# Vardenafil versus Tamsulosin as a Medical Expulsive Therapy for Distal Ureteral Stones

Thesis

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# List of Abbreviations

| Abb. | Full term |
|---|---|
| *AUA* | *American Urological Association* |
| *cAMP* | *Cyclic Adenosine Monophosphate* |
| *cGMP* | *Cyclic Guanosine Monophosphate* |
| *DAG* | *Diacylglycerol* |
| *DUS* | *Distal Ureteric Stones* |
| *EAU* | *European Association of Urology* |
| *ESWL* | *Extracorporeal Shockwave Lithotripsy* |
| *GFR* | *Glomerular Filtration Rate* |
| *GPCR* | *G-Protein-Coupled Receptor* |
| *IP 3* | *Inositol Trisphosphate* |
| *IVP* | *Intravenous Pyelogram (* |
| *KUB* | *Kidney, Ureter and Bladder* |
| *MET* | *Medical Expulsive Therapy* |
| *PDE5* | *Phosphodiesterase 5* |
| *PLC* | *Phospholipase C* |
| *SFRs* | *Stone-Free Rates* |
| *SWL* | *Shockwave Lithotripsy* |
| *TM* | *Transmembrane* |
| *URS* | *Ureteroscopy* |
| *UVJ* | *Ureterovesical Junction* |

# Abstract

Follow-up would be performed every week by asking the patient about stone passage, time of stone passage, attacks of renal colic, analgesic use and side-effects of the drugs. Radiological assessment would be done every week with plain KUB. The patients would be followed-up until stone passage which would be confirmed by plain KUB, non-contrast spiral CT or at the end of the study period (4 weeks).

In this study, we found that the stone expulsion rate was non significantly higher in vardenafil group compared with tamsulosin group that the expulsion rate with vardenafil was 76.0% while with tamsulosin was 72.0 %, and we found the mean of stone expulsion time was non significantly shorter in vardenafil group 9.95 days than tamsulosin group 11.28 day.

Also, both drugs were safe with few side effects as headache, dizziness, orthostatic hypotenion and retrograde ejaculation.

***Keywords:*** G-Protein-Coupled Receptor - Inositol Trisphosphate - Vardenafil

# INTRODUCTION

Urolithiasis is one of the most common diseases of the urinary tract. The lifetime prevalence of urinary stones is around 1% to 15%, and the peak age of incidence is at 30 years. Men are affected 2 to 3 times more often than women. Ureteral stones account for 20% of the calculi in urolithiasis and about 70% of ureteral stones are present in the distal third of the ureter at the time of presentation. About 50% of patients will have a recurrence of renal colic within 5 years of their first episode ***(Pearle and Lotan, 2012).***

Ureteral stones induce ureteral spasms that interfere with stone expulsion. Thus, reducing these spasms while maintaining normal peristaltic activity can facilitate stone expulsion. Almost 50% of ureteral stones will pass spontaneously over time and stone size is the key factor for success. Usually, stones smaller than 5 mm are expected to pass spontaneously, whereas only 20% of stones larger than 8 mm will pass. This conservative approach to treatment is based on the pharmacological control of pain, oedema, ureteric spasm, and infection, all factors trying to favour stone expulsion ***(Ueno et al., 1977).***

The management of ureteric stones had changed greatly over the last two decades, especially after the introduction of shockwave lithotripsy (SWL) and ureteroscopy, as minimally invasive treatments. However, these treatments are not risk free

and are expensive. The overall complications after ureteroscopy have been estimated to be 10-20% in different studies, in which major complications, such as ureteric perforations, strictures and avulsions, occurred in 35% of complicated cases ***(Pickard et al., 2015).***

Multiple management options for ureteric stones are present, such as conservative, medical expulsive therapy (MET), extracorporeal shockwave lithotripsy (ESWL), ureteroscopy and open surgical procedures. MET includes various drugs, such as a-adrenergic blockers, PDE5 inhibitors, calcium channel blockers and anti-inflammatory drugs, which have a relaxant effect on the ureteric smooth musculature ***(Shokeir et al., 2016).***

Alpha-adrenergic blockers, used recently as medical expulsive therapy (MET), have replaced minimally invasive procedures as the first line of management for small ureteric stones, because spontaneous stone passage in patients given α-blockers were 52%, and stone passage in patients taking α-blockers were 44% greater than those not given such medications ***(Parsons et el., 2007).***

Stone clearance of distal ureteral stones (DUS) can be affected by several factors such as stone size, number, site, and also the presence or absence of ureteric smooth muscle spasm and/or submucosal oedema ***(Sur et al., 2015).***

The α receptors have the subtypes α1 and α2. α1-Adrenoceptors were classified into three different subtypes of α-1A, α-1B and α-1D, of which the distribution in the ureter was α-1D > α-1A > α-1B. The α1A- and α1D-adrenoceptors are the most abundant subtypes in the distal ureter. Stimulation of these α1-adrenoceptors leads to increases in both the frequency of ureteric peristalsis and the force of ureteric contractions. So, blockage of these receptors decreases basal ureteric tone, decreases peristaltic amplitude and frequency, leading to a decrease in intra-luminal pressure which increases the rate of urine transport and thus increasing the chance of stone passage ***(Itoh et al., 2013).***

The α-blockers have pain relieving effects which may be explained by the blocking of the conduction of visceral referred pain to the central nervous system, acting on C-fibers ***(Kumar et al., 2015).***

Tamsulosin, an α1-adrenoceptor antagonist, is one of the most popular and effective medical agents, which is used for the expulsive therapy ***(Dell'Atti, 2015).***

Tamsulosin is a selective α1-blocker with a 10-fold greater affinity for the α1A and α1D-adrenoceptor subtypes than for the α1B-adrenoceptor subtype ***(Griwan et al., 2010).***

Tamsulosin is safe and well tolerated, side-effects may occur such as retrograde ejaculation, which is reversible, and orthostatic hypotension. cardiovascular adverse effects may occur

so a Highly selective α1A-adrenoceptor blockers have been developed to minimize the cardiovascular adverse effects with increasing their efficacy on the urinary tract ***(Furyk et al., 2015).***

Regarding the incidence of the retrograde ejaculation, there is a consensus among many urologists, that its occurrence should be considered as a sign of the efficacy, rather than an adverse effect of the treatment. α-blockers appears to relax the smooth muscles of the lower urinary tract and the genital tract enough to induce a retrograde ejaculation. This was reflected in the finding that the patients who had the greatest relief from the lower urinary tract symptoms had a higher likelihood of the retrograde ejaculation. This observation suggests that the retrograde ejaculation is actually an indirect indicator of the relaxation of the smooth musculature that α-blockers induce ***(Sahin et al., 2015).***

Relaxation of the smooth muscles of the lower ureter plays a major role in MET. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important intracellular second messengers mediating cellular responses. An increase in cAMP and cGMP triggers a signal transduction cascade, which leads to smooth muscle relaxation. Cyclic nucleotides (cAMP and cGMP) are degraded by the enzyme phosphodiesterase 5 (PDE5). Thus, using PDE5 inhibitors can play a role in the relaxation of the smooth muscle of the ureter by preservation of cAMP and cGMP. In studies conducted to