



**Semi-rigid Ureteroscopy and Holmium
laser stone dusting for Proximal
Ureteral Stones. Does Adjuvant
Tamsulosin Therapy Increase the
Chance of Success?**

Thesis

*Submitted for Partial Fulfillment of Master
Degree in Urology*

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Dedication

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List of Abbreviations

Abb.	Full term
5-HT.....	5-Hydroxytryptamine
ARs.....	Adrenoceptors
BPH	Benign prostatic hyperplasia
CGRP	Calcitonin Gene-Related Peptide
DAG	Diacylglycerol
EHLs.....	Electrohydraulic lithotriptors
Fr	Francium
FREDDY.....	Frequency-doubled, double-pulse neodymium:YAG
HFU	Hounsfield unit
Ho: YAG.....	Holmium:YAG
IP 3.....	Inositol trisphosphate
LED.....	Light-emitting diode
LLs	Laser lithotriptors
MET	Medical expulsive therapy
NK.....	Neurokinin
NO.....	Nitric Oxide
NPK	Neuropeptide K
NPY.....	Neuropeptide Y
PLC	Phospholipase C
PLs	Pneumatic lithotriptors
PTFE	Polytetrafluoroethylene
SFR	Stone free rate
SP.....	Substance P
ULs	Ultrasonic lithotriptors
URSL	Uretroscopic lithotripsy
UTI.....	Urinary tract infection
VIP.....	Vasoactive intestinal polypeptide

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INTRODUCTION

Urolithiasis is a common and increasing condition. The global mankind prevalence of urinary tract stones has been estimated to be between 2% to 20% and afflicting 13% of men and 7% of women. 20% of whole urinary stones are ureteral stones, where 70% of these ureteral stones are located in the distal portion of the ureters. If intervention is indicated, some investigators prefer ureteroscopic lithotripsy (URSL), which is a single procedure and has been proven to achieve a higher success rate (*Ketabchi and Mehrabi, 2014*).

There are three important narrowings of the ureteric lumen: at the pelvi-ureteric junction, crossing the iliac vessels and at the vesico-ureteric junction. Instrumentation and stones may get held up at these sites (*Wood and Greenwell, 2016*).

Three different subtypes of alpha 1 adrenoceptors (ARs) have been cloned, pharmacologically characterized and named alpha 1 A, alpha 1 B, and alpha 1 D, according to the indications of the International Union of Pharmacology. The distribution of ARs was $\alpha 1d \geq \alpha 1a > \alpha 1b$. Furthermore, the distal ureter expressed the highest alpha 1 AR mRNA gene, compared to other ureteral regions (*Itoh et al., 2007*).

Tamsulosin is a combined $\alpha 1A$ and $\alpha 1-D$ selective adrenergic antagonist, considering studies that demonstrated the existence of $\alpha 1A$ and $\alpha 1-D$ adrenoceptor subtypes in the

smooth muscle cells of the human ureter. Tamsulosin increase the intraureteral pressure above the stone and lowers the pressure below it which leads to increase the rate of stone clearance. Tamsulosin also leads to decrease in the phasic peristaltic contractions in the obstructed ureter, which leads to decrease in the painful stimulus (*Cakiroglu et al., 2013*).

AIM OF THE WORK

We aim to evaluate whether peri-operative tamsulosin in stented ureteroscopic laser lithotripsy for proximal ureteric stones increase the procedure success rate of stone clearance.

Chapter 1

THE HUMAN URETER AND TAMSULOSIN

Physiology and Pharmacology of the Human ureter

Adrenoceptors

Alpha adrenoceptors have been detected both in animal and human ureters. Activation of α_1 -adrenoceptors can activate phospholipase C (PLC), which in turn leads to formation of second messengers (inositol trisphosphate (IP_3) and diacylglycerol (DAG)) pathway and may cause contraction.

Blockage of these receptors inhibits basal tone, peristaltic frequency and ureteral contractions. Noradrenaline, an adrenergic agonist, increases ureteric peristaltic activity and muscle tone upon stimulation.

Tamsulosin, selective α_1A - and α_1D -antagonist, is commonly used in the management of benign prostatic hyperplasia. However, due to its selective anti-adrenergic effects, it has also successfully been used in patients with distal ureteric stones and was found to increase stone expulsion rate, decrease expulsion time and reduce the need for hospitalization and endoscopic procedures.

Beta adrenoceptors: When norepinephrine is released from adrenergic nerves, stimulation of beta adrenoceptors

activates adenylate cyclase to increase cAMP. Then, cAMP activates protein kinase A which in turn causes relaxation. (*Michel and de la Rosette, 2006*).

Muscarinic Acetylcholine Receptors

The presence of five muscarinic receptor subtypes (M 1 – M 5) were immunohistochemically shown in the human ureter. Activation of muscarinic acetylcholine receptors leads to ureteral contraction via activation of phospholipase C (PLC) (*Sakamoto et al., 2006*).

Nitric Oxide (NO)

L -Arginine-derived NO is the major inhibitory non adrenergic non cholinergic neurotransmitter in the lower urinary tract.

Histamine

It was demonstrated that two types of histamine receptors modulate the contractile activity of the human ureter, whereby histamine H 1 –receptors cause contraction and histamine H 2 – receptors cause slight relaxation (*Michel and de la Rosette, 2006*).

Serotonin (5-Hydroxytryptamine, 5-HT)

5-HT was shown to increase the tone of intravesical ureter via 5-HT 2A receptors.

Calcium Channel Blockers

Calcium antagonists are known to reduce ureteral contractions.

Neuropeptides

Neuropeptides such as vasoactive intestinal polypeptide (VIP), endothelins, tachykinins and angiotensins are synthesized in the lower urinary tract. Release of tachykinins, substance P (SP), neurokinin (NK) A and neuropeptide K (NPK) from sensory nerves cause excitation.

Calcitonin Gene-Related Peptide (CGRP)

CGRP inhibits electrically-evoked myogenic contractions of the ureter leading to relaxation of ureter.

Neuropeptide Y (NPY)

Potentiates phasic contractions and tone created by noradrenaline.

Tamsulosin

Pharmacokinetics

Absorption: Completely absorbed following oral administration under fasting conditions.

Distribution: Studies suggest distribution into extracellular fluids and most tissues, including kidneys, prostate, gallbladder, heart, aorta, and brown fat, with minimal distribution into brain, spinal cord, and testes. Drug is extensively bound to plasma proteins but isn't thought to affect other highly bound drugs.

Metabolism: Tamsulosin metabolized by cytochrome P-450 in the liver, with less than 10% excreted unchanged; however, pharmacokinetic profile of metabolites hasn't been established. Metabolites undergo extensive conjugation to glucuronide or sulfate before renal excretion.

Excretion: Tamsulosin excreted primarily in urine (76%); about 21% excreted in feces. Elimination half-life is 5 to 7 hours, with apparent half-life from 9 to 15 hours secondary to rate-controlled absorption pharmacokinetics (*Hermanns et al., 2009*)

Pharmacodynamics

Tamsulosin is a combined $\alpha 1A$ and $\alpha 1-D$ selective adrenergic antagonist, considering studies that demonstrated the existence of $\alpha 1A$ and $\alpha 1-D$ adrenoceptor subtypes in the smooth muscle cells of the human ureter. Tamsulosin increase the intraureteral pressure above the stone and lowers the pressure below it which leads to increase the rate of stone clearance. Tamsulosin also leads to decrease in the phasic

peristaltic contractions in the obstructed ureter, which leads to decrease in the painful stimulus (*Cakiroglu et al., 2013*).

Anti-BPH action: Drug selectively blocks α_1 -receptors in the prostate, leading to relaxation of smooth muscles in the bladder neck and prostate, improving urine flow, and reducing BPH symptoms.

Although ureteral stones less than 5 mm could pass in up to 98% of cases, fragmented stones following lithotripsy interventions cause some degree of ureteral wall congestion and oedema, interfering with straight gravel passing and even leading to stone impaction and obstruction.

In terms of stone expulsion and control of ureteric colic pain, drugs (e.g. calcium channel blockers, nifedipine, corticosteroids, α_1 blockers) that can modulate the function of the ureter, which may be obstructed by a stone, can be used

Many recent studies have demonstrated that the efficacy of α -blockers is preferred to the other medical expulsive therapy efficacies after laser lithotripsy and ESWL procedures for proximal ureter stones and the passing of lower ureter stones. Moreover, α -blockers, especially tamsulosin, which is a highly selective sympatholytic agent, may reduce complications after stone breaking and gravel passing in all lithotripsy procedures.