Comparative Study between Tadalafil versus Tamsulosin versus Halphabarol with Terpenes Mixture as a Medical Expulsive Therapy for Lower Ureteric Stones

Thesis

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Maysara Ebrahim

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List of Abbreviations

Abb.	Full term
AAG	*Alpha-1-Acid Glycoprotein*
Ach	*Acetylcholine*
ATP	*Adenosine Triphosphate*
AUC	*Area under the Curve*
BMI	*Body Mass Index*
BPH	*Benign Prostatic Hyperplasia*
Bpm	*Beats per Minute*
Ca2+	*Calcium ions*
cAMP	*Cyclic Adenosine Monophosphate*
cGMP	*Cyclic Guanosine Monophosphate*
cm	*Centimeter*
Cmax	*Maximum or Peak Concentration*
CT	*Computed Tomography*
CYP	*Cytochrome P450*
CYP	*Cytochrome P450*
DAG	*Diacylglycerol*
DECT	*Dual-Energy Computed Tomography*
EAU	*European Association of Urology*
ED	*Erectile Dysfunction*
ESRD	*End-Stage Renal Disease*
ESWL	*Extracorporeal Shockwave Lithotripsy*
FDA	*Food and Drug Administration*
g/mol	*Grams per Mole*
Gc	*Guanylate Cyclase or Guanylyl Cyclase*
GMP	*Guanosine Monophosphate*
GPCR	*G-Protein-Coupled Receptor*
GTP	*Guanosine Triphosphate*
Ho: YAG	*Laser Holmium: Yttrium-Aluminium-Garnet Laser*

List of Abbreviations (Cont...)

Abb.	Full term
HS	*Highly Significant*
IFIS	*Intraoperative Floppy Iris Syndrome*
IP3	*Inositol Trisphosphate*
IVU	*Intravenous Urography*
K+	*Potassium ions*
kg/m2	*Kilograms per Square Meter*
KUB	*Kidney, Ureter and Bladder Radiography*
L2	*2nd Lumbar Vertebra*
L3	*3rd Lumbar Vertebra*
L4	*4th Lumbar Vertebra*
LUTS	*Lower Urinary Tract Symptoms*
M receptor	*Muscarinic Receptor*
MET	*Medical Expulsive Therapy*
mg	*Milligram*
mg/kg	*Milligramper Kilogram*
mL/min	*Milliliter per Minute*
mm	*Millimeter*
mmHg	*Millimeters of Mercury*
MRHD	*Maximum Recommended Human Dose*
mRNA	*Messenger Ribonucleic Acid*
MRU	*Magnetic Resonance Urography*
NAION	*Non-Arteritic Anterior Ischemic Optic Neuropathy*
NCCT	*Non-Contrast Computed Tomography*
NO	*Nitric Oxide*
NOS	*Nitric Oxide Synthase*
NS	*Non Significant*
NSAIDs	*Non-Steroidal Anti-Inflammatory Drugs*
PAH	*Pulmonary Arterial Hypertension*

List of Abbreviations (Cont...)

Abb.	Full term
PCN	*Percutaneous Nephrostomy*
PDE	*Phosphodiesterase*
PDE5	*Phosphodiesterase Type 5*
PKC	*Protein Kinase C*
PLC	*Phospholipase C*
PSA	*Prostate Specific Antigen*
PUJ	*Pelviureteric Junction*
RBCs	*Red Blood Cells*
RMP	*Resting Membrane Potential*
S	*Significant*
SFRs	*Stone-Free Rates*
SWL	*Shockwave Lithotripsy*
T1/2	*Terminal Plasma Half-Life*
Tmax	*Time to Maximum or Peak Concentration*
UPJ	*Ureteropelvic Junction*
URS	*Ureteroscopy*
US	*Ultrasound*
UTI	*Urinary Tract Infection*
Vd	*Volume of Distribution*
VUJ	*Vesicoureteric Junction*
WBCs	*White Blood Cells*
α	*Alpha*
β	*Beta*

ABSTRACT

Background: urolithiasis is a health problem of worldwide importance. Urolithiasis is the third most common urological disease affecting the urinary tract after urinary tract infections and prostatic diseases. Ureteral stones account for 20% of urolithiasis, and 70% of ureteral stones are located in the lower third of the ureter. Ureteric stones have great bearing on the health as well as quality of life of the patient.

Aim of the Study: to compare the efficacy of tadalafil (a phosphodiesterase-5 inhibitor), tamsulosin (an alpha-1blocker) and halphabarol (Proximol) with terpenes mixture (Rowatinex) as a medical expulsive therapy for lower ureteric stones.

Patients and Methods: this was a prospective randomized comparative study conducted on 60 patients between the ages of 20 and 40 years and complaining of unilateral single lower ureteric stone less than or equal to 8 mm presented through the outpatient clinics of Urology in Ain Shams University Hospitals and Damanhour Medical National Institute over a period of 10 months (from November 2017 to August 2018). The patients were randomly divided into 3 equal groups: Group A (20 patients were treated by tadalafil 5 mg once daily), Group B (20 patients were treated by tamsulosin 0.4 mg once daily) and Group C (20 patients were treated by Proximol with Rowatinex three times daily). Therapy was given for a maximum of 3 weeks. The patients were followed-up until stone passage or the end of the study period.

Results: the results of this study indicate that the stone expulsion rate was significantly higher in tadalafil group and tamsulosin group than Proximol with Rowatinex group (75% vs. 75% vs. 40%, P value = 0.030). Also, the mean stone expulsion time was significantly shorter in tadalafil group and tamsulosin group than Proximol with Rowatinex group (10.20 ± 3.91 days vs. 10.80 ± 3.64 days vs. 14.25 ± 3.28 days, P value = 0.046). The number of patients who experienced renal colic episodes, the number of colic episodes and the number of injectable analgesic uses were significantly lower in tadalafil group and tamsulosin group than Proximol with Rowatinex group (P value < 0.05). The number of follow up ureteroscopic procedures was significantly lower in tadalafil group and tamsulosin group than Proximol with Rowatinex group (25% vs. 25% vs. 60%, P value = 0.030). Also, the drugs are safe with mild few side effects.

Conclusion: PDE5 inhibitors (tadalafil) are equally efficacious to alpha-1 adrenergic antagonists (tamsulosin) in expulsion of lower ureteric stones less than or equal to 8 mm without any serious side effects. Comparing to Proximol with Rowatinex, both tadalafil and tamsulosin increase significantly the stone expulsion rate, decrease significantly the stone expulsion time and provide significant control of renal colicky pain, significantly less analgesic requirements and significantly lower follow up ureteroscopic procedures.

Keywords: *Tadalafil - Tamsulosin - Halphabarol - Terpenes Mixture - Lower Ureteric Stones*

INTRODUCTION

Urolithiasis, the formation of urinary stones, is a health problem of worldwide importance. Urolithiasis is the third most common urological disease affecting the urinary tract after urinary tract infections and prostatic diseases. The prevalence of urolithiasis varies between 2 and 20% throughout the world. The worldwide prevalence of the disease has been on the increase in the last three decades for both adult and children throughout the world ***(Curhan, 2007)***. Improved detection of stones, increasing lifespan, and dietary changes may be related to the increased prevalence of stone disease. There is a great deal of research suggests that the change of external factors take a significant place in the risk of occurrence of urolithiasis, even though genetic components also present a significant cause of urolithiasis ***(Attanasio, 2011)***.

Urinary stones are most prevalent between the ages of 20 and 40 years and are 3 times more common in men than women. Women excrete more citrate and less calcium than men, which partially explains the higher incidence of stone disease in men ***(Manglaviti et al., 2011)***. Some recent researches suggest that the epidemic factors of urolithiasis include: age, gender, obesity, hypertension, diabetes mellitus, gout, hyperparathyroidism, gastrointestinal diseases, diet, dehydration, immobilization, anatomic anomalies, medicines and disorder of calcium-phosphate metabolism ***(Milicevic et al., 2014)***.

Ureteral stones account for 20% of urolithiasis, and 70% of ureteral stones are located in the lower third of the ureter. Ureteric stones have great bearing on the health as well as quality of life of the patient ***(Dellabella et al., 2005)***. About 50% of patients who present with flank pain have a ureteric stone confirmed with imaging studies ***(Smith et al., 1996)***. Renal colic is one of the most painful conditions that may occur and it is often caused by stone in the distal portion of the ureter ***(Segura et al., 1997)***.

Spontaneous stone expulsion decreases with increasing stone size. It is estimated that 95% of ureteral stones smaller than 5 mm will pass spontaneously. This drops to 50% for stones greater than 5 mm. Stones greater than 6 mm have a lower rate of spontaneous passage. Duration of stone passage may be as long as 40 days ***(Preminger et al., 2007)***. The factors affecting spontaneous stone passage are the stone location, size, number, and structure, spasm of ureteral smooth muscles, mucosal oedema or inflammation, and ureteral anatomy. Of these, the location of the stone and its size are the most important factors ***(Sur et al., 2015)***. Therefore, the use of medical therapy is justifiable to reduce oedema, reduce spasm, and relax the smooth muscles for stone expulsion ***(Seitz et al., 2009)***.

Many factors are involved in the interaction between the ureter and stones, therefore it is useful to understand mechanisms involved in the contraction and relaxation of the ureter. These mechanisms would possibly lead to discovery of