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EFFECT OF TADALAFIL ADD-ON THERAPY IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS DUE TO BENIGN PROSTATIC HYPERPLASIA REFRACTORY TO TAMSULOSIN MONOTHERAPY: RANDOMIZED, CONTROLLED TRIAL

By

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is a non-malignant hyperplasia of prostatic cells.Most of patients with BPH present with lower urinary tract symptoms (LUTS). LUTS and BPH are highly prevalent entities in aging men.

Objectives: To assess the efficacy and safety of fixed-dose combination therapy of Tamsulosin 0.4 mg plus Tadalafil 5mg versus Tamsulosin 0.4mg, plus placebo once daily in the treatment of patients with LUTS related to BPH whose were refractory to tamsulosin monotherapy.

Patients and Methods: In this randomized controlled clinical study, carried out at Al-Azhar University Hospitals, 80 patients complaining of LUTS related to BPH were randomly divided into two equal groups. Fortypatients received fixed-dose combinations therapy of Tamsulosin 0.4mg/day and tadalafil 5mg /day for 6 months (group A), and forty patients received Tamsulosin 0.4mg plus placebo/day for 6 months (group B). The International Prostate Symptom Score (IPSS), Qmax, Post void residual urine (PVRU) and International Index of Erectile Function (IIEF-5) score used at baseline before starting treatment, at 3 months and 6 months to assess the efficacy in both groups.

Results: With combination therapy group, there was significant improvement in IPSS score P value (<0.001), significant increase in Qmax P value (<0.001), and significant decrease in PVRU P value (<0.001) compared with placepo group. IIEF- 5 score changes showed no statistically significant difference between bothgroups (P value) (0.102) in tadalafil group.

Conclusion: The fixed-dose combination of Tamsulosin 0.4 mg/day and Tadalafil 5 mg/day are significantly superior to Tamsulosin 0.4 mg/day plus placebo for the treatment of LUTS related to BPH whose were refractory to tamsulosin, supporting favorable benefit-risk balance of the fixed-dose combinations therapy for the treatment of LUTS related to BPH because of its synergistic effects, well toleration and safety.

Key words: Tadalafil, LUTS, BPH, Tamsulosin.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a disorder histologically characterized as the non-malignant hyperplasia of prostatic cells. Most of patients with BPH present with lower urinary tract symptoms (LUTS). About half of men develop BPH, among these; about half develop some

degree of bladder outlet obstruction (BOO). BOO and/or changes in smooth muscle tone and resistance that can accompany BPH may result in (LUTS) *(Gravas et al., 2015)*.

LUTS include storage disturbances (such as daytime urinary urgency and nocturia) and/or voiding disturbances (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding). LUTS affect an estimated 3 percent of men ages 45–49 years old increasing to around 30 percent of men over 85 years old. Urinary hesitancy, weak stream, and nocturia are the most commonly reported LUTS *(Karami et al., 2016)*.

Treatment decisions can typically be based on symptoms and degree of bother without need to perform specialized tests such as uroflowmetry and PVRU measurement. Lifestyle interventions such as modifying fluid intake or toileting behavior are typically the first-line treatments to reduce symptoms in patients with LUTS/BPH. When necessary, pharmacological treatment also may be initiated to reduce symptoms and prevent or delay disease progression *(Strittmatter et al., 2013)*.

Alpha-blockers have been widely used for the treatment of LUTS/BPH for a long time. Some alpha-blockers may cause ejaculatory dysfunction in some individuals.

Tadalafil, a (PDE-5), was approved by the Food and Drug Administration (FDA) for the treatment of (ED) in 2003 and for the treatment of BPH in 2011 *(Singh et al., 2014)*.

The PDE5 inhibitors are used in the treatment of ED and there are increasing data of effects of these drugs on bladder and urethral relaxation as well as of prostatic smooth muscles that may relief the symptoms of BPH *(Wang et al., 2015)*.

The inclusion of Tadalafil in complex of combined conservative therapy of patients with BPH not only improves sexual function but has a positive effect on symptoms of the disease and the psychological state of the patient *(Reges et al., 2012)*.

The aim of this study was to evaluate the efficacy and safety of once daily PDE5-I (tadalafil) as an add-on treatment for men with (BPH/LUTS) refractory to tamsulosin monotherapy.

PATIENTS AND METHODS

This was a prospective study conducted on a total of 80 patients who were complaining of LUTS associated with BPH. They were recruited from Urology Outpatient Clinics at AL-Hussein and Sayed Galal University hospitals from November 2019 to September 2020.

All patients fully under stood the treatment and aim of this study. Written informed consent was obtained from patients as well as the ethicscommittee of University.

The study included BPH patients with persistent LUTS, IPSS ≥ 8 and receiving alpha 1 blocker (tamsulosin) for at least 3 months.

Exlcusion criteria:

- Age < 50 years.
- Prostate size < 20 cc.

- Total serum prostatic specific antigen (PSA) > 4ng/ml.
- History or evidence of prostatic cancer.
- Previous prostatic surgery or other invasive procedure to treat BPH.
- Post voiding residual (PVR) of urine volume > 100 ml (suprapubic ultrasound).
- History of acute urinary retention (AUR) within 3 months prior to study.
- Any case of LUTS other than BPH (urinary bladder stone, neurogenic bladder, bladder neck contracture, urethral stricture, bladder cancer, acute or chronic prostatitis, acute or chronic urinary tract infection).
- Use of any PDE51 within the past 2 weeks prior to the study.
- Contraindication to PDE51 (e.g., patients taking nitrate or nitroglycerin and recent myocardial infarction).

All patients underwent pre-treatment, 3 and 6 months post-treatment assessment of the following parameters:

- Detailed medical and surgical history.
- Physical examination.
- Urine analysis.
- Blood analysis including prostate-specific antigen (PSA), renal function tests (blood urea and serum creatinine).
- Pelvic-abdominal Ultrasound-to assess prostatic size, and determination of post-voiding residual urine (PVR), concomitant urinary bladder pathology and upper urinary tract.
- Uroflowmetry (UFM): to determine peak flow rate, or Qmax. Peak flow rate along voiding pattern and urine volumes, to determine the severity of any blockage or obstruction.
- International index of erectile function (IIEF-5): This is a multidimensional scale that can be used to evaluate ED.

Eligible patients were randomized to receive fixed dose of Tamsulosin 0.4 mg/day plus Tadalafil 5 mg/day (Group A) or Tamsulosin 0.4 mg/day plus daily placebo (Group B) for 6months.

Patients were followed after 3, 6 months by Medical history to evaluate symptoms and possible side effects such as (backache, blurred of vision and hypotension), physical examination, Complete urine analysis, uroflowmetry Changes, Ultrasound with measurement ofPVRU, IPSS, QoL score and IIEF-5 score.

Outcomes measured were the mean changes of IPSS, QOL score, Qmax and PVRU, all of these parameters were also compared with the baseline parameters.

Patients were instructed during the study to avoid hold of micturition, exposure to cold, prolonged setting and drugs that can affect bladder contraction or storage such as antihistamines and anti-muscarinic.

The primary end point is the change in the mean IPSS scores to detect difference in total IPSS from baseline (weak 0) to (weak 24) between tadalafil5 mg and placebo group. The secondary end points are change in the mean values of the following parameters: Qmax and PVRU.

Statistical analysis:

Recorded data were analyzed using the statistical package for the social sciences, version 20.0 (SPSS Inc., Chicago, Illinois,

USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done: Independent-samples t-test of significance was used when comparing between two means. Repeated measures ANOVA tests for whether there are any differences between related means. Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables for parametric data; also Mann-Whitney U test was used to compare between the two groups, and comparison between two related samples for non-parametric data using Wilcoxon Rank Sum test for non-parametric data. Chi-square (x2) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the P-value <0.05 was considered significant.

RESULTS

Baseline characteristics:

No statistically significant difference was found between groups according to baseline characteristics. The Ages in Tadalafil group ranged between 51-76 years old with Mean ± SD was 60.51 ± 6.93 while in placebo it ranged between 51-76 years old with Mean ± SD 62.05 ± 6.87. 43.9% were diabetic in Tadalafil group versus 24.4% in placebo group **(Table 1)**.

Table (1): Comparison between PDE5 I 5mg group and Placebo group according to baseline characteristics

Groups / Baseline characteristics	PDE5 I 5mg Group *(n=41)*	Placebo Group *(n=41)*	t/x2#	p-value
Age (years)				
Mean±SD	60.51±6.93	62.05±6.87	1.017	0.316
Range	51-76	51-76		
DM	18 (43.9%)	10 (24.4%)	2.653#	0.103
HTN	5 (12.2%)	10 (24.4%)	1.306#	0.253
Total PSA				
Mean±SD	2.94±0.63	2.92±0.62	0.020	0.888
Range	1.8-3.9	1.9-3.9		
History of PDE5i	4 (9.8%)	7 (17.1%)	0.416#	0.519
Prostate size				
Mean±SD	43.76±6.69	47.71±7.71	1.143	0.153
Range	32-66	33-62		

There was a statistically significant decrease in the mean PVRU/ml in tadalafil 5mg group compared to placebo after 3and 6 months **(Table 2)**.

Table (2): Comparison between both groups according to PVRU

Groups / PVRU \ml	Tadalafil 5mg group *(n=41)*	Placebo group *(n=41)*	Mann-Whitney U-test	p-value
Before study				
Mean±SD	46.61±24.20	52.85±24.47	1.241	>0.05
Range	0-86	0-92		
After 3 months				
Mean±SD	28.02±20.72	47.85±25.42	4.491	<0.001
Range	0-76	0-100		
After 6 months				
Mean±SD	17.29±23.01	50.41±25.04	7.560	<0.001
Range	0-90	0-110		

There was a statistically significant increase in the mean Qmax in tadalafil 5mg group compared to placebo after 3and 6 months **(Table 3)**.

Table (3): Comparison between both groups according to Q- max

Groups / Q max	Tadalafil 5mg group *(n=41)*	Placebo group *(n=41)*	p-value
Before study			
Mean±SD	11.66±1.93	12.29±1.94	>0.05
Range	7-15	7-15	
After 3 months			
Mean±SD	14.68±2.09	12.27±2.16	<0.001
Range	8-18	8-16	
After 6 months			
Mean±SD	15.51±2.67	12.27±2.18	<0.001
Range	7-19	8-16	

t-Independent Sample t-test;

No statistically significant difference was found between groups according to IIEF% at pre and after 6months **(Table 4)**.

Table (4): Comparison between both groups according to IIEF5

Groups / IIEF5	Tadalafil 5mg group *(n=41)*	Placebo group *(n=41)*	p-value
Before study			
Mild	8 (19.5%)	11 (26.8%)	>0.05
Moderate	14 (34.1%)	16 (39.0%)	
Sever	9 (22.0%)	8 (19.5%)	
No ED	6 (14.6%)	3 (7.3%)	
Not interested	4 (9.8%)	3 (7.3%)	
After 6 months			
Mild	13 (31.7%)	9 (22.0%)	>0.05
Moderate	6 (14.6%)	16 (39.0%)	
Sever	7 (17.1%)	8 (19.5%)	
No ED	11 (26.8%)	5 (12.2%)	
Not interested	4 (9.8%)	3 (7.3%)	

Only fifteen patients of all studied cases complained of the following adverse effects (backache, headache, blurring of vision and hypotension).All of them were received tadalafil. No statistically significant difference was found between groups according to side effect of medical treatment at after 3 months and after 6months **(Table 5)**.

Table (5): Comparison between both groups according to side effect of medical treatment

Groups / Side effects of medical treatment	Tadalafil 5mg group *(n=41)*	Placebo group *(n=41)*	p-value
After 3 months			
Backache	2 (4.9%)	0 (0.0%)	>0.05
Blurred Vision	3 (7.3%)	0 (0.0%)	>0.05
Headache	4 (9.8%)	0 (0.0%)	>0.05
Hypotention	2 (4.9%)	0 (0.0%)	>0.05
After 6 months			
Bachache	1 (2.4%)	0 (0.0%)	>0.05
Blurred Vision	1 (2.4%)	0 (0.0%)	>0.05
Headache	2 (4.9%)	0 (0.0%)	>0.05

There was a statistically significant difference was found between category measurement according to PVRU, Qmax, QoL and IPSS in the pretreatment, after 3 months and after 6 months **(Table 6)**.

Table (6): Comparison between pre, after 3 months and after 6months according to PVRU \ml, Q max, QoL, IIEF5 and IPSS in Tadalafil 5mg group

Duration / Tadalafil 5mg group	Pre (n=41)	After 3 months (n=41)	After 6 months (n=41)	P1	P2	P3
PVRU \ml¥	46.61±24.20	28.02±20.72	17.29±23.01	<0.001**	<0.001**	<0.001
Q max‡	11.66±1.93	14.68±2.09	15.51±2.67	<0.001**	<0.001**	<0.001
QoL¥	3.37±0.62	2.71±0.93	2.17±1.09	<0.001**	<0.001**	<0.001
IIEF5#						
Mild	8 (19.5%)	--	13 (31.7%)	--	0.311	--
Moderate	14 (34.1%)	--	6 (14.6%)	--	3.239	--
No ED	6 (14.6%)	--	11 (26.8%)	--	0.275	--
Not interested	4 (9.8%)	--	4 (9.8%)	--	1.000	--
Sever	9 (22.0%)	--	7 (17.1%)	--	0.778	--
IPSS¥	12.15±3.93	5.88±4.13	4.12±4.76	<0.001**	<0.001**	0.029

Using: ‡Repeated Measurement ANOVA; ¥Wilcoxon Test; #Chi-square test

P1: Comparison between pre and after 3 months; P2: Comparison between pre and after 6 months; P3: Comparison between after 3 months and after 6 months

No statistically significant difference was found between category measurement according to PVRU, Qmax, QoL, IIEF5 and IPSS in pretreatment, after 3 months& after 6 months **(Table 7)**.

Table (7): Comparison between pre, after 3 months and after 6months according to PVRU \ml, Q max, QoL, IIEF5 and IPSS in Placebo group

Duration / Placebo Group	Pre *(n=41)*	After 3 months *(n=41)*	After 6 months *(n=41)*	P1	P2	P3
PVRU \ml¥	52.85±24.47	47.85±25.42	50.41±25.04	0.143	0.620	0.315
Q max‡	12.29±1.94	12.27±2.16	12.27±2.18	0.912	0.921	1.000
QoL¥	3.44±0.63	3.37±0.80	3.49±0.87	0.467	0.756	0.150
IIEF5#						
Mild	11 (26.8%)	--	9 (22.0%)	--	0.803	--
Moderate	16 (39.0%)	--	16 (39.0%)	--	1.000	--
No ED	3 (7.3%)	--	5 (12.2%)	--	0.707	--
Not interested	3 (7.3%)	--	3 (7.3%)	--	1.000	--
Sever	8 (19.5%)	--	8 (19.5%)	--	1.000	--
IPSS¥	12.46±3.71	12.20±3.84	12.46±4.08	0.348	1.000	0.260

Using: ‡Repeated Measurement ANOVA; ¥Wilcoxon Test; #Chi-square test

DISCUSSION

Improvement in BPH/LUTS was evident from in 4 pivotal randomized, double blind, placebo controlled studies that reported a significantly greater mean change in total IPSS from baseline to week 12 *(Egerdie et al., 2012* and *Oelke et al., 2012)*.

However, efficacy of PDE5Itadalafil as an add-on treatment for men with BPH/LUTS refractory to an alpha 1a-blocker has been not reported to date.

Several studies have studied the efficacy of monotherapy with tadalafil and tamsulosin. Also, there are studies on their combination with other drugs or comparing them with each other.

Yagi et al. (2017) in his prospective randomized study showed a significant improvement in LUTS, as indicated by change in the mean IPSS scores in terms of total score, storage sub score, voiding sub score and QOL .The mean Qmax and PVR did not significantly change. The frequency volume chart (FVC) showed significant improvements in hours of undisturbed sleep (HUS), nocturnal polyuria index, and mean number of micturations per night not in the mean number of micturitions per day. There were no significant improvements in sexual function. They study used tamsulosin 0.2 and follow up was shorter, while we used tamsulosin 0.4 mg as fixed dose and follow up was longer.

Our study showed similar results that the improvement in IPSS scores is better with combination therapy compared with Tamsulosin alone in patient that are resistant to a1-blocker.

Kim et al. (2017) in a randomized, double-blinded, active-controlled trial among 510 men with BPH-associated LUTS and ED were included and randomly treated with fixed-dose combinations of Tamsulosin 0.4 mg plus Tadalafil 5 mg, tamsulosin 0.2 mg plus tadalafil 5 mg and tadalafil 5 mg for a 12-week period. We found that the mean changes in total IPSS and IIEF-5 scores were 9.46 and 9.17 for fixed-dose combinations 0.4/5 mg and 8.14 and 9.49 for Tadalafil 5 mg, respectively, which

indicated superiority in LUTS improvement and non-inferiority in ED treatment with fixed-dose combinations 0.4/5 mg compared with tadalafil 5 mg. Our study results were similar to *Kim et al. (2017)*. The fixed-dose combinations of Tamsulosin 0.4 mg/day and Tadalafil 5 mg/day were significantly superior to Tadalafil 5 mg/day alone and tamsulosin 0.2 mg plus tadalafil 5 mg for the treatment of BPH patients with LUTS. They clearly demonstrated the advantage of fixed dose combination (FDC) 0.4/5 mg. The main advantage of FDC 0.4/5 mg was the enhanced efficacy on BPH-associated LUTS; however, the lack of a tamsulosin monotherapy control group was a limitation of this study.

Urakamet al. (2018), in his pilot study, examined the efficacy and safety of tadalafil add-on therapy for BPH/OAB that persists after treatment with an alpha-blocker by comparing tadalafil (5 mg) with solifenacin (5 mg).The study showed that the median prostate volume was 43 and 40 mL, respectively, with no significant differences between the two groups as baseline characteristics.

Significantly improved the IPSS (total), IPSS (storage symptoms), QOL index, and nocturia frequency (IPSS-Q7) improved significantly after 4 and 12 weeks of treatment compared with before treatment in both groups. However, although the IPSS (voiding symptoms) improved significantly after 4 and 12 weeks treatment compared with before treatment in the tadalafil group. Qmax did not improve significantly after 4- and 12-weeks treatment compared with before treatment in either group. A significant improvement in Qave was only seen after 4 weeks treatment (vs before treatment) in the tadalafil group. These results demonstrated the efficacy of tadalafil add-on therapy in the treatment of persistent storage symptoms after alpha-blocker treatment for BPH/LUTS. In addition, nocturia, which markedly decreased the QOL of patients, improved significantly after 4 and 12 weeks tadalafil treatment.

Urakam et al. (2018), showed similar results as improvement in IPSS, Qol and Qave, but no improvement in Qmax. A short duration may be the reason why there were no significant differences in comparisons of some of the parameters evaluated.

Singh et al. (2014) is a prospective randomized study showed better improvement with combination therapy compared with Tadalafil alone. In our study, we obtained similar result.

Strength points:

1. Long time of follow up.
2. Randomized controlled single blind clinical study.

Weak points:

1. The number of patients was small to get a solid conclusion.
2. A patient in combination regimen (tadalafil plus tamsulosin) has the tendency to have greater psychogenic effect of improvement compared with placebo group that may lead to greater perceived benefit in subjective parameters.

CONCLUSION

The fixed-dose combination of Tamsulosin 0.4mg/day and Tadalafil 5mg/day were significantly superior to

Tamsulosin 0.4 mg/day plus placebo for the treatment of BPH patients with LUTS that were refractory to tamsulosin, supporting favorable benefit-risk balance of the fixed-dose combinations of therapy for the treatment of BPH patients with LUTS because of its synergistic effects, well toleration and its safety.

Conflict of interest: None.

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فاعلية عقار التادالافيل كعلاج إضافى فى المرضى الذين يعانون من أعراض الجهاز البولى السفلى بسبب تضخم البروستاتا الحميد والتى لا تستجيب لعقار التامسولوسين كعلاج أحادى: دراسة عشوائية محاكمة

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خلفيـــة البحـــث: يحـــدث تضـــخم البروســـتاتا الحميـــد كأحـــد الاضـــطرابات التشـــريحية غيرالخبيثـــة فـــى خلايـــا البروســـتاتا، ويعـــانى معظـــم المرضـــى المصـــابين بتضـــخم البروســـتاتا الحميـــد مـــن أعـــراض التهـــاب المســـالك البوليـــة الســـفلى (التهـــاب مجـــرى البـــول. ويُعـــرف تضـــخم البروســـتاتا الحميـــد كأحـــد الاضـــطرابات الســـائدة بشـــكل كبيرلدى الرجال المسنين.

الهـــدف مـــن البحـــث: تقيـــيم فعاليـــة وســـلامة تركيبـــات الجرعـــات الثابتـــة، عـــلاج التامسولوســـين 0.4 ملجـــم بالإضـــافة إلـــى التادالافيـــل 5 ملجـــم مقابـــل تامسولوســـين 0,4 ملجـــم؛ والعقـــار الـــوهمى مـــرة واحـــدة يوميًـــا فـــي عـــلاج مرضـــى تضـــخم البروســـتاتا الحميـــد الـــذين يعـــانون مـــن التهـــاب المســـالك البوليـــة الســـفلى فـــي مقاومـــة المـــريض لمـــادة تامسولوسين.

المرضـــى وطـــرق البحـــث: فـــي هـــذه الدراســـة الإكلينيكيـــة العشـــوائية الضـــابطة التـــي أجريـــت فـــي مستشـــفيات جامعـــة الأزهـــر، تـــم تقســـيم 80 مريضًـــا يشـــكون مـــن أعـــراض التهـــاب المســـالك البوليـــة الســـفلى المرتبطـــة بـــتضخم البروســـتاتا الحميـــد بشـــكل عشـــوائي إلـــى مجمـــوعتين متســـاويتين. تلقـــى أربعـــون مريضـــا العـــلاج بجرعـــة ثابتـــة مـــن تامسولوســـين 0.4 ملجـــم/ يـــوم والتادالافيـــل 5 ملجـــم/ يـــوم لمـــدة 6 أشـــهر (المجموعـــة أ)، وتلقـــى أربعـــون مريضـــاً تامسولوســـين 0.4 ملجـــم بالإضـــافة إلـــى دواء وهمي/يـــوم لمـــدة 6 أشـــهر (المجموعـــة ب) المقيـــاس الـــدولى لأعـــراض البروســـتاتا, والقيمـــة العليـــا لانـــدفاع البـــول, ومقياســـالبول المتبقـــي بعـــد الفـــراغ, والمؤشـــر الـــدولي لوظيفـــة الانتصـــاب

المستخدمة في الأساس قبل بدء العلاج، في 3 أشهر و 6 أشهر لتقييم الفعالية في كلا المجموعتين.

نتائج البحث: أظهرت نتائج الدراسة تحسناً كبيراً في درجة الدرجة على مقياس المؤشر الدولى لوظيفة الانتصاب مع مجموعة العلاج المركب، مع زيادة ذات دلالة إحصائية في القيمة العليا لاندفاع البول وانخفاض ذو دلالة إحصائية في قيمة مقياس البول المتبقي بعد الفراغ مقارنة مع المجموعة الثانية. تظهر تغيرات درجة المؤشر الدولى لوظيفة الانتصاب عدم وجود فرق معتد به إحصائياً بين كلا المجموعتين قيمة 0,102في مجموعة التادالافيل.

الاستنتاج: إن تركيبة الجرعة الثابتة من التامسولوسين 0,4 ملجم/يوم والتادالافيل 5 مجم/يومياً تتفوق بشكل كبير على استخدام التامسولوسين 0,4 ملجم/يوم فقط بالإضافة إلى العقار الوهمي لعلاج أعراض التهاب المسالك البولية السفلى المتعلق بتضخم البروستاتا الحميد الذي كان مقاومًا للتامسولوسين، مما يدعم التوازن الإيجابي للمخاطر من العلاج المركب بجرعة ثابتة لعلاج أعراض التهاب المسالك البولية السفلى المرتبط بتضخم البروستاتا الحميد بسبب آثاره التآزرية، والتحمل الجيد وسلامته.

الكلمات الدالة: التادالافيل، أعراض الجهاز البولى السفلى، تضخم البروستاتا الحميد، التامسولوسين.