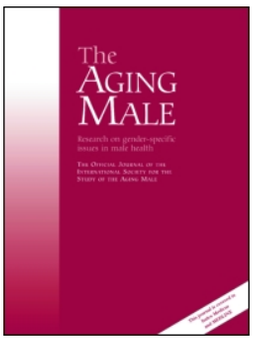

The Aging Male

ISSN: 1368-5538 (Print) 1473-0790 (Online) Journal homepage: http://www.tandfonline.com/loi/itam20

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To cite this article: Kyungtae Ko, Won Ki Lee, Sung Tae Cho, Young Gu Lee, Tae Young Shin, Min Soo Choo, Jun Hyun Han, Seong Ho Lee, Cheol Young Oh, Jin Seon Cho, Hyun Cheol Jeong & Dae Yul Yang (2019): Effect of udenafil administration on postmicturition dribbling in men: a prospective, multicenter, double-blind, placebo-controlled, randomized clinical study, The Aging Male, DOI: 10.1080/13685538.2018.1545834

To link to this article: https://doi.org/10.1080/13685538.2018.1545834

Published online: 16 Jan 2019.

THE AGING MALE
https://doi.org/10.1080/13685538.2018.1545834

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ORIGINAL ARTICLE

Effect of udenafil administration on postmicturition dribbling in men: a prospective, multicenter, double-blind, placebo-controlled, randomized clinical study

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ABSTRACT

Purpose: Postmicturition dribbling (PMD) is a stressful symptom in middle-aged men characterized by urinary leakage after the completion of normal voiding. Appropriate treatments have not yet been introduced. This study assessed the efficacy of treatment of PMD with 75 mg udenafil daily.

Materials and Methods: The study included 138 men with regular sexual lifestyles. The Hallym PMD questionnaire (HPMDQ) was used to assess PMD symptoms. After all basic examinations, patients were randomly assigned to either udenafil or placebo. Patients completed the surveys, uroflowmetry (UFM), a bladder scan, and the paper test during the follow-up visit.

Results: The mean age of the patients was 57.6 years. PMD with one of every three urinations was experienced by 59 patients (42.8%), whereas 45 patients (32.6%) experienced PMD with two of every three urinations. PMD with every urination was experienced by 34 patients (24.6%). More than half of the patients (89 patients, 65.4%) indicated that persistent PMD symptoms would likely result in moderate to severe discomfort in their daily activities. As time passed, the udenafil group showed significant improvement in PMD symptoms ($p = 0.001$).

Conclusion: Udenafil 75 mg once daily can be an effective treatment for patients with PMD symptoms.

ARTICLE HISTORY
Received 30 October 2018
Revised 5 November 2018
Accepted 5 November 2018
Published online 5 December 2018

KEYWORDS
Postmicturition dribbling; lower urinary tract symptoms; phosphodiesterase-5 inhibitors

Introduction

Associated with the feeling of incomplete emptying, postmicturition dribbling (PMD) is one of the seven symptom subgroups that make up lower urinary tract symptoms (LUTS) [1]. PMD is completely distinguishable from terminal dribbling of the voiding symptoms group and is characterized by urinary leakage without awareness as a result of body movement after the completion of normal voiding [2]. The occurrence of this symptom is independent of age or sex, but the prevalence increases with age. Previous reports have shown a rate of 11% in patients aged 20 to 30 years and of 63% in patients aged 70 to 80 years [3,4]. In males, PMD often occurs after pulling the pants up and immediately before leaving the washroom. Despite the severe discomfort experienced by patients that directly affects their quality of life, PMD has not been adequately investigated by urologists [5].

A urodynamic study published in 1977 indicated that the main cause of PMD is residual urine in the bulbar urethra that starts to leak out as body movement resumes after urination [6] (Figure 1). Additional factors associated with PMD include weakening of the bulbocavernosus muscle, an abnormal urethro-corporocavernosal reflex, reduced compliance of the bulbar urethra, weakening of the external urethral sphincter, and bladder neck obstruction [7–9]. Several clinical treatments for PMD include the use of material that can absorb urine (i.e. tissues or pads), removing residual urine by compressing the bulbar urethra, and pelvic floor muscle training (PFMT). However, these treatments are not widely used in clinical settings [10,11].

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Clinical trial registration number: KCT0001383

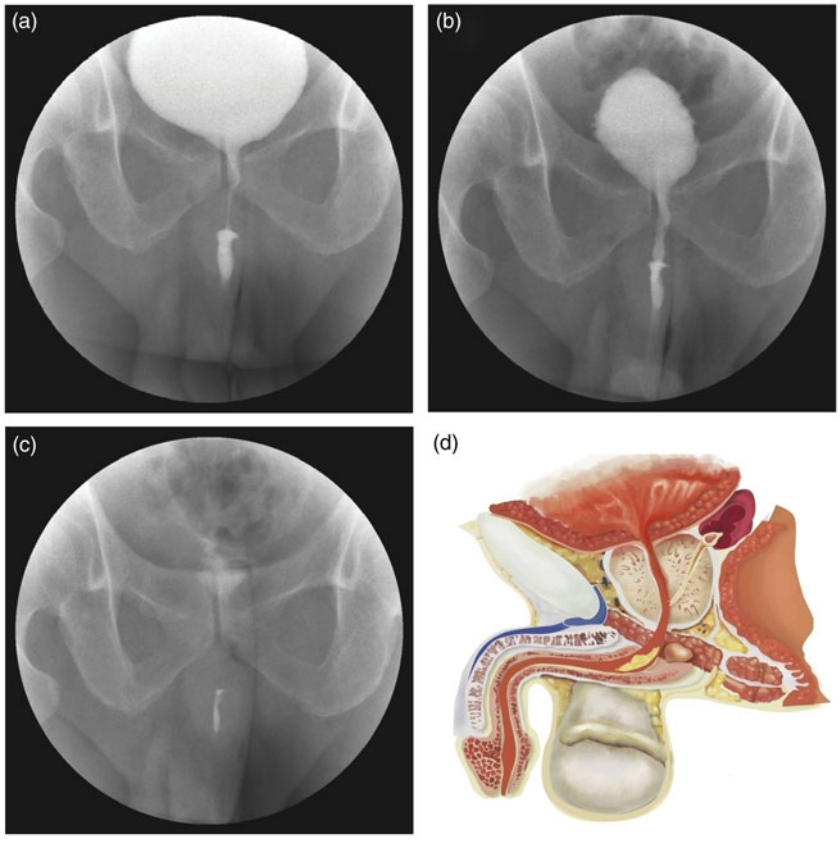

Figure 1.. (a, b) In the voiding phase, urine is leaking through the urethra. (c, d) In the postvoiding phase, after urination is complete and urethral sphincters are closed, there is residual urine in the bulbar urethra (trap).

The number of patients with PMD symptoms is increasing with increased average life expectancy. However, no critical or appropriate treatment methods, aside from conservative management, have been introduced. This study assessed the efficacy of treatment with 75 mg udenafil daily as shown by effects on the corpus cavernosum and corpus spongiosum.

Materials and methods

Participants

This study involved subjects from five different training hospitals and was performed between December 2014 and May 2016 (IRB no. 2014-02-036). The study included 138 men aged 20 to 70 years with LUTS and an International Prostate Symptom Score (IPSS) >8. The Hallym PMD questionnaire (HPMDQ) was used to assess symptoms [12]. The questionnaire was completed by patients who experienced leakage of urine at least once every three urinations in the prior month and who were included in the final cohort (Appendix 1). The following were criteria for exclusion from the study: inability to take a phosphodiesterase-5 inhibitor (PDE5i), irregular sexual activity for over 3 months, actual or anticipated use of a different PDE5i within 2 weeks of participating in this study, and use of other erectile dysfunction treatments such as intracavernous injection. Patients who used medication that affected LUTS (i.e. α-blockers, anticholinergics, or cholinergics) for more than 1 month before study participation were allowed to participate only if they exhibited improvement and remained under regular supervision for medication management throughout the study period.

Study design and outcome

This study was planned as a prospective, multicenter, double-blind, placebo-controlled, randomized clinical study (KCT0001383). The primary outcome was the difference in HPMDQ score change between experimental (udenafil) and control (placebo) groups. Participants were given udenafil 75 mg or a placebo daily. The secondary outcome was the effectiveness of udenafil 75 mg in improving sexual function and LUTS based on changes in the International Index of Erectile Function (IIEF) score and IPSS. In addition, practical improvement was assessed quantitatively by use of the paper test.

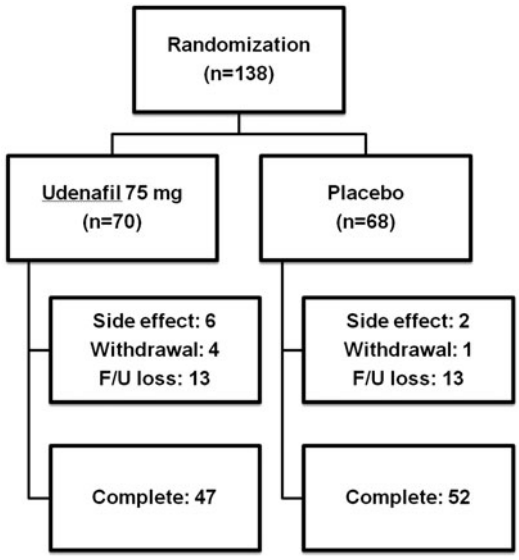

Figure 2.. Flow chart of participants in the study. F/U, follow-up.

Patients who agreed to participate in this study were screened for inclusion and exclusion criteria through an interview with the investigator at a baseline visit. Patients enrolled in the study were asked to complete three different surveys, the HPMDQ, IIEF, and IPSS, and underwent urinalysis and serum prostate-specific antigen (PSA) and testosterone level assessment. Uroflowmetry (UFM) and bladder ultrasound were used to assess urination flow rate and residual urine volume. For quantitative assessment of PMD, patients underwent a paper test developed by the authors.

After all basic examinations were completed, patients were randomly assigned to either udenafil or placebo groups. Monitoring for side effects and drug compliance was performed during follow-up assessments at weeks 4 and 12. In addition, patients completed the surveys, UFM, bladder scan, and the paper test during the follow-up visit. All examinations in the outpatient clinic were performed by a single investigator at each hospital to eliminate differences among investigators.

Paper test

After UFM, patients underwent a bladder scan in the supine position for assessment of residual urine volume. The investigator instructed the patients to place a double folded paper towel inside their underwear before standing. After the patient walked around for a minute, the volume of residual urine leaked into the paper towel was estimated by using a validated quantitation method (Appendix 2).

Randomization and double blinding

Random assignment was performed by an independent statistician before the start of the study by using the Proc Plan procedure of SAS (Ver. 9.3, SAS Institute, Cary, NC). A block randomization method for each clinical trial center was applied, and subjects were assigned to each trial center on the basis of date of random assignment.

Completed random assignment information was given to the clinical trial team and an independent clinical pharmacist and was blindly delivered to each clinical trial center after being sealed with subject numbers. At the trial centers, the subinvestigators provided numbers to the subjects based on their order of registration, and the clinical pharmacist provided the sealed and labeled medication package to the corresponding subject. Because the placebo and experimental (udenafil 75 mg) drugs had an identical appearance and were sealed with labels for each subject, the trial was completely blinded for the investigators, clinical pharmacists, subinvestigators, and subjects.

Statistical analysis and sample size

After treatment with PDE5i drugs, the reduction range of total IPSS scores was reported from 2 to 6 [13]. There are few previous reports on improvement in urination symptoms with the use of udenafil 75 mg daily. The total HPMDQ score, after adding questionnaires 1, 2, and 3, ranged between 0 and 9 and the average difference between the two groups was used for a 1:1 comparison, with inclusion criteria for a score of 3. We calculated the sample size by assuming the percent of patients with reduction of baseline HPMDQ total score by $\geq$2 points were 60% in the udenafil group and the 30% in the placebo group. Standard deviation was defined as 3.7, the maximum value of the 95% confidence interval obtained in a previous study by the study investigators. At $\alpha = 0.05$ and 80% power, 49 subjects were required for each group. Considering a 20% dropout rate during the treatment process, each group required 60 patients, and therefore 120 patients were required for this study.

All clinicopathological and clinical follow-up data were analyzed on an intention-to-treat basis. For early discontinuation of the study, ITT group analysis was performed based on the last observation carried forward. Descriptive statistics were used to summarize the demographic information and characteristics of the two groups. Repeated-measures analysis of variance was used to assess differences in HPMDQ, IIEF,

Table 1. Demographic and clinical characteristics of the study participants.

	Udenafil 75 mg ($n = 70$)	Placebo ($n = 68$)	p
Age (yr)	58.31 ± 9.55	57.28 ± 9.08	0.519
BMI (kg/m^2)	24.75 ± 2.40	25.00 ± 2.39	0.553
Serum PSA (ng/mL)	1.27 ± 1.02	1.54 ± 1.97	0.216
Serum testosterone (ng/mL)	4.82 ± 1.97	5.38 ± 2.49	0.172
IPSS			
Voiding symptoms	10.33 ± 4.57	9.18 ± 3.87	0.117
Storage symptoms	5.84 ± 3.17	4.95 ± 2.89	0.092
IIEF			
Erectile function	15.9 ± 7.46	16.49 ± 7.04	0.634
Orgasmic function	5.34 ± 2.91	5.57 ± 2.72	0.638
Sexual desire	5.43 ± 2.09	5.12 ± 1.96	0.380
Intercourse satisfaction	6.46 ± 3.88	6.97 ± 3.16	0.401
HPMDQ score			
Total	5.47 ± 2.11	5.03 ± 2.20	0.237
Question 1 (frequency)	1.90 ± 0.85	1.73 ± 0.81	0.248
Question 2 (discomfort)	1.44 ± 0.90	1.34 ± 0.93	0.536
Question 3 (anxiety)	2.13 ± 0.99	1.96 ± 0.99	0.282
Uroflowmetry			
Voided volume (mL)	224.88 ± 136.88	199.23 ± 120.22	0.268
Maximum flow rate (mL/s)	13.93 ± 6.79	14.67 ± 7.12	0.553
Mean flow rate (mL/s)	6.60 ± 3.42	6.53 ± 3.79	0.924
Residual urine (mL)	26.45 ± 29.13	27.26 ± 26.80	0.871
Paper test volume (number of grids)	19.88 ± 23.80	19.23 ± 25.37	0.881

Values are mean ± standard deviation.
BMI, body mass index; HPMDQ, Hallym postmicturition dribbling questionnaire; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

and IPSS between the two groups. Statistical analysis was performed with SPSS 24.0 (SPSS Inc. Chicago, IL). All p values were two-sided and were considered to be statistically significant when $p < 0.05$.

Results

Of 138 subjects from five different hospitals in the study (Figure 2), 39 were lost to follow-up, and 99 patients (71.7%) were followed up for the entire 12-week period. The mean age of the patients was 57.6 ± 9.52 years, and their mean body mass index was 24.9 ± 2.39 (Table 1). IPSS voiding and storage scores were 9.69 ± 4.32 and 5.36 ± 3.07, respectively, and there were no significant differences between the two groups. IIEF domain scores were as follows: erectile function (EF), 16.10 ± 7.29; orgasmic function (OF), 5.41 ± 2.84; sexual desire (SD), 5.25 ± 2.04; and intercourse satisfaction (IS), 6.66 ± 3.57. Similarly, there were no significant differences between the two groups. Mean initial serum PSA and testosterone levels were 1.4 ± 1.26 ng/mL and 5.13 ± 2.27 ng/mL, respectively, demonstrating even distribution between the two groups. Mean urination volume was 212.16 ± 129.01 ml. Maximum flow rate was 14.30 ± 6.94 ml/s, and residual urine volume was 26.84 ± 27.91 ml. The number of wet grids confirmed in the paper test was 19.56 ± 24.50, and there was no significant difference between the two groups.

PMD with one of every three urinations was experienced by 59 patients (42.8%), whereas 45 patients (32.6%) experienced PMD with two of every three urinations. PMD with every urination was experienced by 34 patients (24.6%) (Questionnaire 1, Appendix 1). Although a small subset of 21 patients (15.2%) did not report discomfort from PMD in their daily lives, the majority (117 patients, 84.8%) experienced discomfort. A greater than moderate level of discomfort (Questionnaire 2) was experienced by 53 patients (38.4%). More than half of the patients in this study (89 patients, 64.5%) indicated that persistent PMD symptoms would likely result in moderate to severe discomfort in daily activities (Questionnaire 3). Comparison of the total HPMDQ score before treatment (calculated by adding the scores of Questionnaires 1, 2, and 3) between the two groups showed no significant difference (5.47 ± 2.11 for the udenafil group and 5.03 ± 2.20 for the placebo group).

HPMDQ total scores at 4 and 12 weeks of treatment were 3.88 ± 2.30 and 3.30 ± 1.89, respectively, for the udenafil group and 4.21 ± 2.08 and 4.24 ± 2.11, respectively, for the placebo group. The number of patients with reduction of baseline HPMDQ total score by $\geq$2 points at week 12 was 29 (61.7%) in the udenafil group and 14 (26.9%) in the placebo group, indicating a significantly greater number of patients who exhibited improvement in PMD symptoms in the udenafil group ($p = 0.001$, Figure 3(a)). As time passed, the udenafil group showed significant improvement in PMD

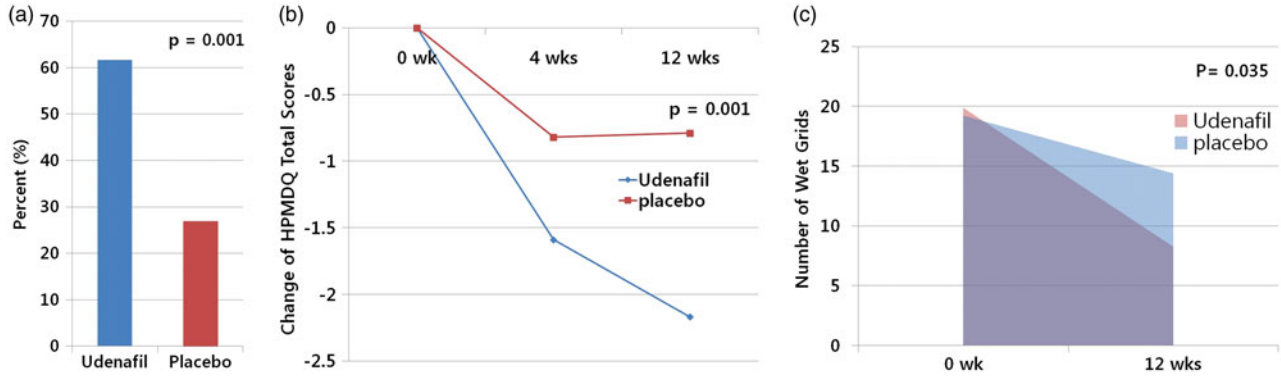

Figure 3.. (a) The number of patients with reduction of baseline HPMDQ total score by ≥2 points was higher in the udenafil group ($p = 0.001$). (b) As time passed, the udenafil group showed significant improvement in PMD symptoms ($p = 0.001$). (c) The number of wet grids was significantly lower in the udenafil group than in the placebo group, demonstrating significant quantitative reduction in the amount of PMD ($p = 0.035$). PMD, postmicturition dribbling; HPMDQ, Hallym PMD questionnaire.

symptoms ($p = 0.001$, Figure 3(b)). The paper test performed to quantitatively measure the amount of PMD at week 12 showed that the number of wet grids was significantly lower in the udenafil group (8.27 ± 7.76) than in the placebo group (14.4 ± 18.37), demonstrating a significant quantitative reduction in the amount of PMD ($p = 0.035$, Figure 3(c)) in the udenafil group.

There was no significant difference in IPSS score, either voiding or storage symptoms, over time between the two groups ($p = 0.302$ and $p = 0.084$, respectively, data not shown). When IIEF was analyzed, EF, OF, and SD function improved significantly over time in the udenafil group ($p = 0.002$, $p = 0.012$, and $p = 0.009$, respectively, Figure 4). IS function in the udenafil group was higher, but the outcome was not statistically significant ($p = 0.109$).

Seven patients (10.0%) reported the occurrence of adverse effect for Udenafil group. Most common adverse effect was facial flushing ($n = 3$, 4.2%). Nasal sniffing, epigastric discomfort, myalgia, knee pain was reported in each one patient. Three adverse effects (4.4%) were reported for Placebo group (headache, ocular pain, dizziness).

Discussion

PMD induces much stress, discomfort, and embarrassment. While other urinary symptoms also cause discomfort, a previous study by Agarwal et al. demonstrated that PMD is the most bothersome symptom of all male LUTS [5]. Patients often place toilet paper in their clothing or even wrap the penis with toilet paper to prevent wetting their pants. In severe cases, patients use condoms or a retracting penile pouch [14]. Nonetheless, physicians have generally not provided adequate treatment, either because they considered PMD to be part of the aging process or were unaware of effective treatment options [9,15].

Studies on PMD have mostly been performed in the field of nursing care [9,10]. The major cause of PMD identified in these studies is weakening of the bulbocavernosus muscle in the pelvic floor. At the end of the micturition process, the bulbocavernosus muscle should contract and milk out the residual urine trapped in the bulbar urethra. However, weakening of this muscle causes residual urine to be retained, leading to PMD. Weakening of the bulbocavernosus muscle, similar to urinary incontinence in females, is thought to be caused by several factors, including constipation, being overweight, lack of physical exercise, chronic cough, neurological disorders, and damaged autonomic nerves due to pelvic surgeries [8,14]. PFMT has been widely used for PMD, because the exercise was the only method known to address these factors [10,11]. However, PFMT did not show immediate treatment effectiveness in males, and patients had difficulty learning the technique without appropriate supervision. Although squeezing or swiping the perineum after urination to remove residual urine is easy to perform, this by itself does not provide satisfactory results.

Few studies have examined changes in the penile corporal tissue and cavernosus muscle during micturition in males, but the following summarizes what is known. The penile urethra is located inside the corpus spongiosum, which is composed of sinusoid tissue. At full erection of the penis, the sinusoids in the corpora cavernosa and corpus spongiosum exhibit maximal relaxation in order to store a large volume of blood, while the bulbocavernosus and ischiocavernosus muscles exhibit maximal contraction to prevent blood from leaking [16,17]. Similarly, for urination, the sinusoids show mild relaxation and the cavernosus muscle

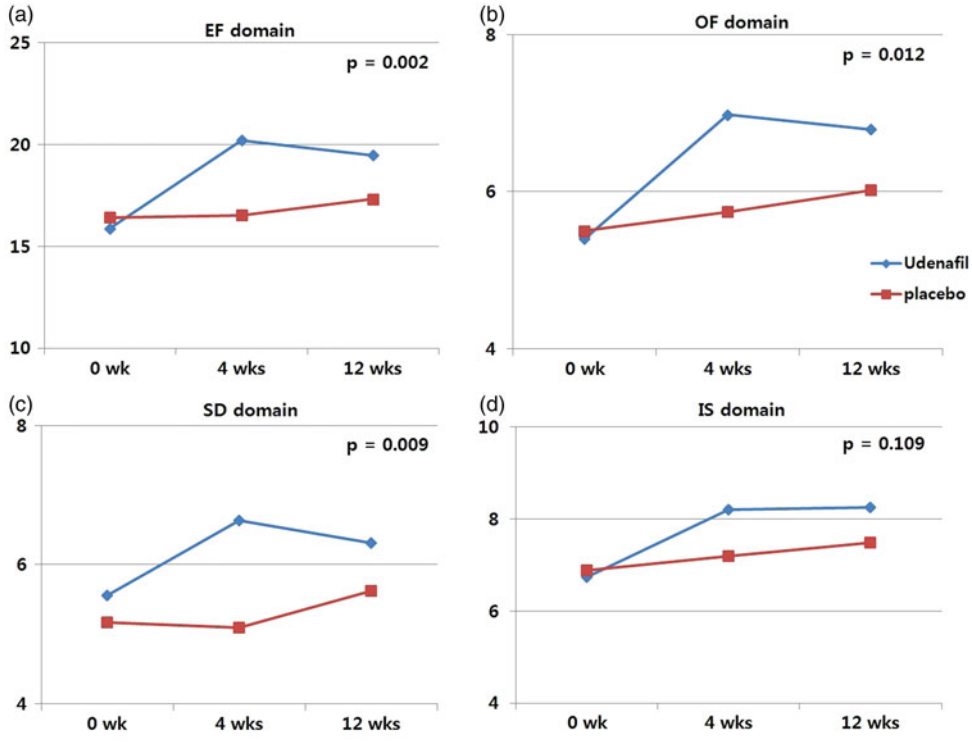

Figure 4.. Changes in domain scores on the IIEF. OF and SD function improved significantly over time in the udenafil group ($p = 0.002$, $p = 0.012$, and $p = 0.009$). The outcome of IS function was not statistically significant ($p = 0.109$). IIEF, International Index of Erectile Function; OF, orgasmic function; SD, sexual desire; IS, intercourse satisfaction.

shows mild contraction [18]. In summary, the penis during urination does not enlarge as much as during erection but is in a mildly congested state, and the stretched penile urethra allows urine to be easily discharged. In addition, increased corporal muscle tone increases penile consistency, assisting with contraction of the bulbous urethra.

According to previous studies on erectile dysfunction, the corpus cavernosum exhibits several changes as the body ages. First are morphological changes including reduced smooth muscle and increased collagen content [19]. Second, the reduced number of smooth muscle cells causes the cavernosal angioarchitecture to loosen, resulting in reduced elasticity and an increase in vascular caliber [20]. Third, proliferating cell density in the corpus cavernosum decreases and apoptotic cell density increases [21]. Previous studies have reported that continuous usage of a PDE5i for erectile dysfunction can reverse changes in erectile tissue caused by aging. Ferrini et al. reported that continuous use of sildenafil for a prolonged period (45 days) resulted in an increased number of smooth cells and decreased fibrosis in the rat penis, which was already exhibiting corporal fibrosis [22]. Another animal study showed that vardenafil increases the number of smooth muscle cells but does not alter the ratio of collagen (III:I), and that vardenafil reduces the total collagen amount in erectile dysfunction accompanied by aging [23]. Udenafil 75 mg is a long-acting drug with a half-life of 11 to 13 h. Long-acting drugs (i.e. tadalafil and udenafil) act on the aged sinusoid tissue of the corpus cavernosum and corpus spongiosum for a longer period and may improve symptoms more consistently or rapidly.

We developed a hypothesis based on the results of this study. Aging of cavernosal tissue occurs not only in the corpus cavernosum but also in the corpus spongiosum. The loosened vascular structure in the sinusoids and reduced smooth muscle results in loss of elasticity and causes the bulbar urethra to dilate. The dilated bulbar urethra will likely induce or worsen PMD symptoms. PDE5i drugs act not only on the corpus cavernosum but also on the corpus spongiosum to restore elasticity to the sinusoids, which may correct the dilated bulbar urethra. As a result of this mechanism, we observed subjective improvement of symptoms as reported in the questionnaires and objective reductions in the quantitative measure of PMD in the udenafil group in this study.

A low daily dose of PDE5i is already widely used, and not only improves erectile function in many patients but also brings significant improvement in LUTS in some patients with benign prostatic hyperplasia [24,25]. Nevertheless, compared with the well-

known mechanism of PDE5i drugs in erectile dysfunction, the mechanism in LUTS requires additional studies. Several mechanisms have been identified, but one of the major mechanisms lies in the effectiveness of PDE5i in controlling smooth muscle tone in the bladder neck, prostate, and urethra, consequently increasing the arterial blood supply to pelvic organs and affecting the afferent nerves that control the bladder, eventually strengthening the micturition reflex [26,27]. We believe that both mechanisms for improvement of erectile function and LUTS could serve as evidence for the claim that PDE5i drugs can relieve PMD symptoms. Furthermore, as demonstrated in this study, restoring the function of the corpus spongiosum that wraps around the urethra will improve both micturition and postmicturition symptoms.

In patients who undergo radical prostatectomy for prostate cancer, the main cause of stress urinary incontinence is insufficient external urethral sphincter tone. However, many patients suffer not only from stress urinary incontinence but also PMD symptoms, causing leakage after normal urination [8]. PMD symptoms in patients who undergo radical retropubic prostatectomy (RRP) are caused by the loss of postvoiding urethral milking caused by sensory nerve damage to the external urethral sphincter, independent of damage in the bladder or urethral sphincter. Until now, the only treatment available for PMD after RRP was perineal squeezing. Nonetheless, there was a breakthrough in the treatment of erectile dysfunction in RRP patients after the introduction of penile rehabilitation. Similarly, daily doses of a PDE5i can promote rehabilitation and mild congestion of the penis at urination, thereby reducing the residual urine volume in the bulbar urethra and improving PMD symptoms [9]. Future studies should not only focus on elderly patients but also patients after RRP.

Our study had some limitations. First, the number of patients lost to follow-up was greater than anticipated. There was no difference between the 2 groups in simple follow-up loss, but losses from side effects and withdrawal were greater in the udenafil group. However, compared with a previous study with udenafil 75 mg daily, the rate of occurrence of side effects (8.5%) was not significantly different [28]. Second, no instrument (questionnaire) was available to accurately assess PMD, and therefore a new survey questionnaire had to be developed by the investigators. However, as demonstrated by the outcomes of both previous studies and this study, we believe our questionnaire is sufficient to objectively assess PMD symptoms. For the first time, this study assessed the ability of drug-based therapy to relieve PMD symptoms, independent of activity-based therapies such as PFMT and perineal squeezing. In addition, this study will provide medical evidence for novel therapies for both functionality and urinary symptoms in aging males with PMD.

Disclosure statement

The authors declare no conflict of interest.

Funding

This research was supported by a grant from Dong-A ST Cooperation, Seoul, Korea.

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Appendix

Appendix 1. The Hallym postmicturition dribbling questionnaire

1. Over the last month, how often have you experienced dribbling after voiding when you feel you have finished urination?
   ① not at all, ②1 out of 3 times, ③2 out of times, ④almost all or always
2. Do you feel frustrated because of dribbling after voiding, when you feel you have finished urination?
   ① not at all, ② slightly, ③ moderately, ④ very
3. If you were to spend the rest of your life with dribbling after voiding when you feel you have finished urination, how would you feel about that?
   ① not dissatisfied, ② slightly dissatisfied, ③ moderately dissatisfied, ④ very dissatisfied

Appendix 2. The investigator instructed the patients to place a folded paper towel inside their underwear before standing

After the patient had walked around for a minute, the amount of residual urine volume leaked onto the paper towel was estimated.