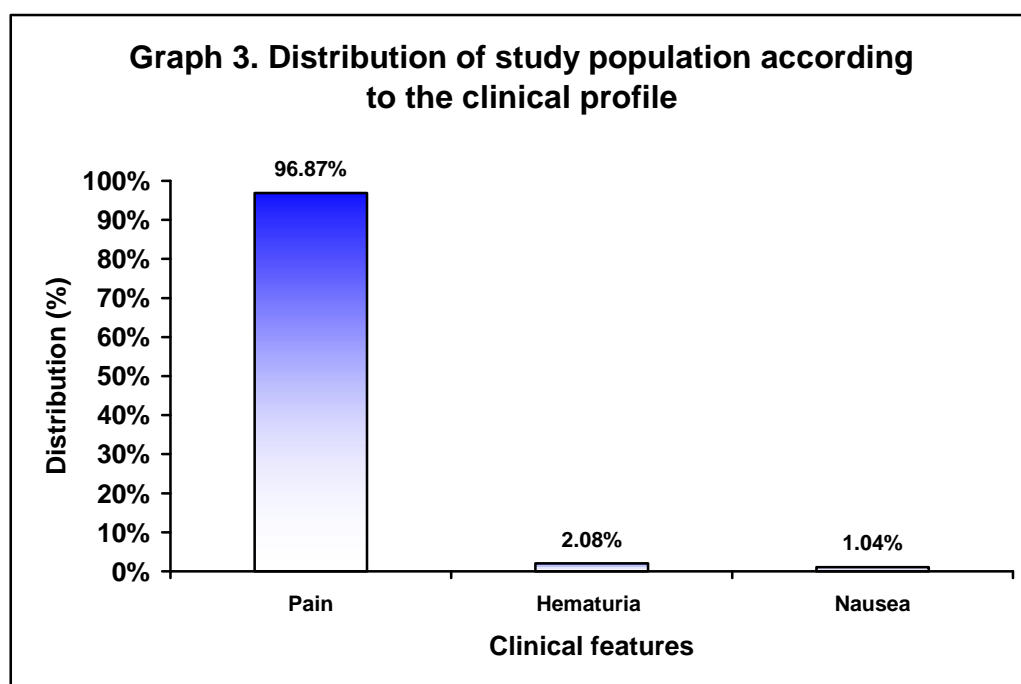
Age group (Years)	Distribution (n=64)	
	Number	Percentage
18 to 30	12	18.75
31 to 40	20	31.25
41 to 50	20	31.25
51 to 60	10	15.63
> 60	2	3.13
Total	64	100.00



In this study most of the patients were aged between 31 to 40 years and 41 to 50 years (31.25% each). The mean age was 40.88 ± 10.46 years with median age of 41 years and range 24 being minimum and 61 years being maximum.

Table 3. Distribution of study population according to the clinical profile

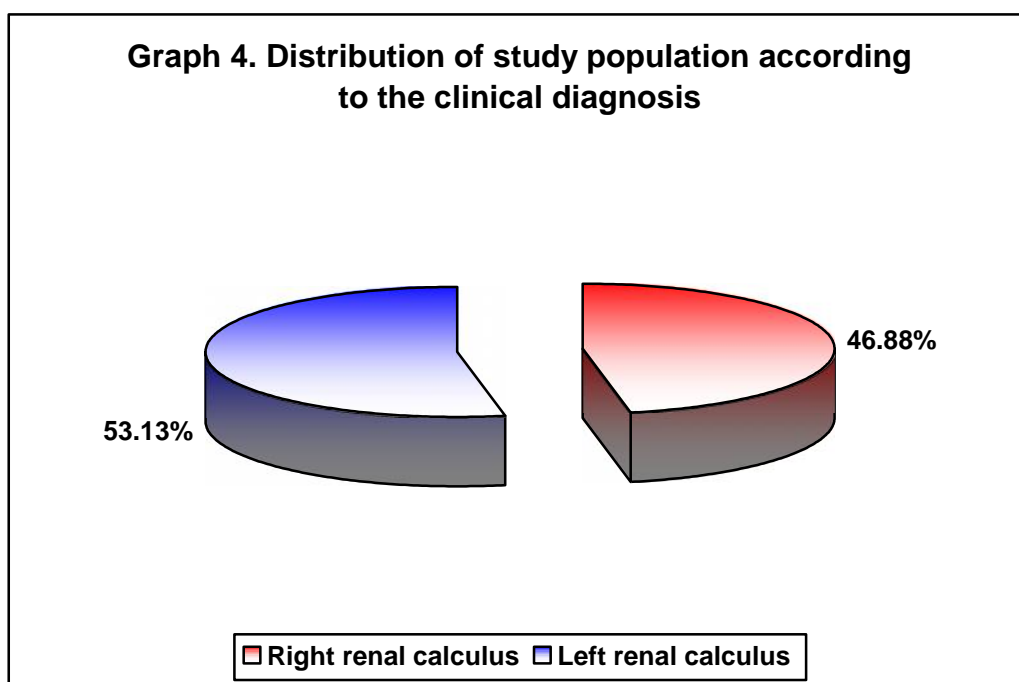
Clinical features	Distribution (n=64)	
	Number	Percentage
Pain	62	96.87
Hematuria	2	2.08
Nausea	1	1.04
Total	64	100



In the present study most of the patients presented with pain (96.87%) followed by hematuria (2.08%) and nausea (1.04%).

Table 4. Distribution of study population according to the clinical diagnosis

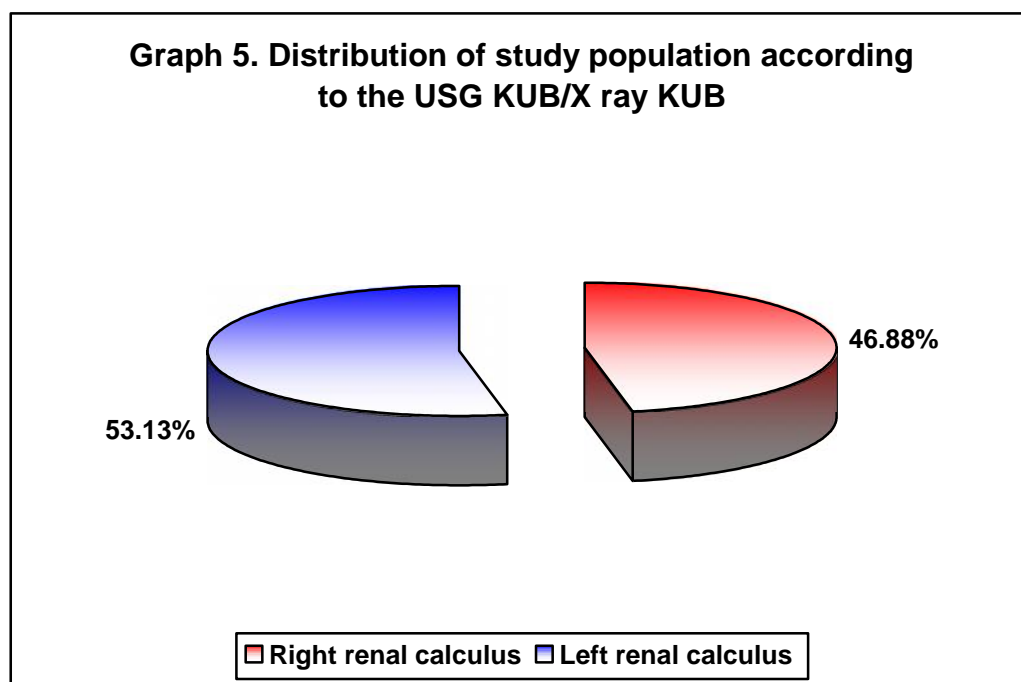
Diagnosis	Distribution (n=64)	
	Number	Percentage
Right renal calculus	30	46.88
Left renal calculus	34	53.13
Total	64	100.00



In the present study most of the patients had left renal calculus (53.13%) while right renal calculus was noted in 46.88% of the patients.

Table 5. Distribution of study population according to the USG KUB/X ray KUB

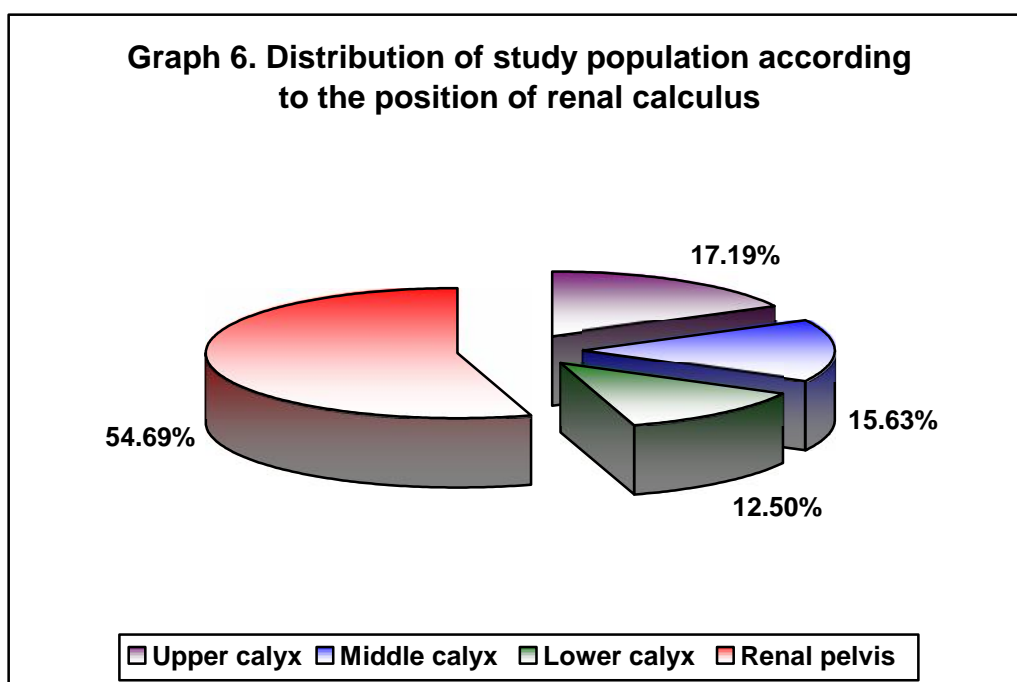
Findings	Distribution (n=64)	
	Number	Percentage
Right renal calculus	30	46.88
Left renal calculus	34	53.13
Total	64	100.00



In the present study USG KUB/X ray KUB examination revealed most of the patients with left renal calculus (53.13%) followed by right renal calculus (46.88%).

Table 6. Distribution of study population according to the position of renal calculus

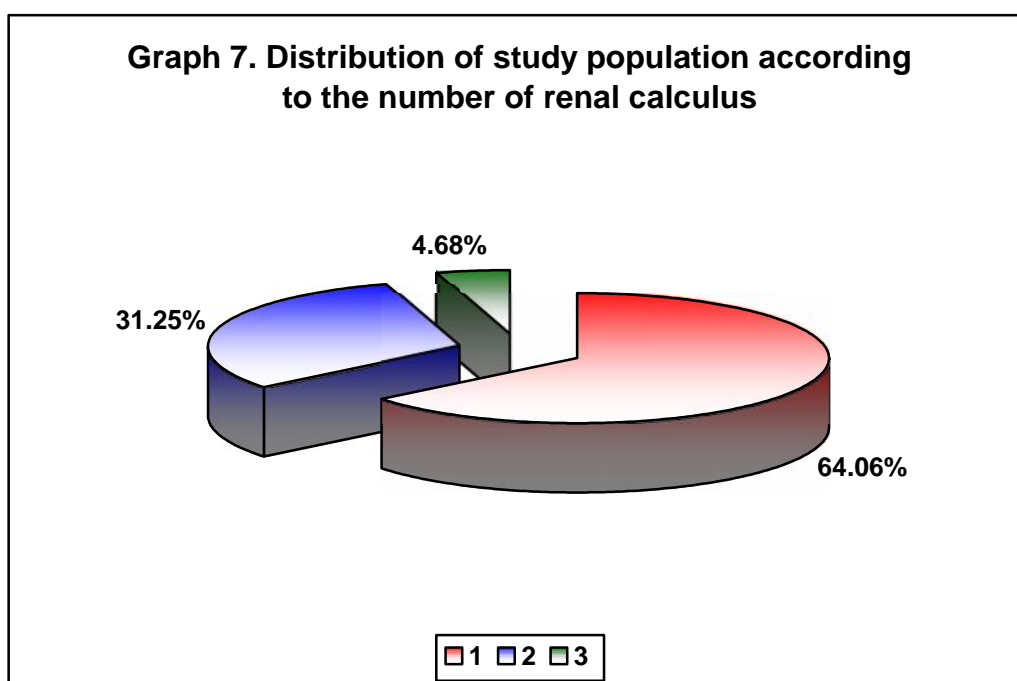
Position	Distribution (n=64)	
	Number	Percentage
Upper calyx	11	17.19
Middle calyx	10	15.63
Lower calyx	8	12.50
Renal pelvis	35	54.69
Total	64	100.00



In the present study maximum number of patients had renal calculus in the renal pelvis (54.69%) followed by upper calyx (17.19%), middle calyx (15.63%) and lower calyx (12.5%)

Table 7. Distribution of study population according to the number of renal calculus

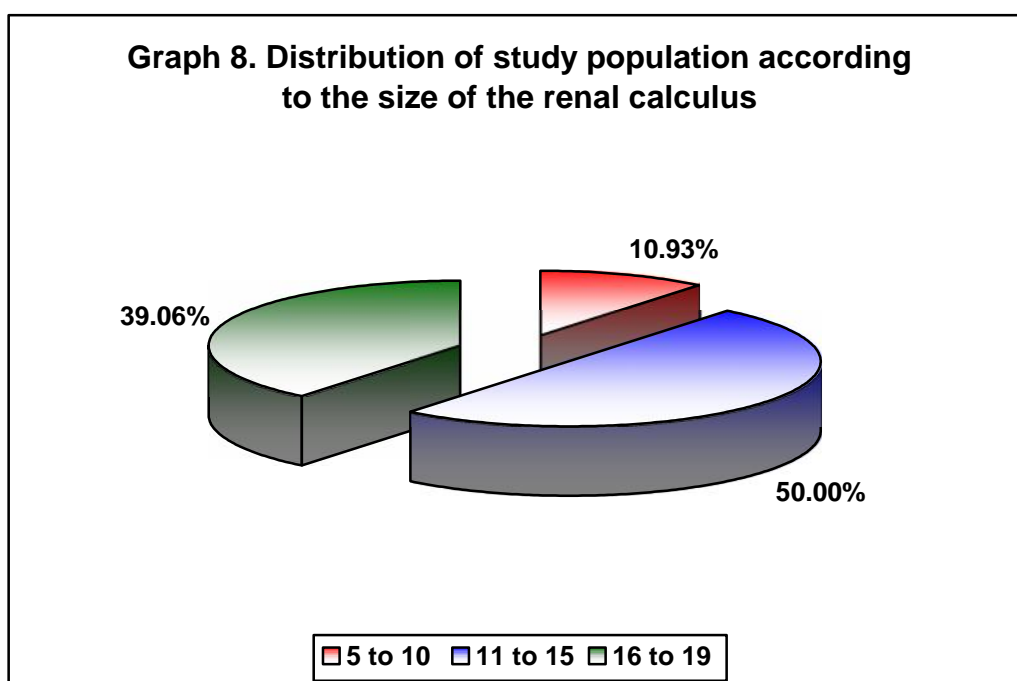
Number of renal calculi	Distribution (n=64)	
	Number	Percentage
1	41	64.06
2	20	31.25
3	3	4.68
Total	64	100



In the present study maximum number of patients had one (64.06%) renal calculus followed by two (31.25%) and three (4.68%) with mean \pm SD of 1.41 \pm 0.58.

Table 8. Distribution of study population according to the size of the renal calculus

Size of the renal calculus (mm)	Distribution (n=64)	
	Number	Percentage
5 - 10	7	10.93
11 – 15	32	50.00
16 - 19	25	39.06
Total	64	100.00



In this study most of the patients had calculus of size between 11mm to 15mm. The mean size was 14.48 ± 2.92 mm.

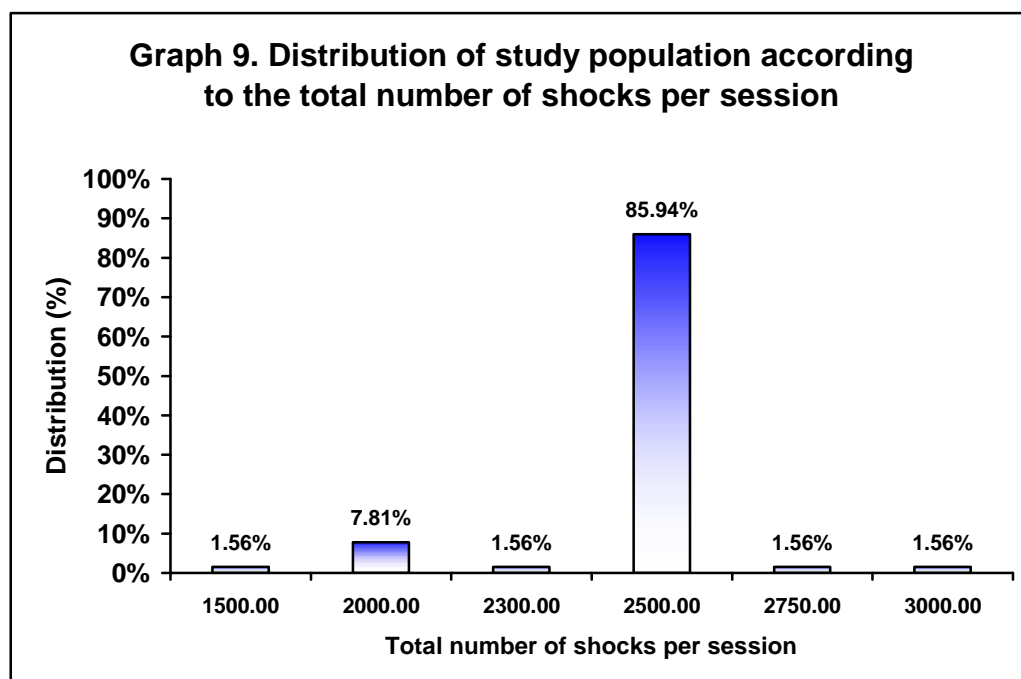
Table 9. ESWL characteristics

Variables	Mean	SD
Number of shocks (min)	60.00	0.00
Total number of shocks	2457.03	207.95
Energy (J)	78.88	13.79
Intensity (W)	3.59	0.60
Duration (minutes)	55.30	8.23

In this study the mean \pm SD of number of shocks/min used was 60 ± 0 , total number of shocks used per session was 2457.03 ± 207.95 , energy used in joules (J) was 78.88 ± 13.79 , intensity used in watts (W) was 3.59 ± 0.60 and duration in minutes (min) was 55.30 ± 8.23 .

Table 10. Distribution of study population according to the total number of shocks per session

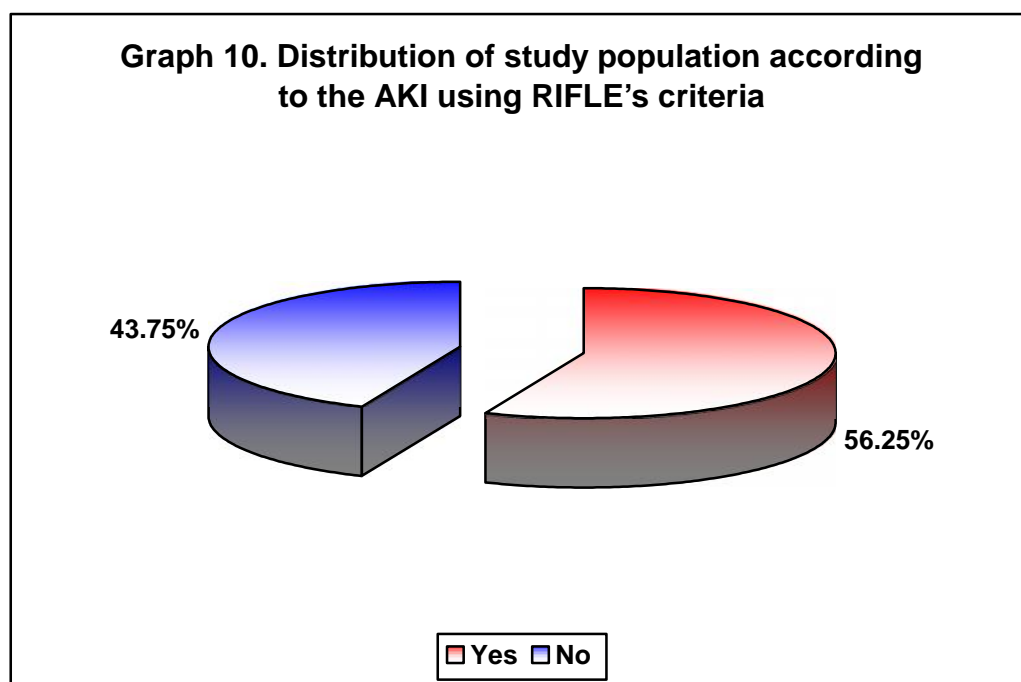
Total number of shocks	Distribution (n=64)	
	Number	Percentage
1500.00	1	1.56
2000.00	5	7.81
2300.00	1	1.56
2500.00	55	85.94
2750.00	1	1.56
3000.00	1	1.56
Total	64	100.00



In the present study, most of the patients underwent 2500 total number of shocks (85.94%). The mean number of shocks was 2457 ± 207.95 shocks.

Table 11. Distribution of study population according to the AKI using RIFLE's criteria

Distribution (n=64)		
AKI	Number	Percentage
Yes	36	56.25
No	28	43.75
Total	64	100.00

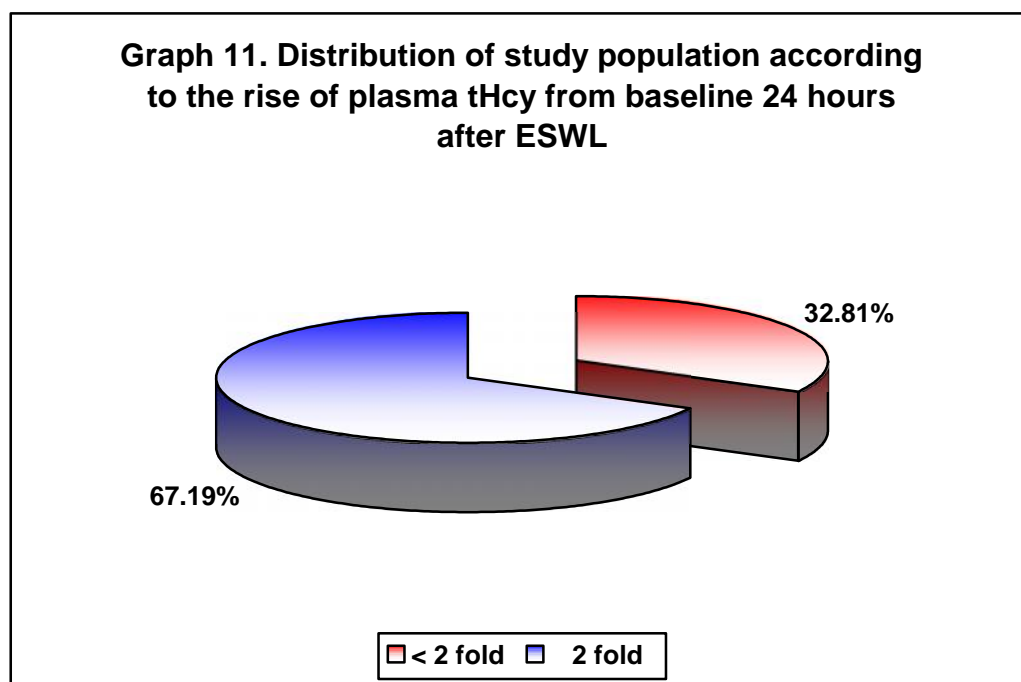


In this study post ESWL, AKI was developed in 56.25% of the patients.

Table 12. Distribution of study population according to the rise of plasma total homocysteine from baseline 24 hours after ESWL

Rise of plasma tHcy from baseline ($\mu\text{mol/L}$)	Distribution (n=64)	
	Number	Percentage
< 2 fold	21	32.81
2 fold	43	67.19
Total	64	100.00

Graph 11. Distribution of study population according to the rise of plasma tHcy from baseline 24 hours after ESWL

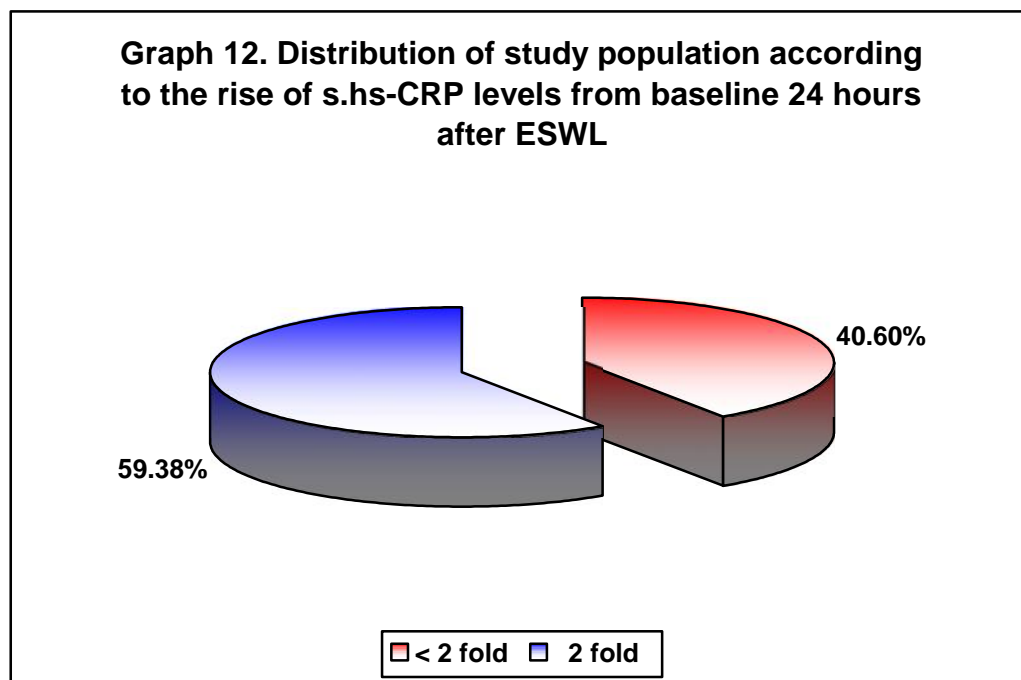


In the present study two fold rise of plasma tHcy levels from baseline 24 hours after ESWL were found in 67.19% of the patients while 32.81% of the patients had less than two fold rise.

Table 13. Distribution of study population according to the rise of serum hs-CRP levels from baseline 24 hours after ESWL

Rise of s.hs-CRP from baseline (mg/dL)	Distribution (n=64)	
	Number	Percentage
< 2 fold	26	40.60
2 fold	38	59.38
Total	64	100.00

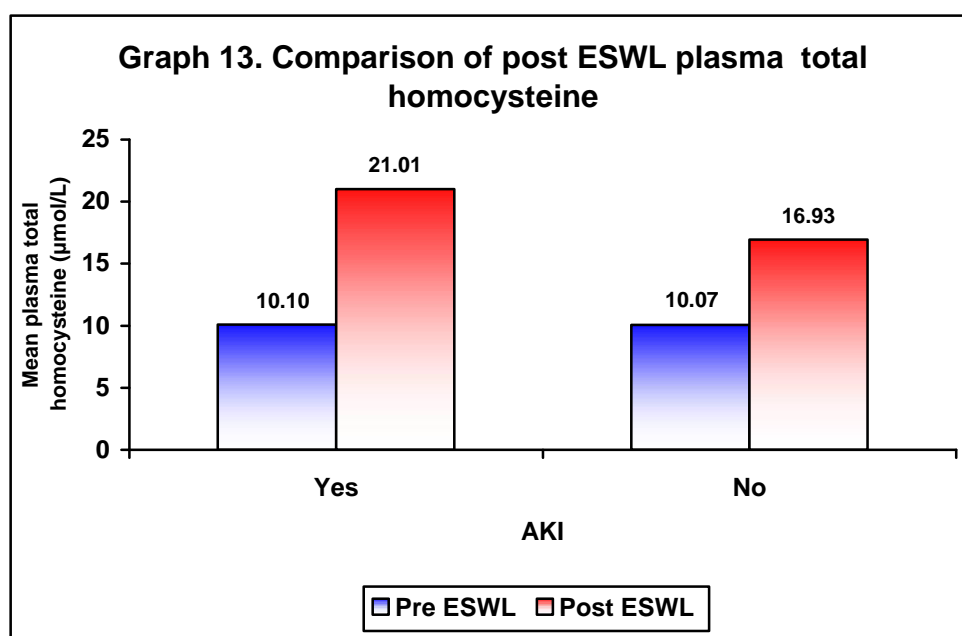
Graph 12. Distribution of study population according to the rise of s.hs-CRP levels from baseline 24 hours after ESWL



In the present study two fold rise of s.hs-CRP levels from baseline 24 hours after ESWL were found in 59.38% of the patients while 40.60% of the patients had less than two fold rise.

Table 14 Comparison of post ESWL plasma total homocysteine.

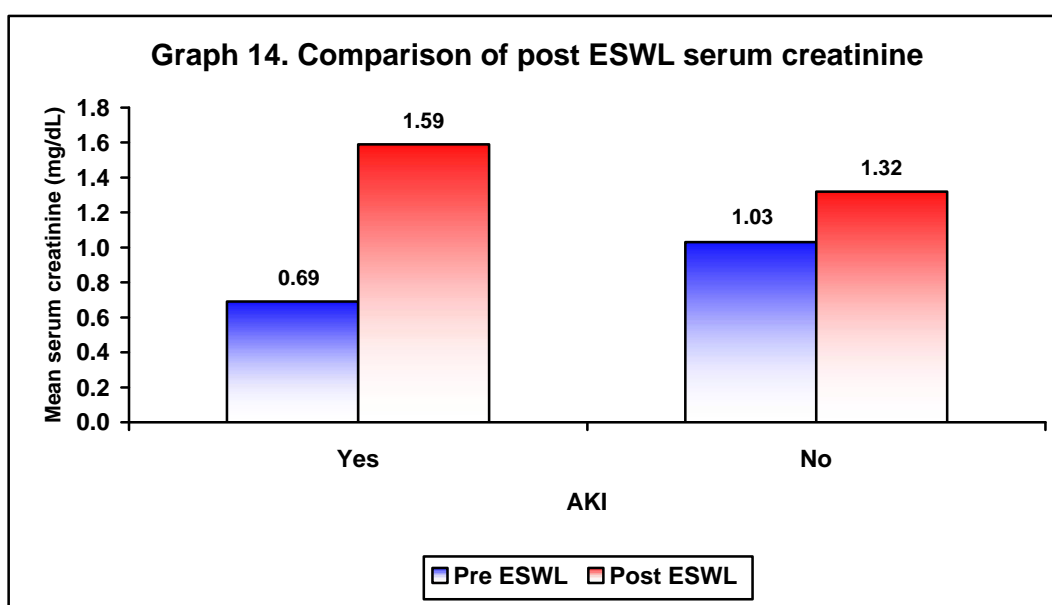
AKI	Mean plasma total homocysteine ($\mu\text{mol/L}$)					
	Pre ESWL		Post ESWL		Change	
	Mean	SD	Mean	SD	Mean	SD
Yes	10.10	3.42	21.01	7.67	10.90	4.87
No	10.07	2.94	16.93	7.44	6.85	6.06
t value	0.036		2.136		2.963	
p value	0.971		0.036		0.004	



In this study pre ESWL mean plasma homocysteine levels were comparable in patients who developed AKI and who did not develop (p=0.971). But, post ESWL mean plasma homocysteine levels were significantly high in patients with AKI ($21.01 \pm 7.67 \mu\text{mol/L}$) compared to those who did not develop AKI ($16.93 \pm 7.44 \mu\text{mol/L}$) (p=0.036). Similarly the mean change in plasma homocysteine levels in patients with AKI was significantly high ($10.90 \pm 4.87 \mu\text{mol/L}$) compared to those who did not develop AKI ($6.85 \pm 6.06 \mu\text{mol/L}$) (p=0.004).

Table 15. Comparison of post ESWL serum creatinine

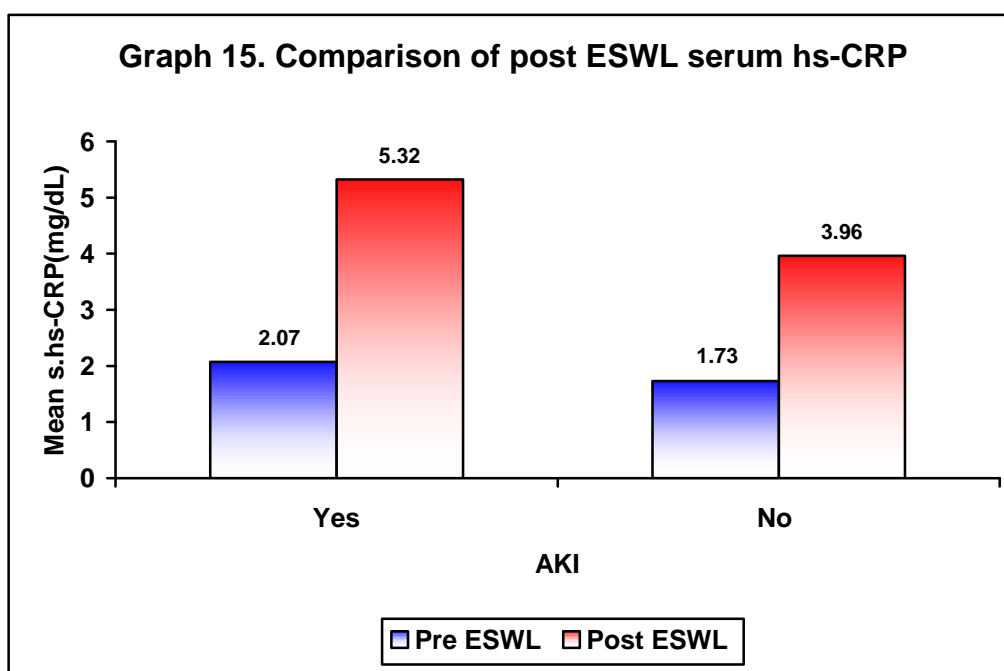
AKI	Serum creatinine (mg/dL)					
	Pre ESWL		Post ESWL		Change	
	Mean	SD	Mean	SD	Mean	SD
Yes	0.69	0.22	1.59	0.44	0.9	0.25
No	1.03	0.24	1.32	0.29	0.28	0.24
t value	-5.903		2.822		9.643	
p value	<0.001		0.006		<0.001	



In this study pre ESWL mean serum creatinine levels were significantly high in patients who did not develop AKI (1.03 ± 0.24 mg/dL) compared to those who developed AKI (0.69 ± 0.22 mg/dL) ($p < 0.001$). The post ESWL mean serum creatinine levels were significantly high in patients with AKI (1.59 ± 0.44 mg/dL) compared to those who did not develop AKI (1.32 ± 0.29 mg/dL) ($p = 0.006$). Similarly the mean change in serum creatinine levels in patients with AKI was significantly high (0.90 ± 0.25 mg/dL) compared to those who did not develop AKI (0.28 ± 0.24 mg/dL) ($p < 0.001$).

Table 16. Comparison of post ESWL serum hs-CRP

AKI	Mean s.hs-CRP (mg/dL)					
	Pre ESWL		Post ESWL		Change	
	Mean	SD	Mean	SD	Mean	SD
Yes	2.07	1.59	5.32	3.89	3.24	2.71
No	1.73	0.83	3.96	2.65	2.22	2.12
t value	1.015		1.578		1.635	
p value	0.314		0.120		0.107	



In this study pre ESWL mean serum hs-CRP levels were comparable in patients who did not develop AKI and who developed AKI ($p=0.314$). Similarly the post ESWL mean s.hs-CRP levels were also comparable in patients with AKI and those who did not develop AKI ($p=0.120$). Furthermore, the mean change in s.hs-CRP levels in patients with AKI and those who did not develop AKI was almost similar statistically ($p=0.107$).

Table 17. Association of rise in plasma total homocysteine with respect to AKI

Rise in serum creatinine (fold)	Rise in plasma total homocysteine (tHcy)				Total	
	2 fold		< 2 fold		No.	%
	No.	%	No.	%		
< 1.5	9	42.86	12	57.14	21	100.00
1.5	4	57.14	3	42.86	7	100.00
2.0	30	83.33	6	16.67	36	100.00
Total	43	67.19	21	32.81	64	100.00

p=0.006

In this study, 83.33% of the patients have significant rise i.e. two fold rise of plasma tHcy from the baseline in patients with AKI (patients with two fold rise in serum creatinine from the baseline). 57.14% of the patients have significant rise i.e. two fold rise of plasma tHcy from the baseline in patients with risk of AKI (patients with one and half fold rise in serum creatinine from the baseline).

Table 18. Association of rise in serum hs-CRP with respect to AKI

Rise in serum creatinine (fold)	Rise in serum hs-CRP				Total	
	> 2 fold		< 2 fold		No.	%
	No.	%	No.	%		
< 1.5	8	38.10	13	61.9	21	100.00
1.5	4	57.14	3	42.86	7	100.00
2.0	26	72.22	10	27.78	36	100.00
Total	38	59.38	26	40.63	64	100.00

p=0.040

In this study 72.22% of the patients have significant rise i.e. two fold rise of serum hs-CRP from the baseline in patients with AKI (patients with two fold rise in serum creatinine from the baseline). 57.14% of the patients have significant rise i.e. two fold rise of serum hs-CRP from the baseline in patients with risk of AKI (patients with one and half fold rise in serum creatinine from the baseline).

DISCUSSION

The increased prevalence of renal stone disease is pandemic.¹ Extracorporeal Shock wave lithotripsy is a commonly used procedure for treating upper urinary tract stones in patients who require treatment. It is a noninvasive approach that can be performed as an outpatient procedure.¹⁴³ Despite its proven safety and efficacy, there are many studies on the complications occurring after ESWL.^{144,145} ESWL does cause a predictable pattern of acute renal injury by causing rupture of blood vessels in the medulla and cortex which is accompanied by intraparenchymal bleeding, oxidative stress, inflammation and impairment of renal haemodynamics.¹⁴ Resolution of the acute injury may result in scar formation with loss of functional renal tissue.¹⁴ The risk of developing irreversible changes following SWL is influenced by the number of shock waves and rate at which it is administered, the energy and the number of SWL treatment sessions. Yet, the relationship between these risk factors is not understood.¹⁴³ There is a need for identification of new renal injury markers to prevent the progression of the renal injury and for early initiation of treatment.

Homocysteine is a sulphur containing amino acid with a reactive sulfhydryl group (-SH) which can undergo oxidation to disulfide (RSSR) in the presence of O₂ and at physiological pH. It is formed by demethylation of methionine and can be reversibly converted back to methionine and irreversibly to cysteine. These reactions are catalyzed by transition metals, vitamin B₆, B₁₂ and folic acid. Homocysteine can cyclize to provide homocysteine thiolactone, a five membered heterocycle. Due to this “self looping” reaction, peptides containing homocysteine tend to cleave

themselves by reactions generating oxidative stress. Homocysteine is cleared in the body by renal and extrarenal metabolism. Renal metabolism includes urinary excretion after glomerular filtration just like creatinine. Elevated total homocysteine (tHcy) levels have association with atherothrombotic vascular disease^{145,146} and numerous other diseases including Alzheimers disease, deep vein thrombosis, osteoporosis and pulmonary embolism in general population.

Recently it is suggested that, plasma homocysteine levels increase in patients with renal dysfunction. Several studies have demonstrated that renal function is the most important determinant of plasma total homocysteine (tHcy) concentration.^{138,147,148} In this study we aimed to evaluate the relationship between plasma total homocysteine levels and extracorporeal shock wave lithotripsy (ESWL) in patients with renal stone.

Furthermore, serum creatinine is raised in any kidney disease either acute or chronic.¹⁴⁹ It is excreted by glomerular filtration and is one of the well known renal injury marker. Serum high sensitivity C Reactive Protein (hs-CRP) is a non specific marker of any injury and inflammatory process.^{150,151}

This prompted us to assess plasma homocysteine as a marker of acute renal injury marker in patients undergoing extracorporeal shock wave lithotripsy (ESWL) for renal stone disease and compare the same with other markers i.e. serum creatinine and serum hs-CRP.

The present study was conducted in the Department of General Surgery and Department of Urology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015 in a sample size of 64

patients. These patients underwent ESWL for renal stone disease with Siemen's modularis lithotripter either under local anaesthesia using gel or under IV sedation. Blood samples for measurement of plasma total homocysteine, serum creatinine and serum hs-CRP were taken 24 hours before and 24 hours after ESWL. Later change in levels noted. Patients were divided into two groups post ESWL i.e. those who developed acute kidney injury (AKI group) and those who did not develop acute kidney injury (non AKI group).

Acute kidney injury was defined based on RIFLE criteria as two fold rise in serum creatinine from the baseline value after ESWL and risk was considered as 1.5 fold rise in serum creatinine from the baseline value after ESWL.

Two fold rise in plasma total homocysteine and serum hs CRP from the baseline value after ESWL was considered significant.

In a study done by Demir E et al.¹⁵ the aim was to evaluate the relationship between tHcy levels and extracorporeal shock wave lithotripsy (ESWL) for patients with kidney stones and to see if the change in homocysteine levels continued on improvement of renal dysfunction. In their study, tHcy levels showed a statistically significant increase from 9.4 ± 1.4 to 18 ± 4.8 and 11.2 ± 2.1 at 2 days and at 3 months, respectively. Serum creatinine also showed a statistically significant increase compared to baseline at 2 days and at 3 months after ESWL.

In a study done by Jayesh Modi et al.¹⁵³ mean high sensitivity C-reactive protein (hs-CRP) value increased in all three groups i.e. group A (no antioxidant), group B (Vitamin E) and group C (Vitamin C) after 48 hrs of lithotripsy but then gradually it came down. The mean hs-CRP levels were significantly lower

in Group B (Vitamin E) and Group C (Vitamin C); (Student's t-test, $P < 0.05$) compared to Group A (no antioxidant) on day 2, 7 and 28 after the lithotripsy. In Group C (Vitamin C) mean hs-CRP value was lower than Group B (Vitamin E), but was not statistically significant (Student's t-test, $P > 0.05$). Lowest mean hs-CRP value achieved in Group C (Vitamin C) patients at day 28 (1.52)

Demographic characteristics

In our study majority of the patients were males (71.88%) and (28.13%) females. The male to female ratio was 2.55:1. In a study by Demir E et al,¹⁵ out the 20 patients of renal stones 60% were male and 40% were female patients with a ratio of 1.5:1. In another study by Kardakos IS et al,¹⁴³ the study population comprised 37 patients out of which 20 (54%) were male and 17 (46%) were female with a ratio of 1.18:1.

In this study most of the patients were aged between 31 to 40 years and 41 to 50 years (31.25% each). The mean age was 40.88 ± 10.46 years with median age of 41 years and range 24 being minimum and 61 years being maximum. In a study by Demir E et al.,¹⁵ they had a mean age of 42.8 ± 11.7 years and was comparable to this study. In another study by Kardakos IS et al,¹⁴³ the mean age was 55.3 ± 14.16 years.

Clinical profile

In the present study most of the patients presented with pain (96.87%) followed by hematuria (2.08%) and nausea (1.04%). According to an article by Glenn M Preminger et al.¹⁵⁴ pain is the most common symptom of renal stone

disease followed by hematuria and nausea and the results of our study corresponds with this article.

Diagnosis

In the present study most of the patients had left renal calculus (53.13%) while right renal calculus was noted in 46.88% of the patients. This supports the study that the chances of extrarenal injury to liver by ESWL is low which is one of the organ involved in homocysteine metabolism.¹⁵⁵

In this study USG KUB and X-ray KUB revealed most of the patients with left renal calculus (53.13%) followed by right renal calculus (46.88%). Sensitivity of USG is reported to be 96% for renal stones and is 100% sensitive for calculus greater than 5 mm in reported literature^{156,157}. In a study done by Ather MH et al¹⁵⁸ USG had sensitivity and negative predictive value of 81 and 77%. If X-ray KUB is added the sensitivity increased to 95%. In our study CT KUB was not done in all patients due to cost factor.

Stone characteristics

In this present study, the calculi were located in the renal pelvis in 35 patients (54.68%), in upper calyx in 11 (17.18%), in midcalyx in 10 (15.63%), and in lower calyx in 8 patients (12.5%). In a study done by Kardakos IS et al,¹⁴³ the calculi were located in the renal pelvis, upper calyx, midcalyx and lower calyx in 21 patients (56.8%), 4 (10.8%), 7 (18.9%) and in 4 patients (10.8%) respectively.

In another study done by Hassouna ME et al,¹⁵⁹ the calculi were located in the renal pelvis, upper calyx, midcalyx and lower calyx in 412 patients (59.1%), 96

(13.8%), 74 (10.6%) and in 116 patients (16.6%). In all these studies maximum patients had calculi in the renal pelvis.

In this study overall 41(64.06%), 20(31.25%) and 3(4.68%) patients had one, two and three calculi respectively. In a study done by Kardakos I et al.¹⁴³ 29 patients (78.4%) had 1 calculus, 7 (18.9%) had 2, and 1 (2.7%) had 3 calculi. On comparison of both the studies, maximum patients had only one calculus.

In our study the mean size of the renal calculus was 1.41 ± 0.58 mm. 7 patients(10.93%), 32 patients(50%) and 25 patients(39%) had calculus size in between 5-10 mm, 11 – 15 mm and 16 – 19 mm respectively. The maximum stone size considered was <2 cm. In a study done by Kardakos I et al.¹⁴³, the size of calculus was 7.5-12.5 mm, 12.5-17.5 mm, 22.5-27.5 mm, and 27.5-32.5 mm in 48.6%, 37.8%, 8.1%, and 5.4% of patients respectively. The mean calculus size was 10.95 ± 5.15 mm.

In another study done by Hassouna ME et al.¹⁵⁹ the mean \pm SD stone size in this study was 12.8 ± 3.8 mm.

Shock wave characteristics

In the present study, most of the patients underwent 2500 total number of shocks per session (85.94%). The mean number of shocks was 2457 ± 207.95 shocks. The maximum shocks delivered was 3000. In a study done by Kardakos I et al.¹⁴³ where they used electromagnetic lithotripter (Dornier SII) (2), the mean number of shocks waves per session was 2856 ± 499 .

Consideration of total energy delivered per session in this study, it averaged 78.88 ± 13.79 J which was comparable to a study done by Kardakos I et al.¹⁴³, where the total energy delivered averaged 71.6 ± 23.6 J. In another study done by Hassouna ME et al.¹⁵⁹ where they used electromagnetic lithotripter (Dornier SII) (20), the mean \pm SD and range of total energy delivered for renal stones per session was 112 ± 34 J and 60–179 J respectively; a higher power (159 J) was required to clear stones of 21–25 mm.

In this study, the average intensity used was 3.59 ± 0.60 W, whereas in the study done by Kardakos I et al.¹⁴³, the intensity used was 4.8 ± 1.7 W.

On consideration of total duration of ESWL per session, in our study it averaged 55.30 ± 8.23 min which was comparable to a study done by Kardakos I et al.¹⁴³ where the mean duration per SWL session was 52 minutes.

Considering RIFLE criteria for Acute Kidney Injury as two fold rise in serum creatinine from the baseline value after ESWL, AKI was seen to develop in 36(56.25%) patients in this study. Hence patients were divided into two groups – AKI group and Non AKI group. To the best of our knowledge we did not find any other studies with such division after ESWL for comparison. In one study done by Moriyama T. et al.¹⁶⁰ based on AKI criteria (KDIGO criteria), 50 patients who underwent cardiac surgery with cardiopulmonary bypass were divided into two groups: AKI group (n = 11) and non-AKI group (n = 39), with respect to postoperative serum creatinine (Cr) levels i.e. 11 patients developed acute kidney injury postoperatively.

We considered two fold rise in plasma total homocysteine post ESWL from the baseline value pre ESWL as significant rise. Also we considered two fold rise in serum hs-CRP post ESWL from the baseline value pre ESWL as significant rise.

In the present study post ESWL plasma total homocysteine levels was significantly raised in 67.19% of the patients while 32.81% of the patients had no significant rise.

Also in this study, post ESWL serum hs-CRP levels was significantly raised in 59.38% of the patients while 40.63% of the patients had no significant rise.

In this study, pre ESWL mean plasma total homocysteine levels were comparable in patients who developed AKI and who did not develop ($p=0.971$). But, post ESWL mean plasma homocysteine levels were significantly high in patients with AKI ($21.01 \pm 7.67 \mu\text{mol/L}$) compared to those who did not develop AKI ($16.93 \pm 7.44 \mu\text{mol/L}$) ($p=0.036$). Similarly the mean change in plasma homocysteine levels in patients with AKI was significantly high ($10.90 \pm 4.87 \mu\text{mol/L}$) compared to those who did not develop AKI ($6.85 \pm 6.06 \mu\text{mol/L}$) ($p=0.004$). Considering the significant rise of plasma total homocysteine post ESWL it can be concluded that plasma tHcy can be considered acute renal injury marker following ESWL. In a study done by Demir E et al.¹⁵ tHcy levels showed a statistically significant increase from 9.4 ± 1.4 to 18 ± 4.8 and 11.2 ± 2.1 at 2 days and at 3 months, respectively post ESWL for renal stones.

In the present study the post ESWL mean serum creatinine levels were significantly high in patients with AKI ($1.59 \pm 0.44 \text{ mg/dL}$) compared to those who did not develop AKI ($1.32 \pm 0.29 \text{ mg/dL}$) ($p=0.006$). Similarly the mean change in

serum creatinine levels in patients with AKI was significantly high (0.90 ± 0.25 mg/dL) compared to those who did not develop AKI (0.28 ± 0.24 mg/dL) ($p < 0.001$) confirming creatinine as acute renal injury marker post ESWL. This was in accordance to the study done by Demir E et al.¹⁵ where serum creatinine showed a statistically significant increase compared to baseline at 2 days and at 3 months after ESWL.

In this study pre ESWL mean serum hs-CRP levels were comparable in patients who did not develop AKI and who developed AKI ($p = 0.314$). Similarly the post ESWL mean serum hs-CRP levels were also comparable in patients with AKI and those who did not develop AKI ($p = 0.120$). Furthermore, the mean change in hs-CRP levels in patients with AKI and those who did not develop AKI was almost similar statistically ($p < 0.107$). But when percentage is considered in patients with AKI, 72.22% of the patients had significant rise in s.hs-CRP levels and all patients had raised serum hs-CRP levels compared to the baseline values following ESWL, which is the only cause of insult on kidney in 24 hours suggesting the role of serum hs-CRP as acute renal injury marker whose significance could not be proved due to small sample size of this study. Similar result was shown in a study done by Modi J et al.¹⁵³ in which mean high sensitivity C-reactive protein (hs-CRP) value increased in all three groups – Group A (no antioxidant), Group B (Vitamin E) and Group C (Vitamin C) after 48 h of lithotripsy but then gradually it came down.

Considering, RIFLE's criteria for Acute Kidney Injury as two fold rise in serum creatinine from the baseline value after ESWL and risk of developing ARI as one and half fold rise in serum creatinine from the baseline value after ESWL and

two fold rise in plasma total homocysteine and s.hs-CRP post ESWL from the baseline value pre ESWL as significant rise following results were obtained:

In patients with AKI, 83.33% of the patients had significant rise in s. tHcy levels and 72.22% of the patients had significant rise in s. hs-CRP levels 24 hours post ESWL.

In patients with risk of developing ARI, 57.14% of the patients had significant rise in s.tHcy levels and 57.14% of the patients had significant rise in s. hs-CRP levels.

Overall the findings of this study suggest that, plasma tHcy and s. creatinine can be considered as renal injury markers. With aforementioned explanation s. hs-CRP can also be considered as renal injury marker but needs to be further evaluated.

An important limitation of this study was long term recovery of these markers and kidney function could not be assessed and a smaller sample size of the study population.

CONCLUSION

Although ESWL is considered a safe and effective procedure in the treatment of renal stone disease yet it may cause acute renal injury. In this study Plasma total homocystine and serum hs-CRP rise significantly in addition to serum creatinine following acute renal injury caused by ESWL. Hence Plasma total homocystine, s. hs-CRP and s. creatinine can be used as acute renal injury markers following ESWL in patients with renal stone disease.

SUMMARY

The increased prevalence of renal stone disease is pandemic. Extracorporeal Shock wave lithotripsy is a commonly used procedure for treating upper urinary tract stones in patients who require treatment. Despite its proven safety and efficacy, there are many studies on the complications occurring after ESWL. The present study was aimed to assess plasma homocysteine as a marker of acute renal injury marker in patients undergoing extracorporeal shock wave lithotripsy (ESWL) for renal stone disease and compare the same with other markers i.e. serum creatinine and serum hs-CRP.

This one year cross-sectional study was done in the Department of General Surgery and Department of Urology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 64 patients undergoing ESWL were studied. Patients were investigated for plasma total homocysteine, serum creatinine and s.hs-CRP before and after ESWL procedure.

Majority of the patients were males (71.88%). The male to female ratio was 2.55:1. Most of the patients were aged between 31 to 40 years and 41 to 50 years (31.25% each) mean age was 40.88 ± 10.46 years. Most of the patients presented with pain (96.87%) followed by hematuria (2.08%) and nausea (1.04%). Based on USG KUB/X ray KUB, left renal calculus was noted in 53.13% of the patients while right renal calculus was noted in 46.88% of the patients. Post ESWL, AKI was developed in 56.25% of the patients according to RIFLE's criteria. Two fold rise of plasma tHcy levels from baseline 24 hours after ESWL was found in 67.19% of the

patients while 32.81% of the patients had less than two fold rise. Two fold rise of serum hs-CRP levels from baseline 24 hours after ESWL was found in 59.38% of the patients while 40.60% of the patients had less than two fold rise. pre ESWL mean plasma homocysteine levels were comparable in patients who developed AKI and who did not develop (p=0.971) But, post ESWL mean plasma homocysteine levels were significantly high in patients with AKI ($21.01 \pm 7.67 \mu\text{mol/L}$) compared to those who did not develop AKI ($16.93 \pm 7.44 \mu\text{mol/L}$) (p=0.036). The mean change in plasma homocysteine levels in patients with AKI was significantly high ($10.90 \pm 4.87 \mu\text{mol/L}$) compared to those who did not develop AKI ($6.85 \pm 6.06 \mu\text{mol/L}$) (p=0.004). Pre ESWL mean serum creatinine levels were significantly high in patients who did not develop AKI ($1.03 \pm 0.24 \text{ mg/dL}$) compared to those who developed AKI ($0.69 \pm 0.22 \text{ mg/dL}$) (p<0.001). The post ESWL mean serum creatinine levels were significantly high in patients with AKI ($1.59 \pm 0.44 \text{ mg/dL}$) compared to those who did not develop AKI ($1.32 \pm 0.29 \text{ mg/dL}$) (p=0.006). Similarly the mean change in serum creatinine levels in patients with AKI was significantly high ($0.90 \pm 0.25 \text{ mg/dL}$) compared to those who did not develop AKI ($0.28 \pm 0.24 \text{ mg/dL}$) (p<0.001). Pre ESWL mean serum hs-CRP levels were comparable in patients who did not develop AKI and who developed AKI (p=0.314). Similarly the post ESWL mean hs-CRP levels were also comparable in patients with AKI and those who did not develop AKI (p=0.120). Furthermore, the mean change in serum hs-CRP levels in patients with AKI and those who did not develop AKI was almost similar statistically (p<0.107). But 72.22% of the patients with AKI has significant rise of s.hs-CRP (2 fold of baseline) level after ESWL which is the only insult on kidney in 24 hours.

Based on the findings of this study it may be concluded that, Plasma total homocystine, s. hs-CRP and s. creatinine can be used as acute renal injury markers following ESWL in patients with renal stone disease.

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ANNEXURE I – CONSENT FORM

Mr./Mrs./Miss. _____ we are requesting you to enroll yourself in study titled “Assessment of plasma homocysteine as a marker of Acute Renal Injury in patients undergoing extracorporeal shock wave lithotripsy(ESWL) for renal stone disease – One year Cross sectional study” conducted by Dr. *****, Post Graduate in M.S. General Surgery under the guidance of Dr. *****, Professor, Department of General Surgery and DR. *****, Department of Urology, J. N. Medical College, Belagavi under KLE university, Belagavi.

Respected Sir /Madam We request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J. N. Medical College. If you decide to participate you are free to withdraw at any time.

Purpose of the study

The purpose of the study is to find out a new kidney injury marker following shock treatment for kidney stones that is to Assess plasma homocysteine as a marker of Acute Renal Injury in patients undergoing extracorporeal shock wave lithotripsy(ESWL) for renal stone disease .

Procedure Involved

If you agree to enroll yourself in my study, you will be asked your detailed history. Then you will be clinically examined in detail and routine investigations like

CBC, RBS, Minirenal, LFT, Chest X-ray, ECG, will be done accordingly. S. total homocysteine, s.hs-CRP and S. Creatinine is done 24 hours before and 24 hours after ESWL and the difference in findings noted.

Risks

No additional study related risks and side effects.

Benefits

Results will help the doctors to better diagnose renal injury using renal injury markers and hence allow for a better treatment plan.

Voluntary Participation/Withdrawal

Taking part in the study is voluntary. You may choose not to enrol yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E. hospital.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Privacy and Confidentiality

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

In emergency to protect your rights and welfare. If required by law.

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity will remain confidential.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury related to the study, treatment will be made available through KLES' Hospital & MRC, Belagavi. There is no compensation or payment for such medical treatment by law. If you are injured you may contact.

DR. * ***** *******
Department of General Surgery
KLES Hospital & MRC,
Belagavi – 590 010
Phone Number: **** *****.

Contact details

In case you have any queries related to the study, in future or in case of study related injury or illness, you can contact

DR. ** *******
Post graduate
Department of General Surgery
KLE Hospital and MRC,
Belagavi-590 010
Phone no.:*** *****

DR. * *******
Professor
Department of General Surgery
KLE Hospital and MRC,
Belagavi-590 010
Phone no.: *** ***** *

DR. ** *******
Professor
Department of Urology
KLE Hospital and MRC,
Belagavi-590 010
Phone no.: ***** *****

If you have any queries about your rights as a study subject, you may call

DR. * *******

Professor, Department of Pathology and Chairman,
Jawaharlal Nehru Medical College Institutional Ethical Committee for Human
Subjects Research,
Extension no. *****
Jawaharlal Nehru Medical College,
Belagavi 590 010

Consent statement

I, Mr. /Ms. /Mrs. _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights. I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____

Date:

Witness Name : _____ Signature: _____

Investigators Name: Dr. **** * Signature: _____

Date:

Place: _____

ANNEXURE II - PROFORMA

“Assessment of plasma homocysteine as a marker of Acute Renal Injury in patients undergoing extracorporeal shock wave lithotripsy(ESWL) for renal stone disease – One year Cross sectional study”

Case No.

DOA:

DOD:

IP. No.

Name:

Age/Sex:

Occupation:

Address with phone no. :

PRE PROCEDURE EVALUATION :

Chief Complaints:

History of presenting illness:

Past History:

Family History:

General Physical Examination:

Vitals:

Temperature	Pallor	Weight:
PR	Icterus	Height
BP	Cyanosis	BMI
RR	Clubbing	
	Edema	
	Lymphadenopathy	

SYSTEMIC EXAMINATION :

Per Abdomen:

Cardiovascular System:

Respiratory System:

Central Nervous system:

Diagnosis:

INVESTIGATIONS:

CBC	MR	LFT
ECG:		
Hb%:	Urea:	T.bil:
PCV:	Creatinine:	D.bil:
TC:	Na:	SGOT:
DC:	K:	SGPT:
Platelet:	HCO ₃ :	ALP:
ESR:	Cl:	T.Protein:
PT INR:		S.Alb:
PS:		A:G:

CXR:

USG/X Ray report:

Proposed Procedure : Extracorporeal shock wave lithotripsy

Date: Time:

No. of shocks/min:

Total no. of shocks:

Intensity:

Measurements: (Fasting levels)	Pre ESWL (24 hrs before)	Post ESWL (24 hrs after)	Change in levels (increased/decreased/ No change)
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Plasma total homocysteine:
(N: 5.9 – 16 µmol/L)Serum creatinine:
(N: 0.5 -1.4 mg/dl)S.hs-CRP:
(N: 0 – 3 mg/dl)

ANNEXURE III – ETHICAL CLEARANCE



K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: <http://www.jnmc.edu>
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 233

Date: 13/11/2014

To,

PG student in Surgery,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **“ASSESSMENT OF PLASMA HOMOCYSTEINE AS A MARKER OF ACUTE RENAL INJURY IN PATIENTS UNDERGOING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY(ESWL) FOR RENAL STONE DISEASE – ONE YEAR CROSS SECTIONAL STUDY”**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE IV – KEY TO MASTER CHART

-	-	Absent
+	-	Present
A	-	Absent
BP	-	Blood pressure
CBC	-	Complete blood count
ESWL	-	Extracorporeal shock wave lithotripsy
F	-	Female
Hb%	-	Hemoglobin in gram percent
hrs	-	Hours
HTN	-	Hypertension
INR	-	International normalized ratio
J	-	Joules
L	-	Lower calyx
lt	-	Left
Lt RC	-	Left renal calculi
M	-	Male
m	-	Middle calyx
meq/L	-	Milli equivalent per litre
mg/dL	-	Milligram per deciliter
min	-	Minute
mm	-	Millimeter
mmHg	-	Millimeters of mercury
μmol/L	-	Micromole per litre

MR	-	Mini Renal
N	-	Normal
NS	-	Nothing significant
P	-	Present
p	-	Renal pelvis
PR	-	Pulse rate
PT	-	Prothrombin time
RR	-	Respiratory rate
rt	-	Right
Rt RC	-	Right renal calculi
hs-CRP	-	High sensitivity C reactive protein
TC	-	Total count
U	-	Upper calyx
USG-KUB	-	Ultrasonography Kidney Ureter Bladder
W	-	Watts