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Effects of a single dose 20 mg tadalafil on resistive index value of prostate zones

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ABSTRACT

Objectives: Although there are several studies addressing the efficacy of phosphodiesterase type 5 inhibitors for the management of benign prostatic hyperplasia-lower urinary tract symptoms (BPH-LUTS), unfortunately, there is a lack of high evidence data to support their effect at the prostate level. The existing studies suggested that resistive index (RI) could be used as a hemodynamic parameter to measure the severity of benign prostatic hyperplasia and intraprostatic pressure or bladder outlet obstruction. The aim of this study was to evaluate the effect of a single dose 20 mg tadalafil on resistive index value in prostate zones to evaluate the mechanism of action of phosphodiesterase type 5-inhibitors at the prostate level.

Methods: Twenty consecutive patients aged between 54-67 years with BPH-LUTS [International Prostate Symptom Score ≥ 12] and erectile dysfunction [five-item International Index of Erectile Function (IIEF) questionnaire < 22] underwent RI measurement in prostate transitional zone (TZ) and peripheral zone (PZ) using transrectal power Doppler ultrasonography baseline and within 16 hours after the administration of 20 mg tadalafil. The primary study end point is the change in prostate TZ RI values.

Results: The mean baseline total prostate scores and peak urinary flow were 16.2 ± 4.34 (range: 12-26) and 10.45 ml/s (range: 7-13 ml/s), respectively. The mean baseline total IIEF was 12.8 ± 4.22 (range: 6-20). The mean TZ RI at baseline and after tadalafil administration were 0.4985 and 0.5497, respectively (p = 0.232). No statistically significant differences for RI changes between baseline and after the administration of a single dose 20 mg tadalafil were observed in the prostatic zones.

Conclusion: A single dose 20 mg tadalafil showed no impact on prostate TZ RI.

Keywords: tadalafil, prostate, phosphodiesterase type 5 inhibitors, resistive index, erectile dysfunction

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The incidence of lower urinary tract symptoms (LUTS) secondary to clinical benign prostatic hyperplasia (BPH) increases with aging and is often a comorbid condition with erectile dysfunction [1]. Given the multiple pathways by which nitric oxide influences and mediates male prostatic function by increasing the blood perfusion, there has been substantial interest in the potential of phosphodiesterase type 5 inhibitors (PDE5i) in the treatment of LUTS [2, 3].

Tadalafil is an oral selective inhibitor of the enzyme phosphodiesterase type 5 (PDE5) that is currently used for the management of erectile dysfunction and LUTS associated with BPH. Many studies in men with benign prostatic hyperplasia-lower urinary tract symptoms (BPH-LUTS) have

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consistently demonstrated statistically significant improvements in International Prostate Symtom Score (IPSS) with tadalafil [1, 3].

In the literature, several clinical studies of tadalafil and other PDE5i have reported significant symptom reduction as assessed by IPSS in patients with BPH compared to placebo [1-4]. It is not completely clear what role PDE5 inhibition plays in the treatment of LUTS since most of those studies failed to demonstrate a significant effect on the urinary flow [1, 2, 4, 5]. Roehrborn *et al*. [5] reported that improvements in LUTS occurred without a significant increase in overall peak urinary flow (Qmax) and different doses of tadalafil provided similar results. In a recent dose-finding study in more than 1000 men with moderate to severe BPH-LUTS, while tadalafil was associated with significant improvements in multiple measures of LUTS and quality of life compared to placebo, no statistically significant effect of treatment compared to placebo was noted for Qmax at any tadalafil dose [1].

Although all those studies reported limited Qmax improvement, the precise mechanism of action of PDE5i at the prostate level remains unclear. The most widely accepted hypothesis, based on studies conducted on prostate tissue specimens [6, 7], is that those agents act by reducing the smooth muscle tone, but this effect could produce vascular changes as well [8]. However, this effect has not been adequately shown in vivo until now.

On the other hand, recent studies have demonstrated the potential value of resistive index (RI = maximum velocity-minimum velocity/maximum velocity) measurement (by using transrectal pulsed-wave spectral Doppler imaging) of prostate in the evaluation of the severity of BPH and the degree of intraprostatic pressure or bladder outlet obstruction [9-11]. In a series examining 214 men with BPH, power Doppler imaging revealed that RI was discriminative between normal patients and patients with BPH [12]. Thus, if PDE5i showed their effect on LUTS by reducing the smooth muscle tone of the prostate, it is reasonable to expect a relationship between mechanism of action of PDE5i at the prostatic level and RI of prostate.

Therefore, the aim of this study was to assess whether a single dose 20 mg tadalafil administration induces changes in prostatic vasculature as a marker of the smooth muscle tone of the prostate that can be detected with RI.

METHODS

Men aged over 45 years and who were diagnosed as erectile dysfunction determined by a score of less than 22 in International Index of Erectile Function (IIEF) questionnaire and BPH-LUTS, as clinically diagnosed more than 6 months before screening, with IPSS > 13 were enrolled in the study. All patients underwent uroflowmetry and a peak urinary flow rate (Qmax) of less than 15 mL/s (from an ultrasonography-assessed prevoid total bladder volume of > 150 to < 550 mL and a minimum voided volume of 125 mL) were included.

Men were excluded from the study if they met any of the criteria such as being nitrate or nitric oxide donors, use of α-blockers, anti androgens, 5α-reductase inhibitors within the previous 6 months; a history of pelvic surgery, radiotherapy and prostate biopsy. In addition, men with an evidence on baseline transrectal ultrasound (TRUS) of any conditions that could interfere with ultrasonographic blood flow measurement such as lower urinary tract malignancy, trauma or recent instrumentation; urinary retention; urethral obstruction due to stricture, sclerosis or tumor; bladder calculi; neurogenic bladder; detrusor-sphincter dyssynergia; urinary tract inflammation or infection; prostate cancer; any drug administration or neurologic diseases affecting the lower urinary system and a post-voiding residual volume of ≥ 350 ml at the screening visit were also excluded from the study.

The study was approved by local-ethics committee (Protocol no:188/29-2015). An informed consent before the study was obtained from each participant. The effect of tadalafil on the smooth muscle tone of the prostate was assessed by RI measurement. By using this approach, it was able to demonstrate that prostatic blood flow was altered following tadalafil administration and this change could be detected in a reproducible and noninvasive manner with transrectal power Doppler ultrasonography (PDUS).

TRUS Procedures and Measurement of Blood Flow Parameters

All TRUS examinations were performed using the

Table 1. RI values of various prostate zones before and after the administration of 20 mg tadalafil

Prostate zones	RI		*p* value
	Mean ± SD	Median (min-max)	
Left side PZ			< 0.001
Baseline	0.51 ± 0.05	0.52 (0.42-0.65)	
After tadalafil	0.57 ± 0.03	0.56 (0.50-0.66)	
Right side PZ			0.001
Baseline	0.54 ± 0.04	0.54 (0.47-0.60)	
After tadalafil	0.56 ± 0.03	0.56 (0.49-0.61)	
Left side TZ			0.007
Baseline	0.49 ± 0.06	0.49 (0.37-0.59)	
After tadalafil	0.54 ± 0.06	0.53 (0.42-0.71)	
Right side TZ			0.298
Baseline	0.49 ± 0.04	0.50 (0.40-0.57)	
After tadalafil	0.55 ± 0.03	0.54 (0.48-0.61)	

RI = resistive index, PZ = peripheral zone, TZ = transition zone

same patient position throughout the study that is left decubitus and on men with an empty or nearly-empty bladder to avoid extrinsic compression affecting intraprostatic vessels. TRUS examinations were performed using a SSI-8000 ultrasound machine equipped with ultrasound-angio for power Doppler imaging with a 5.0 MHz end-fire probe. Blood flow samples were obtained and followed by spectral waveform analysis. When pulsatile waveforms of a given Doppler spectrum became stable, RI (maximum velocity-minimum velocity/maximum velocity) was measured from each blood flow sample using on-board software and the mean value was recorded. Power Doppler imaging of both right and left lobes of the prostate was performed and prostate transitional zone (TZ) RI and peripheral zone (PZ) RI were measured. Mean RI values were calculated by dividing the sum of right and left lobe RI results into two. All patients underwent RI measurement in prostate TZ and PZ using transrectal PDUS at baseline and within 16 hours after administration of single dose 20 mg tadalafil. The primary end point was the change in prostate TZ RI values. All measurements were performed by the same examiner (EE), who was blinded to the symptom scores of the patients at the time of the sonographic studies.

Statistical Analysis

Data were expressed as mean ± standard deviations or as medians and ranges. Post-hoc power analysis were conducted using RI values of four prostate zones before and after the administration of 20 mg tadalafil and the minimum power was calculated as 97.5%. A related-samples Wilcoxon Signed Rank test was performed to compare RI values. Calculations were performed using G*Power version 3.1.9.2 (Franz Faul, Universitat Kiel, Germany) and SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

The mean baseline IPSS and Qmax were 16.2 ± 4.34 (range: 12-26) and 10.45 ml/s (range: 7-13 ml/s), respectively. Fifteen (75%) patients had moderate BPH-LUTS (total IPSS = 8-19) at baseline. The mean baseline total IIEF was 12.8 ± 4.22 (range: 6-20). Mild to moderate erectile dysfunction (total IIEF = 12-16) was 60% (n =12) in the study population.

The mean TZ RI at baseline and after tadalafil administration were 0.4985 and 0.5497, respectively ($p = 0.232$). According to the prostate zones, statistically significant differences for changes between baseline and after the administration of a single dose 20 mg tadalafil were observed in RI of the left side TZ, and both sides of PZ appeared in the form of increasing while no statistically significant difference was observed in RI of the right side TZ. RI values in different prostate zones at baseline and after tadalafil administration are shown in Table 1.

DISCUSSION

The available studies on the use of PDE5i for the treatment of LUTS are promising. Criticism of the use of PDE5i in LUTS has centered over the lack of precise understanding of the mechanism of action of these agents at the prostate level [13-15]. There are some studies to explain the effect of PDE5i at prostatic level. Bertolotto *et al*. [14] reported that after single dose tadalafil administration, the enhancement peak and area under curve (AUC) increased significantly ($p < 0.01$), reflecting changes in prostatic vasculature which can be detected with contrast-enhanced US. Haaga *et al*. [15] showed that sildenafil increased the enhancement and blood flow of the normal prostate on contrast-enhanced magnetic resonance imaging.

Clinical data on the effect of PDE5i on smooth muscle tone of the prostate are limited [13, 14]. RI, which is emerging as a new and promising parameter, measures the intraprostatic pressure changes and blood flow and, thereby, can be used to explain the mechanism of action of PDE5i on the prostate. Prior observational studies have suggested that RI in the prostate TZ of men with BPH is higher than that measured in healthy controls, suggesting decreased prostate blood flow in those men [12].

In the present study, we assessed whether a single dose 20 mg tadalafil administration induces changes in prostatic tone that can be detected with RI measurement in the patients with erectile dysfunction and LUTS. The primary analysis of our results did not reveal an effect of single dose 20 mg tadalafil on the RI measured in the prostate TZ. This may be due to the high rate of patients (75%) with moderate LUTS and the mean TZ RI (0.4985) at baseline was lower than expected range of mean arterial RI in the prostate of men with BPH (0.70 to 0.80) [10, 16-20]. Moreover, the role of the effect of PDE5i on prostate may be more pronounced in men with true obstruction (Qmax < 10 ml/s) than the men with a Qmax of > 10 ml/s. Roehrborn *et al*. [1] reported that tadalafil treatment resulted in larger numeric improvements in Qmax, bladder capacity and voiding efficiency compared with placebo in men with uroflowmetrically verified obstruction at baseline. In our study, the mean baseline Qmax was 10.45 ml/s (range: 7-13 ml/s).

In a randomized placebo-controlled study, Pinggera *et al*. [13] reported that tadalafil 5 mg once daily for 8 weeks did not provide detectable decreases in arterial RI in the prostate or bladder neck in men with BPH-LUTS. Our results are consistent with that study. According to that study, detection of changes may not be possible because of already low baseline, insufficient sensitivity of techniques used, or may have been confounded by methodologic variability across sites.

One possibility is that the lack of effect of PDE5i on flow rate in some patients with LUTS suggests that smooth muscle relaxation of the prostate and/or urinary outlet are only a partial mechanistic contributor to PDE5i-related improvements in BPH-LUTS. A randomized, double-blind, placebo-controlled study investigated the effects of a twice-daily treatment with vardenafil 10 mg in 222 patients (IPSS ≥ 12, mean age of 56 yr) on irritative and obstructive LUTS secondary to BPH with or without erectile dysfunction [2]. After 8 weeks of treatment, there was a significant improvement in the IPSS scores in the vardenafil group compared with placebo (-5.9 vs. -3.6, $p < 0.0013$) as well as in irritative and obstructive IPSS sub-scores and in a quality-of-life questionnaire. The authors also reported that the effects of PDE5i on storage symptoms are more marked than on the voiding symptoms, and maximal flow rate and post-void residual volume did not change. Besides, the superiority of combination of alpha-blocker and PDE5i over either single agent in the treatment of LUTS also suggests that alternative mechanisms may be involved [21]. In addition to aforementioned studies, the present study provided evidence that the effects of PDE5i on urinary symptoms are not predominantly mediated through its effects on prostate.

The Limitations of the Study

It should be mentioned that our study had several major limitations. First, it was conducted on a small patient series, so our findings require validation on larger populations. Second, the imaging techniques used were technically complex and are not part of routine clinical management for BPH. Third, the mean TZ RI at baseline was lower than expected range of mean arterial RI in the prostate of men with BPH. This limitation could potentially be addressed by only enrolling patients with a prostatic RI confirmed to be at least 0.70 or higher at baseline. In addition, since

peripheral zone of the prostate was not thought to be involved in the development of LUTS, we did not discuss the significant PZ RI differences and mean prostate RI values in the study.

Moreover the mean Qmax at baseline was 10.45 ml/s (range: 7-13 ml/s). Lack of measurement of prostate sizes is another limitation of the study. Further clinical trials into account the RI measurement of prostate in the men with Qmax ≤ 10 ml/s will better clarify the mechanism of action of PDE5i at the prostate level. Lastly, our results based on a single dose of 20 mg tadalafil which is not indicated for daily use.

CONCLUSION

The available studies on the use of PDE5i for the treatment of LUTS are promising. However, clinical data on the effect of PDE5i on the prostate level are limited. Resistive index measurement allows objectively evaluation of tone of the smooth muscle of the prostatic stroma (the dynamic component of bladder outlet obstruction) and can therefore help to explain the mechanism of action of PDE5i at the prostate level. In the present study, single dose 20 mg tadalafil in men with BPH-LUTS and erectile dysfunction did not result in decreases in arterial RI in prostate. The missing effect on RI may be due to the fact that we included predominantly men without obstruction or smooth muscle relaxation of the prostate and/or urinary outlet tract are only a partial mechanistic contributor to PDE5i-related improvements in BPH-LUTS. A bigger sample size consist with men with true obstruction (Qmax < 10 ml/s) is required in order to confirm our results.

Author contributions

TŞ = Project development, conception and design, data collection and management, manuscript writing. EE = Conception and design, data collection, manuscript writing. HCE = Data analysis, statistical analysis, manuscript editing. FK = Data collection and management, data analysis, manuscript writing and editing.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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