Sildenafil Vs. Tadalafil for The Treatment of Benign Prostatic Hyperplasia: A Single-arm Self-controlled Clinical Trial

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Purpose: To compare the efficacy and adverse events of sildenafil monotherapy for benign prostatic hyperplasia (BPH) with its FDA-approved counterpart, tadalafil.

Materials and Methods: In this single-arm self-controlled clinical trial, 33 patients were enrolled. All patients underwent a 6-week treatment with sildenafil, followed by a 4-week washout period and finally a 6-week treatment with tadalafil. Patients were examined on each appointment and post-void residual (PVR) urine, International Prostate Symptom Score (IPSS) and Quality of life index (IPSS-QoL index) were recorded subsequently. Efficacy of each drug regimen was then evaluated by comparing these outcome parameters.

Results: Both sildenafil and tadalafil were shown to improve PVR (both $p < .001$), IPSS (both $p < .001$) and IPSS-QoL index (both $p < .001$) significantly. Sildenafil was more effective than tadalafil in reducing PVR (mean difference (95%CI) = 9.91% (4.11, 15.72), $p < .001$) and ameliorating IPSS-QoL index (mean difference (95%CI) = 19.3% (4.47, 34.41), $p = .027$). Moreover, although not significant, sildenafil reduced IPSS more than tadalafil (mean difference (95%CI) = 3.33% (-0.22, 6.87), $p = .065$). Concurrent erectile dysfunction did not affect responsiveness to therapy with either sildenafil or tadalafil but age was inversely related to post-treatment IPSS in both sildenafil (B = 0.21 (0.04, 0.37), $p = .015$) and tadalafil (B = 0.14 (0.02, 0.26), $p = .021$) regimens with a more prominent role in responsiveness to sildenafil ($\beta = 0.31$) compared to tadalafil ($\beta = 0.19$).

Conclusion: Considering the significantly better improvement of PVR and IPSS-Qol index with sildenafil, this drug can be nominated as a suitable alternative for tadalafil as a BPH treatment, especially in younger patients who don't have any contraindications.

Keywords: lower urinary tract symptoms; phosphodiesterase 5 inhibitors; prostatic hyperplasia; sildenafil citrate; tadalafil

INTRODUCTION

With an estimated lifelong cumulative prevalence of 26%, benign prostatic hyperplasia (BPH) is the most prevalent urological disease in male individuals[1,2]. The substantial burden of this disease necessitates proper treatment in order to decrease morbidity, complications and subsequent costs.

Historically, various treatments (i.e., medications, surgeries and alternative medicine) have been developed for BPH[3]. During the last three decades, medical treatment has overtaken surgical techniques to become the mainstay of treatment. Alpha-1A adrenergic receptor blockers (ABs) and 5-alpha reductase inhibitors (5ARIs) are the most commonly prescribed medications for BPH[4]. Despite their high efficacy, both medications are associated with fairly prevalent sexual, sympathetic, anxiogenic, and deppresogenic side effects; ultimately leading to remarkably low adherence to these treatments[5-7].

In the last two decades, phosphodiesterase inhibitors (PDE5is) have been nominated as effective alternative treatments for BPH[8]. The main rationale behind this proposition is the shared pathological pathways between BPH and erectile dysfunction (ED) and the ample presence of phosphodiesterase (PDE) isoenzyme 5 in enlarged prostate tissue [9-11]. To date only tadalafil has been approved by the U.S. Food and Drug Administration (FDA) for BPH/lower urinary tract symptoms (LUTS), and despite the abundant body of evidence in favor of sildenafil's efficacy in combination therapies and its lower price and easier accessibility compared to tadalafil[12-15]; it has not yet been approved for BPH/LUTS. This appears to be mainly due to a paucity of evidence on sildenafil's efficacy and possible side effects as a monotherapy regimen in BPH and also due to a lack of direct comparative studies between sildenafil and tadalafil. To our best knowledge, this is the first study to directly compare the effectiveness of sildenafil and its FDA-approved counterpart, tadalafil, for BPH treatment.

PATIENTS AND METHODS

This non-blinded, single-arm clinical trial was conducted at three university-affiliated medical centers,

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Table 1. Characteristics of study patients at the first appointment

age (range)	59.8 ± 5.5 (50 – 71)
IPSS (range)	19.3 ± 4.0 (12 - 26)
IPSS-Qol	2.0 (2.0, 3.0)
PVR (mL)	43.0 (30.0, 57.5)
Number of patients with concurrent ED (%)	10 (30.3%)

ED = Erectile Dysfunction; IPSS = International Prostate Symptom Score; IPSS-Qol = IPSS quality of life question; PVR = post-void residual volume. All data are reported as mean ± SD or median (interquartile range).

from December 2020 to September 2021, according to the Declarations of Helsinki and Istanbul. Respective laws and regulations and principles of good clinical practice were closely followed. All patients were thoroughly informed of the study procedure and written consent was obtained prior to any interventions. The study protocol was approved by the institutional review board (accreditation ID: IR.IAU.TMU.REC.1399.339). This study has been registered in the Iranian registry of clinical trials (IRCT) (accreditation code: IRCTID: IRCT20210925052576N1).

Subjects

The inclusion criteria of our study were: men aged ≥ 50 years old, clinically diagnosed with BPH through medical history (mainly secondary LUTS) and physical exam (including digital rectal exam) for at least 6 months, initial International Prostate Symptoms Score (IPSS) ≥ 10, total serum Prostatic Specific Antigen (PSA) < 4.0 ng/mL, willing to take part and grant written informed consent and act in accordance with study protocols.

The exclusion criteria were: previous treatment with BPH medications during the past month, total PSA ≥ 4 ng/mL, evidence of concurrent prostate pathology (e.g., malignancy, acute or chronic bacterial prostatitis, prostatodynia), history of prior prostatic surgery, extensive pelvic or perineal surgeries, bladder diseases(e.g., bladder malignancy, neurogenic bladder or bladder neck contracture), cardiovascular pathologies(e.g., unstable angina, myocardial infarction, poorly controlled hypertension and idiopathic orthostatic hypotension), lumbar degenerative disc disease or associated lumbar spinal surgery, simultaneous treatment with short- or long-acting nitrates, current upper or lower urinary tract infection and unwillingness to participate in the study. Included patients agreed to avoid all BPH medications other than our treatment regimen during the study.

Efficacy measures

Efficacy outcomes were evaluated through both subjective (IPSS, IPSS-QoL index) and objective (post-void residual volume/PVR) measurements. Therefore, all patients filled out the IPSS questionnaire (questions 1 to 7) and answered the IPSS-QoL index (question 8, "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?") on every appointment. Similarly, an abdominal ultrasonography (AUS) was performed on

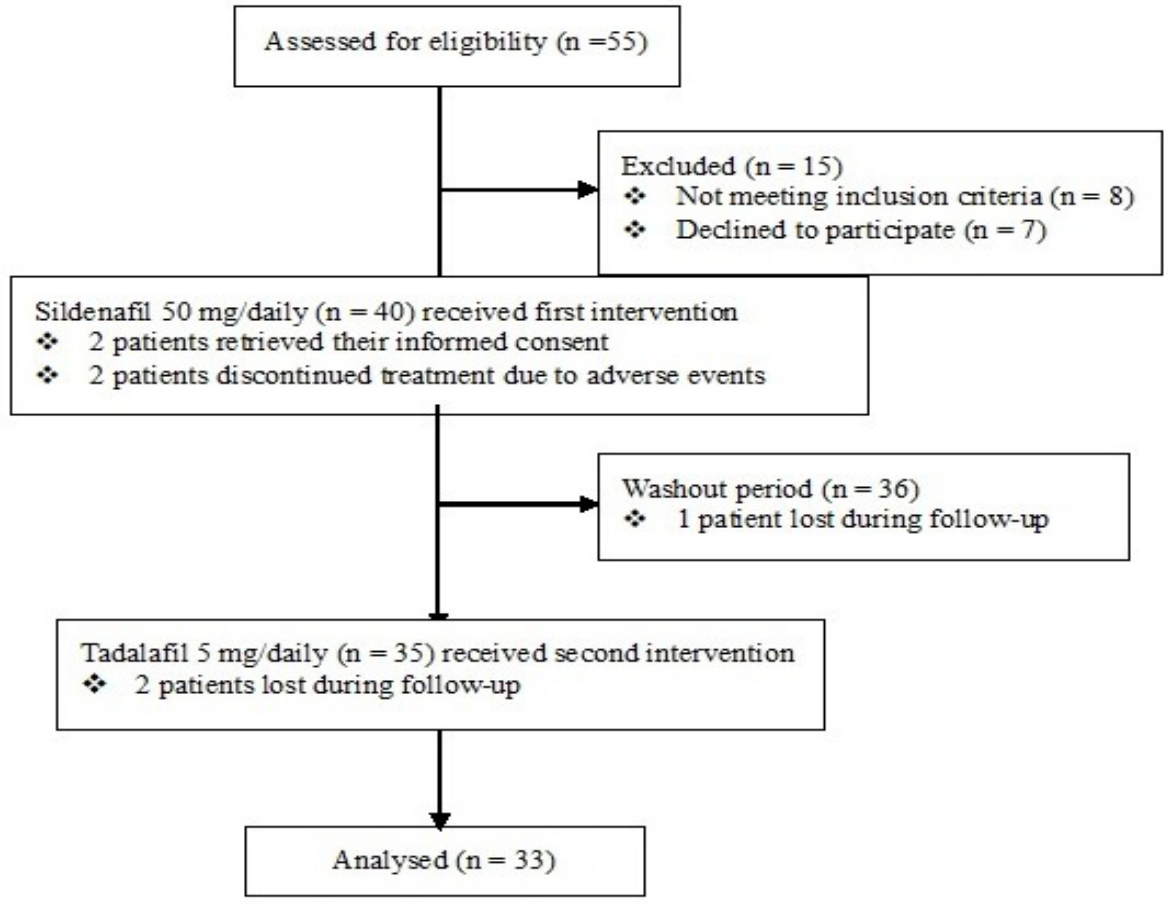

Figure 1. Flow diagram illustrating the study design

Table 2. Comparison of IPSS, IPSS-Qol index, and PVR before and after each treatment regimen

	Sildenafil			Tadalafil		
	Before	After	*p*-value	Before	After	*p*-value
IPSS	19.3 ± 4.1‡	11.6 ± 3.7‡	< .001†	14.0 (11.5, 18.0)	10.0 (6.0, 13.0)	< .001*
IPSS-Qol	2.0 (2.0, 3.0)	1.0 (0.0, 2.0)	< .001#	2.0 (1.0, 3.0)	1.0 (0.0, 1.5)	< .001#
PVR (mL)	43.0 (30.0, 57.5)	15.0 (10.0, 27.5)	< .001*	30.0 (20.0, 45.0)	15.0 (10.0, 26.5)	< .001#

IPSS = International Prostate Symptom Score; IPSS-Qol = IPSS quality of life question; PVR = post-void residual volume. All values are expressed as medians (interquartile ranges) except for ‡ which are expressed as means ± SD. † Paired t-test; # Wilcoxon signed ranks test; * Sign test.

every appointment, immediately after micturition in order to determine the PVR.

Safety measures

Medical history, drug history and physical examination were performed on all patients during the initial appointment. Cardiology consultation was requested for all patients older than 60 years of age to rule out any possibly neglected cardiac comorbidity prior to initiation of medications. Safety was evaluated by assessing the incidence rate of patient-reported side effects in course of the study.

Study design

As shown in Figure1 our study was uniquely designed as a single arm study with two consecutive drug regimens, separated by a washout period. Firstly, each patient was treated with sildenafil (Viagra) 50mg/day for 6 weeks, then went through a 4 week washout period to abolish the effect of sildenafil[16]; and lastly, was treated with Tadalafil (Cialis) 5mg/day – FDA-approved dose for BPH - for 6 weeks. The main rationale behind this study design was to eliminate the confounding effect of initial prostate size on responsiveness to treatment and clinical outcome[17,18]. Subjects were instructed to take the medications at the approximately similar time every night, regardless of the timing of sexual activity or food consumption. All patients filled in the IPSS questionnaire, answered the IPSS-QoL index and underwent an AUS before and after each intervention (weeks 0, 6, 10 and 16). The recorded IPSS, IPSS-QoL and PVR figures were then used to evaluate the efficacy of each treatment regimen and determine the superior treatment choice.

Statistical analysis

To calculate the required sample size for the primary outcome – IPSS – the correlation induced by the paired study design was taken into account. A previous clinical trial suggested a corresponding standard deviation (SD) of 2.5 for IPSS scores in PDE5is treatments[19]. Assuming an equal SD and a correlation coefficient of 0.6 between the IPSS scores in the two consecutive treatments for the same patient, a superiority margin of 4 IPSS points and a significance level of 0.05, a minimum of 30 patients would be required to guarantee a 80% power to detect a least true difference of 3 IPSS points in the tadalafil and sildenafil treatment groups (20,21). Statistical analyses of all data were performed using SPSS software version 23 (IBM, Armonk, NY, United States). Data were described as mean ± standard deviation and frequency (percentage) for quantitative and qualitative variables, respectively. Shapiro-Wilk test was used to assess the normality of data distribution. Based on normality test results and symmetry of differences; a paired t-test, Wilcoxon signed ranks test or sign test was used to compare PVR, IPSS and IPSS-QoL before and after each treatment. Similarly, the percentages of PVR, IPSS and IPSS-QOL change with either of the drugs were compared with paired t-test or sign test in order to compare the efficacy of the drugs. Finally, considering the results from previous studies which suggested a possible confounding effect for age and ED in responsiveness to PDE5is[11,22], multivariable linear regressions were utilized to evaluate the possible effects of these two variables on treatment outcome. The latest standards for reporting research results were followed[23]. $P < .05$ was considered statistically significant.

RESULTS

Study population

Of the 55 patients screened for this experiment, 40 were assigned to treatment. 33 patients (83%) completed the study and 7 patients (17%) were either lost during follow-up (N=5) or discontinued their treatment due to adverse events (N=2). Baseline clinical characteristics of patients who completed the study are shown in Table 1. The baseline characteristics of excluded cases were not significantly different from the patients who completed the study. Regarding adverse events, 2 patients had severe headache with sildenafil which led to withdrawal from the study while no patient reported any serious side effect with tadalafil.

Efficacy on LUTS and PVR volume

As illustrated in Table 2, IPSS improved significantly after 6 weeks of treatment with both sildenafil (mean difference (95%CI) = 7.67 (6.57, 8.77), $p < .001$) and tadalafil (mean difference (95%CI) = 5.15 (4.48, 5.82), $p < .001$). This improvement was slightly higher with sildenafil compared to tadalafil but this difference was not statistically meaningful (mean difference (95%CI) = 3.33% (-0.22, 6.87), $p = .065$) (Table 3). Likewise, IPSS-QoL significantly improved with both sildenafil (mean difference (95%CI) = 1.70 (1.42, 1.97), $p < .001$) and tadalafil (mean difference (95%CI) = 1.06 (0.78, 1.34), $p < .001$). However, contrary to IPSS, the reduction observed in IPSS-QoL was meaningfully more in sildenafil treatment compared to tadalafil (mean difference (95%CI) = 19.3% (4.47, 34.41), p = .027). Similarly, there was a significant amelioration of PVR with both sildenafil (mean difference (95%CI) = 32.82 (21.32, 44.31), $p < .001$) and tadalafil (mean difference (95%CI) = 15.67 (12.47, 18.87), $p < .001$). Furthermore, sildenafil was shown to be more efficient than tadalafil in this regard (mean difference (95%CI) = 9.91% (4.11, 15.72), $p < .001$). Finally, 25 patients (75.7%) stated that they personally preferred sildenafil.

Evaluating the possible effect of age and concurrent ED on responsiveness to treatment

As illustrated in **Table 4**, considering post-treatment IPSS, IPSS-QoL and PVR as outcome measures; concurrent ED was shown to be unrelated to the degree of responsiveness to therapy with either sildenafil or

Table 3. Comparison of the efficacy of Sildenafil and Tadalafil according to the percentage of change of IPSS, IPSS-Qol index, and PVR before and after each treatment regimen

	Sildenafil	Tadalafil	*p*-value
% of IPSS change (after vs. before treatment)	39.9 ± 14.1	36.6 ± 15.2	.065†
% of IPSS-QoL change (after vs. before treatment)	66.6 (50 , 100)‡	50 (12.5 , 100)‡	.027*
% of PVR change (after vs. before treatment)	59.3 ± 21.0	49.4 ± 21.4	< .001†

IPSS = International Prostate Symptom Score; IPSS-Qol = IPSS quality of life question; PVR = post-void residual volume. All values are expressed as means ± SD except for ‡ which are expressed as medians (interquartile ranges). † Paired t-test; * Sign test.

tadalafil (Table 4). Similarly, age didn't show any significant effect on post-treatment IPSS-QoL or PVR in either sildenafil or tadalafil regimen. However, age was shown to contribute significantly to post-treatment IPSS with both sildenafil (B = 0.21 (0.04, 0.37), p = .015) and tadalafil (B = 0.14 (0.02, 0.26), p = .021). Additionally, it was shown that this contribution is relatively larger with sildenafil (β = 0.31) in comparison with tadalafil (β = 0.19).

DISCUSSION

In spite of the very long history of surgical management of BPH and its staggering improvements during the last century[24], medical treatment has become the fundamental part of treatment since mid-90s[4]. According to the latest version of American Urological Association (AUA) guideline for BPH management, ABs are still the first-line treatment; usually followed by 5ARIs (25). Adherence to treatment with ABs and 5ARIs remains a major challenge in BPH treatment with previous studies reporting 12-month adherence rates as low as 35% and 9% respectively[6]. This unwillingness towards long-term therapy with these agents seems to be mainly due to the perceived lack of efficacy among patients and the relatively high rates of medical (i.e., orthostatic hypotension, syncope, depression, anxiety, and impaired cognition) and sexual (i.e., ED, anejaculation, decreased libido and loss of penis sensitivity) side effects[5,7,25]. These adverse events seriously hamper effective treatment and obligate the investigation for suitable alternatives; especially in younger sexually active patients. PDE5is are a plausible substitute, especially in relatively younger sexually active patients with prostate size < 30 cc[25].

PDE5is were initially proposed for the treatment of BPH/LUTS after observing common pathologic pathways and clinical association between ED and BPH. For instance, an abundant body of evidence supports the fundamental role of nitric oxide / cyclic guanosine monophosphate (NO – cGMP) disruption in the etiopathology of both diseases[26,27]. Similarly, a large meta-analysis of 24 clinical studies underscored the association between BPH/LUTS and ED[28]. Moreover, PDE isoenzyme 5 is known to be abundantly expressed in the hypertrophied prostate, further supporting the possible role of PDE5is[9,11]. Previous clinical studies have shown that PDE5is can effectively relaxate prostate, bladder, and urethral tissues; thus alleviating the irritative symptoms of BPH[11]. However, only tadalafil has been approved by FDA for BPH/LUTS and sildenafil has not yet been granted approval.

Previous studies have confirmed sildenafil's efficacy in combination therapies for BPH/LUTS. For instance, a combination of sildenafil (50mg/daily) and doxazosin (2mg/daily) was shown to improve PVR and IPSS more than monotherapy with either of the drugs[14]. Moreover, a lower dose of sildenafil (25mg/daily) was shown to further improve nocturia, frequency, PVR, and IPSS when added to alfuzosin (10mg/daily) or tamsulosin (0.4mg/daily)[10,13]. Nevertheless, Tuncel et al.[29] argued that dosages lower than 25mg/daily cannot effectively improve clinical outcomes when added to combination regimens. They evaluated a combination of sildenafil (25mg/four doses per week) and tamsulosin (0.4mg/

Table 4. Evaluation of the possible effect of age and concurrent ED on responsiveness to treatment.

	Sildenafil		Tadalafil	
Model	**Dependent variable : Post-treatment IPSS**		**Dependent variable : Post-treatment IPSS**	
	R2 = 0.57 , Adj R2 = 0.53	< .001	R2 = 0.82 , Adj R2 = 0.80	< .001
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Pre-treatment IPSS	0.63 (0.40, 0.85)	< .001	0.94 (0.76, 1.12)	< .001
Age	0.21 (0.04, 0.37)	.015	0.14 (0.02, 0.26)	.021
Concurrent ED	- 0.36 (-2.33, 1.62)	.714	0.10 (-1.42, 1.42)	.989
Model	**Dependent variable : Post-treatment IPSS-QoL**		**Dependent variable : Post-treatment IPSS-QoL**	
	R2 = 0.64 , Adj R2 = 0.60	< .001	R2 = 0.59 , Adj R2 = 0.55	< .001
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Pre-treatment IPSS-QoL	0.55 (0.39, 0.71)	< .001	0.52 (0.35, 0.70)	< .001
Age	0.02 (-0.01, 0.06)	.162	0.00 (-0.03, 0.04)	.845
Concurrent ED	- 0.09 (-0.51, 0.34)	.658	0.17 (-0.30, 0.64)	.459
Model	**Dependent variable : Post-treatment PVR**		**Dependent variable : Post-treatment PVR**	
	R2 = 0.51 , Adj R2= 0.46	< .001	R2 = 0.75 , Adj R2 =0.72	< .001
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Pre-treatment PVR	0.22 (0.14, 0.30)	< .001	0.62 (0.48, 0.75)	< .001
Age	- 0.26 (-0.85, 0.33)	.374	0.09 (-0.33, 0.51)	.659
Concurrent ED	- 0.18 (-7.17, 6.81)	.959	2.47 (-2.52, 7.45)	.321

ED = Erectile Dysfunction; IPSS = International Prostate Symptom Score; IPSS-Qol = IPSS quality of life question; PVR = post-void residual volume. Adj R2 = Adjusted R2; B = Regression coefficient; CI= Confidence interval.

daily) and showed that this combination is not superior to either of the medications alone in improving objective or subjective outcomes[29].

Despite the aforementioned, only a few reports have been published on BPH/LUTS single-drug therapy with sildenafil. In two distinct studies, McVary et al. showed that sildenafil (50 and 100 mg/daily) can significantly improve IPSS and erectile function, irrespective of demographic and anthropometric indices[30,31]. Likewise, Ko et al. stated that sildenafil (50 or 100mg/daily) can lower IPSS significantly but didn't have any effect on PVR[12]. Parallel to these studies, our results confimed the significant improvement of IPSS and IPSS-QoL with sildenafil 50mg/daily. However, contrary to Ko et al.[12], our results demonstrated a significant decrease of PVR with sildenafil treatment. This discrepancy can be partly due to different dose frequency and timing between the two studies.

Our results also confirmed the established efficacy of tadalafil (5mg/daily) in improving IPSS, IPSS-QoL and PVR. Interestingly, the improvement of PVR and IPSS-QoL score were shown to be significantly higher with sildenafil in comparison with tadalafil. Besides, although not statistically significant, IPSS reduction was also more prominent with sildenafil compared to tadalafil. We also evaluated the possible contribution of age and concurrent ED on responsiveness to either therapy. While concurrent ED did not affect any of the outcome parameters, age was shown to directly influence post-treatment IPSS in both regimens and its impact was more prominent in treatment with sildenafil. Considering the higher post-treatment IPSS in older patients, it can be postulated that older age is inversely related to responsiveness to treatment, especially with sildenafil. This finding is in accordance with a previous study by Lee et al., which showed a significantly better response to sildenafil in younger patients[22].

A notable point to ponder is that 5 (12.5%) patients from the original 40 patients who were recruited for our study were lost to follow-up, either due to retrieval of their consent form (N = 2) or not returning for follow-up appointments (N = 3). Consequently, the reason for treatment discontinuation in neither of these patients is available. The most reasonable explanation is discontinuation of the treatments due to perceived inefficiency or side effects[32]. This finding is of value since it suggests that a number of patients may not benefit from treatment with PDE5is and these treatments must be reserved for patients who are willing to try them and especially those who suffer from concurrent ED.

Finally, It is also worth mentioning that a recent study has shown that sildenafil is significantly more cost-effective in treating ED in comparison with other PDE5is [15]. This can be mainly due to a loss of exclusivity and generic entry of sildenafil. Consequently, it can be deduced that a relatively cheaper price and more accessibility makes sildenafil a more convenient choice than tadalafil, especially in developing countries.

Our study was subject to some limitations. The most important shortcomings of our study were those inherent to the single-arm design (e.g., reduced internal validity due to selection bias, regression to the mean, social interaction, attrition and etc.). Moreover, although sample size was calculated accurately as described before, the relatively small sample size limits the strength of our findings and calls for future double arm randomized clinical trials with larger sample sizes to further evaluate these findings. Finally, we were unable to measure and compare maximum urinary flow rate because of limited access to uroflowmetry diagnostic test in our medical centers. Nevertheless, the novelty of our study and accurate control of confounding factors can compensate for these shortcomings to a large degree.

CONCLUSIONS

In conclusion, our results revealed the amelioration of all outcome parameters with both treatments. Sildenafil was shown to be significantly superior to tadalafil in improving PVR and IPSS-QoL. Although not significant, sildenafil was also shown to reduce IPSS more than tadalafil. However, sildenafil was associated with two cases of severe headache leading to termination of treatment. Considering the abovementioned evidence, lower price and easier accessibility; sildenafil can be nominated as a suitable alternative for tadalafil in treating BPH/LUTS, especially in younger patients who don't have any contraindications.

SUMMARY

In this study we compared the efficacy of sildenafil (Viagra) with tadalafil (Cialis) in improving the symptoms and signs related to benign prostatic hyperplasia. Although only tadalafil is FDA-approved for BPH, our study showed that sildenafil is even more efficient in resolving symptoms and improving medical outcomes. Moreover, sildenafil is more affordable and easily accessible and can be thus considered as a possible alternative for tadalafil.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

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