Tamsulosin as an adjuvant treatment after SWL for patients with renal and upper ureteric stones

A prospective randomized study.

THESIS

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Abtracta

To assess tamsulosin as an adjuvant treatment for patients with renal and upper ureteric stones after shock wave lithotripsy (SWL), regarding stone expulsion rate and analgesic dose.

Patients and methods:

This is a prospective randomized study carried out on 96 male patients with upper urinary tract stones who were divided randomly into 2 groups. Group I (47 patients): received Tamsulosin 0.4mg once daily plus diclofenac (50/75mg) oral or parenteral as needed for pain relief. Group II (49 patients): received only diclofenac (50/75mg) oral or parenteral for pain relief. SWL was performed with an electrohydraulic lithotripter.

All patients were investigated two weeks after the SWL session by (K.U.B), and (U/S) to assess disintegration of stones or clearance and the need for further sessions with a maximum of 3 sessions per patient and follow up duration of 2 weeks after 3rd session. All patients with fragments 5mm or greater were considered as candidates for another SWL session. Patients with residual less than 5mm were considered as clinical insignificant fragment (CIF).

Cases with no evidence of clearance or (CIF) after 2 weeks follow up of 3rd SWL session were considered failure. Reassessment and another treatment modality were chosen for the patient. Documentation of clearance rate, time and analgesics dose was noted for each patient in both groups.

Results:

The mean age for group I was 28.6 years and for group II was 29.5 years. The p-value was 0.980 and therefore, no significant difference in

the age group was present. The mean stone size for group I was 13mm and for group II was 12.3.The p-value was 0.1071with no significant difference.

In our study, total patients in group I had an expulsion rate of 80.9%. In contrast, group II had an expulsion rate of 57.1%. The p-value of this parameter was 0.022 which was found statistically significant.

Considering the expulsion in patients with kidney stones, group I had expulsion rate of 80%. In contrast, group II had expulsion rate of 48.5%. The p-value of this parameter was 0.013 which was significant.

Regarding patients with ureteric stones, the expulsion rate was 83.3% in group I and 75% in group II, having p-value of 0.947 which was not significant.

The mean analgesic dose was 565 mg in group I and 1512 mg in group II. The p-value of this parameter was <0.001 which was significant.

Conclusion:

The use of tamsulosin as a medical expulsive therapy appears to augment the outcome of SWL by improving the overall stone clearance rate and time. Also it seems to lower the post SWL analgesic dose required.

Key words:

Tamsulosin as an adjuvant treatment after SWL for patients with renal and upper ureteric stones

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Introduction

Worldwide urolithiasis prevalence varies from 4-17 cases per 1000 inhabitants. It affects 12% of the world population. It can create pain, hematuria, infection, fever, nausea, vomiting and even uraemia. The goal of treating urinary calculi is to achieve complete stone clearance with minimal morbidity for the patient.

The composition of the urinary stones can vary considerably (calcium oxalate, calcium phosphate, uric acid, ammonium urate, sodium urate, magnesium ammonium phosphate, carbonate apatite, cystine, xanthine, and sulfonamide and indinavir stones). **(Kijvikai K, et al 2007)**

Many theories have been proposed for the pathogenesis of urolithiasis, including nucleation theory, the crystal inhibitor theory or the crystal retention theory. Moreover there are a number of diseases associated with stone formation (i.e. hyperparathyroidism, renal tubular acidosis, cystinuria, hyperoxaluria, intestinal malabsorptive conditions) as well as medications (i.e. calcium supplements, vitamin D, triamterene, indinavir).

Predisposing factors for stone formation include anatomical abnormalities (i.e. ureteral strictures, vesico-ureteral reflux, ureteropelvic stenosis, extrinsic ureteral compression and ureterocele among others).

Calculus location and size, expressed in millimeters on its two major axes, continue to be important factors for deciding which therapeutic option to utilize. **(Stefanos P, et al 2006)** The contemporary guidelines state that stones 0.5 cm or less in diameter have a 80% chance of spontaneous passage, 0.5 cm stones have the chance of 20-50%, and for stones greater than 0.5 cm the patient should consult urologist.

Although most ureteral stones pass spontaneously, the pain and cost associated with repeated episodes of renal colic are substantial.(**Dellabella M, et al 2003)** Current standard treatment for urolithiasis follows the non-invasive to more invasive spectrum depending on the size of the stone and the location within the ureter.

Watchful waiting with conservative analgesic therapy is the first-line in urolithiasis treatment. Non-steroidal anti-inflammatory medication, such as ketorolac and diclofenac, have the possible advantage of decreasing ureteral smooth muscle tone, thereby directly treating the mechanism by which pain is thought to occur namely, ureteral spasm**. (Cole R, et al 1988)**

On the more invasive end of the spectrum, therapies such as single shock wave lithotripsy, endoscopy, and finally open surgical stone extraction have been the traditional second and third line treatments for urolithiasis. Although there have been vast improvement in the last 20 years with the above mentioned minimally invasive procedures for ureteral stones, there has also been a significant increase in treatment costs.

The costs that Dellabella et al is referencing are not only financial, rather the overall cost to the body in terms of surgical infection, post intervention pain, and other possible post-surgical sequelae. **(Dellabella M, et al 2003)**

In 2004, Sigala et al published a paper entitled evidence for the presence of alpha-1 adrenergic receptors subtypes in the human ureter, showing increased density of alpha-1_a adrenergic receptors in the smooth muscle of the ureter.

The implication of their research is crucial in terms of urolithiasis treatment. Urolithiasis migration down the ureter is modulated by the sympathetic nervous system via the alpha-1 adrenergic receptors and the movement of the stone is facilitated by peristaltic movement of the tubular ureter. **(Sigala S, et al 2004)**

The pain pathway of urolithiasis arises from the increased intraureteral pressure and peristaltic muscle movements in the presence of urolithiasis. Thus, sympathetic alpha adrenergic antagonists such as tamsulosin might have the ability to inhibit basal tone, peristaltic amplitude and frequency, dilating the urethral lumen and decreasing intraureteral pressure, thereby increasing the rate of fluid transport and ultimate facilitation of the passage of the stone. **(Sun X, et al 2009)**

After the general assessment of intense patient discomfort, risk versus benefit of minimally invasive urologic procedures, and overall cost of urolithiasis treatment, the question still begs: if an adjunctive therapy in the form of an off-label benign prostate hypertrophy medication like tamsulosin could help with the passage of ureteral stones, should it not be prescribed?

This study will help to answer that question by primarily analyzing the direct correlation of therapeutic success, ureteral expulsion and overall dosage of analgesia used.

Classification of renal stones

Kidney stones are typically classified by their location and chemical composition.

Chemical composition:

- **Calcium-containing stones**

By far, the most common type of kidney stones worldwide contains calcium. For example, calcium-containing stones represent about 80% of all cases in the United States; these typically contain calcium oxalate either alone or in combination with calcium phosphate in the form of apatite or brushite.

Factors that promote the precipitation of oxalate crystals in the urine, such as primary hyperoxaluria, are associated with the development of calcium oxalate stones.

The formation of calcium phosphate stones is associated with conditions such as hyperparathyroidism and renal tubular acidosis. **(Vijaya T, et al 2013)**

- **Struvite stones**

About 10–15% of urinary calculi are composed of struvite (ammonium magnesium phosphate, $NH_4MgPO_4 \cdot 6H_2O$). Struvite stones (also known as "infection stones", urease or triple-phosphate stones), form most often in the presence of infection by urea-splitting bacteria.

Using the enzyme urease, these organisms metabolize urea into ammonia and carbon dioxide. This alkalinizes the urine, resulting in favorable conditions for the formation of struvite stones. Proteus mirabilis, Proteus vulgaris, and Morganella morganii are the most common organisms isolated; less common organisms include Ureaplasma

urealyticum, and some species of Providencia, Klebsiella, Serratia, and Enterobacter.

These infection stones are commonly observed in people who have factors that predispose them to urinary tract infections, such as those with spinal cord injury and other forms of neurogenic bladder, ileal conduit urinary diversion, vesicoureteral reflux, and obstructive uropathies.

They are also commonly seen in people with underlying metabolic disorders, such as idiopathic hypercalciuria, hyperparathyroidism, and gout. Infection stones can grow rapidly, forming large calyceal staghorn (antler-shaped) calculi requiring invasive surgery such as percutaneous nephrolithotomy for definitive treatment. **(Vijaya T, et al 2013)**

- **Uric acid stones**

About 5–10% of all stones are formed from uric acid. People with certain metabolic abnormalities, including obesity14 may produce uric acid stones. They also may form in association with conditions that cause hyperuricosuria (an excessive amount of uric acid in the urine) with or without hyperuricemia (an excessive amount of uric acid in the serum).

They may also form in association with disorders of acid/base metabolism where the urine is excessively acidic (low pH), resulting in precipitation of uric acid crystals.

A diagnosis of uric acid urolithiasis is supported by the presence of a radiolucent stone in the face of persistent urine acidity, in conjunction with the finding of uric acid crystals in fresh urine samples. **(Vijaya T, et al 2013)**

- **Other types**

People with certain rare inborn errors of metabolism have a propensity to accumulate crystal-forming substances in their urine. For example, those with cystinuria, cystinosis, and Fanconi syndrome may form stones composed of cystine.

People afflicted with xanthinuria often produce stones composed of xanthine. People afflicted with adenine phosphoribosyl transferase deficiency may produce 2,8-dihydroxyadenine stones, **(Kamatani N 1996)** alkaptonurics produce homogenetisic acid stones, and iminoglycinurics produce stones of glycine, proline and hydroxyproline. **(Coskun T, et al 1993)**

Urolithiasis has also been noted to occur in the setting of therapeutic drug use, with crystals of drug forming within the renal tract in some people currently being treated with agents such as indinavir, **(Merck S and Dohme 2010)** sulfadiazine (**Schlossberg and Samuel 2011)** and triamterene. **(Carr M, et al 1990)**

Location:

Urolithiasis refers to stones originating anywhere in the urinary system, including the kidneys and bladder. **(Pearle M, et al 2007)** Nephrolithiasis (from the Greek νεφρός (nephros, "kidney") and λίθος (lithos, "stone")) refers to the presence of such calculi in the kidneys.

Calyceal calculi refer to aggregations in either the minor or major calyx, parts of the kidney that pass urine into the ureter.

The condition is called ureterolithiasis when a calculus is located in the ureter. Stones may also form or pass into the bladder, a condition referred to as cystolithiasis.

Ureteral pathophysiology of obstruction

An increase of cytoplasmatic free calcium concentration is one principal mechanism initiating ureteral contraction. It was demonstrated that calcium channel inhibitors counteract the phasic-rhythmic activity in isolated human caliceal segments **(Hertle L and Nawrath H 1984)** and in the ureter. **(Borghi L, et al 1994)**

Smooth muscle in the ureteral wall contracts, in an attempt to resolve obstruction, and becomes spastic if its effort fails. A long isotonic contraction leads to an increased lactic acid production that will irritate type A slow fibers (myelinated) and type C rapid fibers (unmyelinated). These nerve impulses generated travel to medullary segments T11-L2, reaching the central nervous system, where they are specified by location, character, and intensity, which will potentiate the attack.

Endogenous prostaglandin synthesis and calcium influx induce spontaneous rhythmic contractions of the human ureter, which are inhibited by the calcium channel blockers nifedipine and verapamil .This negative effect on ureteral contractility has evoked interest in using calcium channel blockers to facilitate medical-induced stone passage. **(Sahin A 1993)**

Three different subtypes of adrenergic receptors have been pharmacologically identified: alpha-1_a, alpha-1_b, and alpha-1_d.**(Hieble J, et al 1995)** A heterogeneous distribution of alpha-1 adrenergic receptor binding sites was detected, with the highest density in the distal ureter. **(Sigala S, et al 2005)**

The distribution of adrenergic receptors throughout the inner and outer smooth muscle of the ureter was highest for alpha-1_d, especially in

the distal ureter, followed by alpha-1_a and alpha-1_b adrenergic receptors. **(Itoh Y, et al 2007)**

Heterodimers alpha-1_a/alpha-1_b and alpha-1_b/alpha-1_d do occur, whereas alpha-1_a/alpha-1_d adrenergic receptors do not heterodimerize, suggesting a possible regulatory role of alpha-1_b. This ability to oligodimerize could influence future drug development. **(Uberti M, et al 2003)**

The exact pathophysiology of ureteral colic and stone passage is not completely understood. A ureteral stone tends to induce a ureteral inflammatory response by ureteral stone obstruction and ureteral wall tension stimulating prostaglandin synthesis. Prostaglandins have a dilating effect on afferent arterioles resulting in an increased renal blood flow, further increasing ureteropelvic pressure, inflammation, and edema. **(Ahmad M, et al 1991)**

A subsequent increase of smooth muscle contraction impairs propulsive antegrade peristalsis aggravating ureteral obstruction, impaction, and pain. **(Yamaguchi K, et al 1999)**

Therefore the ideal agent to facilitate stone expulsion would reduce ureteral inflammation, edema, ureteral spasm, and uncoordinated ureteral contractions without altering propulsive peristalsis.One possible pathway for medical treatment is anti-inflammatory and anti-edematous treatment by glucocorticoids. Another option is the relaxation of ureteral smooth muscle, by alpha-1 adrenoceptor antagonists or calcium channel blockers.

A number of randomized clinical trials have tested these drugs, and the resulting findings have almost always been interpreted as proof of efficacy. **(Hertle L, et al 1984)**