Effectiveness of mirabegron vs tamsulosin in patients with ureteral stent: A randomized placebo control, prospective clinical trial (743)

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Hypothesis/ aims of study

Ureteral stents can induce discomfort in patients, primarily attributed to irritation of the bladder mucosa, smooth muscle spasm, and urine reflux into the ureters. The initial response to injury caused by a ureteral stent is acute inflammation, marked by vasodilation, increased vascular permeability, leukocyte migration, and activation of a biochemical cascade releasing mediators that induce symptoms of bladder mucosa irritation. This manifestation is evident through the disappearance of the urothelium and its replacement by granulation tissue, with thinning and/or ulceration observed at the microscopic tissue level [1]. Mild fever may occur as a result of the systemic release of inflammatory mediators [2].

Mirabegron, a β3 adrenergic receptor agonist, exerts a dual antioxidant effect, crucial in the initial stages of the antimicrobial response and resolution of inflammation [3]. This property potentially contributes to the resolution of post-stent complaints, akin to overactive bladder (OAB) symptoms [4]. Tamsulosin, a selective α1A- and α1D-adrenoceptor antagonist, alleviates stent-related symptoms by relaxing smooth muscle in the prostate, bladder neck, and distal ureter, leading to a reduction in inflammatory reactions and improvement in oxidative stress through the modulation of proteins such as p83, IL-6, TNF-α, and IL-8 at the protein level. [5].

To date, no studies have directly utilized the inflammatory mediator IL-6 to evaluate the incidence of inflammation during mirabegron and tamsulosin therapy in patients with ureteral stents.

This study is the first to look at inflammatory cytokines, histological changes in the bladder mucosa, and their impact on lower urinary tract complaints by comparing the efficacy of mirabegron 50 mg/day and tamsulosin 0.4 mg/day in patients with ureteral stents installation.

Study design, materials and methods

This is a double blind, prospective, randomized clinical trial of patients treated with unilateral ureteral stents. Patients were divided randomly into three groups (placebo/ tamsulosin 0.4mg/ mirabegron 50mg). Blood, urine, and bladder mucosal biopsies were collected before placement and when the ureteral stent was removed. Lower urinary tract symptoms (LUTS) were assessed using the USSQ-urinary symptoms following ureteral stent placement.

Inclusion Criteria
1. Individuals aged over 18 years. 2. Underwent ureterorenoscopy (URS) with either a semi-rigid or flexible ureteroscope. 3. Had their first ureteral stent installed on one side.
Exclusion Criteria
1. History or current diagnosis of urinary tract malignancy. 2. Lower urinary tract symptoms (LUTS) attributable to benign prostate enlargement, bladder stones, or urethral stricture. 3. Regular catheter use or undergoing independent catheter therapy. 4. Urinary diversion. 5. Post-void residual volume exceeding 350 mL. 6. Neurogenic bladder or overactive bladder (OAB) syndrome. 7. Stress incontinence or mixed stress/urge incontinence. 8. Uncontrolled chronic pain or undergoing chronic pain therapy. 9. Symptomatic urinary tract infections. 10. History of or ongoing radiation therapy, hormonal therapy, or minor pelvic surgical procedures. 11. History of ureter reconstruction surgery. 12. Primary neurological disorders (e.g., multiple sclerosis, Parkinson's). 13. Diabetic nephropathy, uncontrolled hypertension, or other neurological conditions affecting bladder function. 14. Hypersensitivity to mirabegron and tamsulosin or their derivatives. 15. Contraindications to these medications. 16. Inability to adhere to the research protocol due to organic brain or psychiatric disorders, autoimmune diseases, or other inflammatory conditions. 17. Taking immunosuppressant drugs

The dropout criteria included the necessity for ureteral stent removal before 6 weeks, the presence of macroscopic hematuria, and the occurrence of symptomatic urinary tract infection (UTI) during the observation phase.

Samples for IL-6 analysis was collecting from blood and urine before the stent is installed and before the stent is removed/replaced

Bladder mucosa biopsy is meticulously conducted within the trigonum vesicae, specifically around the contralateral ureter opening during cystoscopy preceding ureteral stent installation. Additionally, biopsies are undertaken on the ipsilateral side when the ureteral stent is scheduled for removal or replacement during the 6th week post-ureteral stent placement. Following biopsy collection, the obtained samples undergo Hematoxylin-Eosin (HE) staining

All research participants completed the Urinary Symptoms-USSQ, either in-person upon arrival or via telephone.

Data were analyzed using the Kruskal-Wallis test with p-value ≤ 0.05, then tested with pairwise comparisons.

Results and interpretation

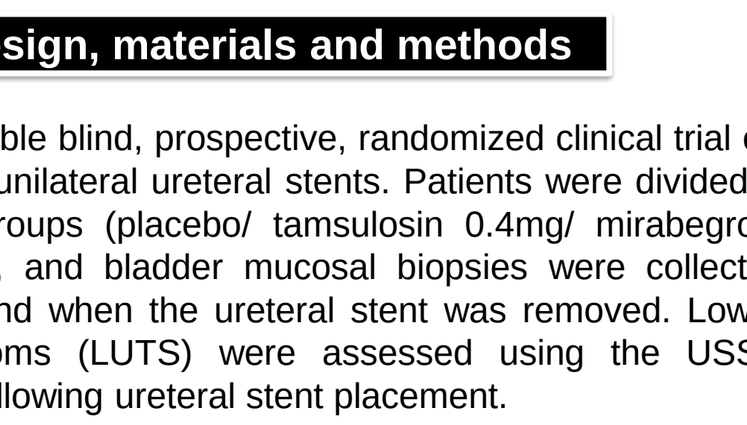

Figure 1. Flow diagram of the randomized clinical trial process.

Table 1. Relationship Between Bladder Mucosa Inflammation and Lower Urinary Tract Complaints (USSQ - urinary symptom)

	Pathological Anatomy Grading After Stent Placement	n	Median	Min	Max	P-Value
Delta Score of USSQ-Urinary symptoms	Grade 0	5	-1	13	7	0,016
	Grade 1	11	-6	23	18	
	Grade 2	14	-6	25	14	
	Grade 3	10	0	21	12	
	Grade 4	10	-2	12	6	

Note: Kruskal-Wallis test with p≤0,05

Table 2. The relationship between the degree of inflammation of the bladder mucosa and IL-6 levels in serum and urine was investigated in patients with ureteral stent placement.

Variable	Delta IL-6 in the Serum (pg/ml)				
Pathological Anatomy Grading After Stent Placement	n	Median	Min	Max	P-Value
Grade 0	5	1,04	-3,63	13,81	0,02
Grade 1	11	0,76	-0,12	5,77	
Grade 2	14	-0,91	-52,1	2	
Grade 3	10	0,01	-0,48	0,65	
Grade 4	10	5,33	-103,3	4,06	
	Delta IL-6 in the Urine (pg/ml)				
Pathological Anatomy Grading After Stent Placement	n	Median	Min	Max	P-Value
Grade 0	5	0,15	-6,74	3,45	0,003
Grade 1	11 *	0,78	-8,32	7,33	
Grade 2	14	-4,21	-152,5	-1,41	
Grade 3	10	-2,7	-141,85	5,33	
Grade 4	10	-71,8	-199,7	0,09	

Note: Kruskal-Wallis test with p≤0,05

Table 3. Relationship Between Type of Therapy and Changes in Bladder Mucosa Histology

Variable	Group	N	Median	Min	Max	P-Value
Prior Stent Placement	Placebo	16	1	0	2	0,960
	Tamsulosin	17	1	0	2	
	Mirabegron	17	1	0	2	
Post Stent Placement	Placebo	16	3	0	4	0,004
	Tamsulosin	17	2	0	4	
	Mirabegron	17	2	0	3	

Note: Kruskal-Wallis test with p≤0,05

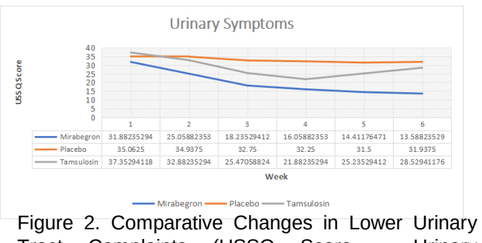

Figure 2. Comparative Changes in Lower Urinary Tract Complaints (USSQ Score – Urinary Symptoms) from the Placebo, Tamsulosin, and Mirabegron Therapy Groups from the First Week to the Sixth Week

Table 4. Comparison of types of therapy on changes in the histology of the bladder mucosa

Variable	P-value
Mirabegron-Tamsulosin	0,337
Mirabegron-Placebo	0,001
Tamsulosin-Placebo	0,021

Note: Pairwise Comparison test with p≤0,05

Table 5. Comparison of Types of Therapy on USSQ (Urinary Symptoms) Results Weekly

Variable	P-value
mirabegron-tamsulosin	0,000
mirabegron-plasebo	0,000
tamsulosin-plasebo	0,050

Note: pairwise comparison test with p≤0,05

Table 5. Differences in Mean Serum IL-6 Levels Based on Type of Therapy

Variable	Group	N	median	min	max	p-value
Prior Stent Placement	Placebo	16	7,027	0,523	34,517	0,967
	Tamsulosin	17	2,772	0,502	8,692	
	Mirabegron	17	2,569	0,622	4,893	
After Stent Placement	Placebo	16	25,446	0,802	137,547	0,019
	Tamsulosin	17	3,746	0,723	8,234	
	Mirabegron	17	2,135	0,232	8,998	

Note: Kruskal-Wallis test with p≤0,05

Table 6. Comparison of types of therapy on serum IL-6 levels

Variabel	Nilai p
Mirabegron-Tamsulosin	0,036
Mirabegron-Plasebo	0,007
Tamsulosin-Plasebo	0,538

Note: Pairwise Comparison test with p≤0,05

Table 7. Differences in average urine IL-6 Levels Based on Type of Therapy

Variable	Therapy	N	median	min	max	P-Value
IL-6 urine pre stent	Plasebo	16	7,604	0,637	67,177	0,122
	Tamsulosin	17	5,090	0,624	12,465	
	Mirabegron	17	3,187	0,754	12,529	
IL-6 urine post stent	Plasebo	16	57,751	2,750	202,568	0,024
	Tamsulosin	17	31,758	0,778	154,227	
	Mirabegron	17	6,372	0,449	29,353	

Note: Kruskal-Wallis test with p≤0,05

Table 8. Comparison of Types of Therapy on Urine IL-6 Levels

Variables	P Value
Mirabegron-Tamsulosin	0,115
Mirabegron-Plasebo	0,007
Tamsulosin-Plasebo	0,246

Note: Pairwise Comparison test with p≤0,05

Of the 78 research subjects, only 50 completed the trial (figure 1). There was a significant relationship between the degree of bladder mucosal inflammation and LUTS ($p<0.05$), as well as an increase in blood serum and urine IL-6 ($p<0.05$). Mirabegron and tamsulosin had the same effectiveness ($p=0.337$) and significantly inhibited changes in the degree of bladder mucosal inflammation better than placebo ($p=0.001$ and $p=0.021$). Mirabegron is better than tamsulosin and placebo ($p = 0.000$) and tamsulosin is better than placebo ($p = 0.05$) in reducing LUTS. Mirabegron was better than tamsulosin and placebo ($p=0.036$ and $p=0.007$) in reducing serum IL-6 levels, but mirabegron was only effective than placebo in urine ($p=0.007$). There were no side effects from the medication during this study.

Inflammation of the bladder mucosa has a direct impact on bladder function in the form of lower urinary tract disorders. Interleukin-6 can worsen the inflammatory response in interstitial cystitis and IL-6 antagonists can reduce the inflammatory response in bladder mucosal.

These results are under the mechanism of action of mirabegron which can inhibit the increase of IL-6 through several pathways and has anti-inflammatory power through antioxidant effects by directly inhibiting NADPHox-mediated ROS production and inducing the expression of the enzyme catalase which is the main scavenger of H2O. (Figure 2)

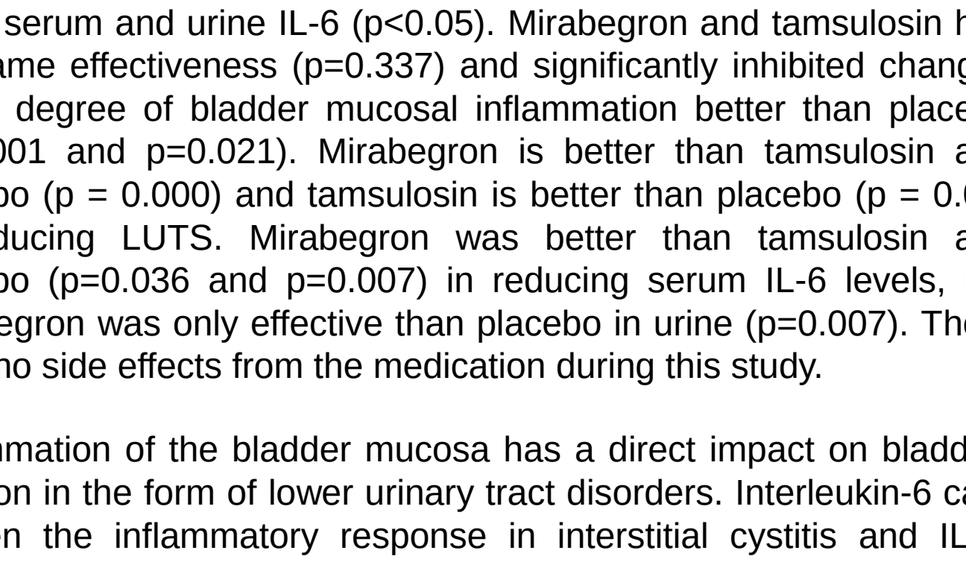

Figure 2. The mechanism of action of mirabegron in inhibiting inflammatory reactions and treating lower urinary tract complaints in patients who have had ureteral stents installed.

Conclusions

Mirabegron has been proven to be more effective in treating lower urinary tract complaints than tamsulosin and can be considered the main therapy in patients with ureteral stent placement. However, tamsulosin can be an alternative for treating lower urinary tract complaints. Although mirabegron and tamsulosin can reduce the effects caused by ureteral stents (stent-related symptom), however, the use of ureteral stents needs to be more selective in patients undergoing surgery.

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