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ORIGINAL ARTICLE

Clinical efficacy of combination therapy with an alpha blocker and low-dose sildenafil on post-therapy lower urinary tract symptoms after low-dose-rate brachytherapy for prostate cancer

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Abstract
Purpose To investigate the efficacy of tamsulosin monotherapy and tamsulosin with low-dose sildenafil combination therapy on lower urinary tract symptoms (LUTS) following low-dose-rate (LDR) brachytherapy in early prostate cancer patients.
Methods From March 2008 to June 2014, of the 212 prostate cancer patients with a Gleason score ≤7 who received LDR brachytherapy, 80 patients with a prostate volume ≤35 g and progressed LUTS following implantation were selected. All 80 patients took tamsulosin 0.4-mg monotherapy until 1 month after implantation. Then, the patients were divided into two groups; 45 patients received tamsulosin 0.4-mg monotherapy, and 35 patients received tamsulosin 0.4-mg plus sildenafil 25-mg combination therapy due to erectile dysfunction. LUTS were compared between the two groups using the International Prostate Symptom Score (IPSS), the mean maximum flow rate (Q_{max}) and the pre-implantation post-voiding residual (PVR) volume at 1 and 3 months after implantation.
Results The pre-implantation total IPSS, Q_{max} and PVR for the monotherapy and combination therapy groups were 14.0 ± 6.7, 14.3 ± 3.2 ml/s and 36.3 ± 16.7 ml and 15.3 ± 5.6, 13.7 ± 4.5 ml/s and 39.0 ± 23.4 ml, respectively. At 1 month post-implantation, both groups showed increases in total IPSS and PVR, but no statistically significant differences were observed ($P = 0.078$, $P = 0.23$). At 3 months post-implantation, the combination therapy group showed a greater decrease in total IPSS compared with the monotherapy group ($P = 0.035$), but there were no statistically significant differences in the Q_{max} and PVR between the two groups.
Conclusion Tamsulosin plus low-dose sildenafil combination therapy is a beneficial treatment for post-implantation progression of LUTS.

Keywords Brachytherapy · Sildenafil · Lower urinary tract symptoms · Prostatic neoplasm

Introduction

The number of early stage prostate cancer diagnoses has increased together with a rise in prostate specific antigen (PSA) examinations in Korea, and prostate brachytherapy has been increasingly used as a treatment for early localized prostate cancer. The popularity of brachytherapy is mainly based on its short hospitalization time and the fact that it is a minimally invasive and relatively uncomplicated treatment procedure.

Many studies have demonstrated favorable long-term biochemical outcomes for brachytherapy and have reported biochemical freedom from disease recurrence for stage T1–T2 prostate cancer following brachytherapy, external beam radiotherapy (EBRT), and radical prostatectomy [1–4]. However, because of the lack of definitive evidence supporting the curative superiority of radical prostatectomy, EBRT, or brachytherapy for clinically localized prostate

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cancer, quality-of-life (QOL) parameters have assumed a greater importance [5].

Brachytherapy is generally reported to be well tolerated, but bowel symptoms, decreased erectile function, and lower urinary tract symptoms (LUTS) often occur following the implantation [5–9]. The bowel symptoms are usually minor, and most patients do not have any bowel-related problems [10]. Reduced sexual function is relatively common, but little is known regarding the origin of this problem [5, 6]. LUTS are the most common side effects. The majority of patients experience LUTS to some degree during the first year post-implantation, and the urinary symptoms include incontinence and problems with frequency, retention, hematuria and dysuria. The severities of these urinary symptoms increase immediately after implantation, usually reach their maximum severity within 3 months and resolve within 1 year [11, 12]. However, a subset of patients develop persistent, bothersome symptoms and require medical therapy.

Many studies, including the study by Tsui et al. [13], have reported that post-implantation LUTS can be managed with tamsulosin. To the best of our knowledge, only a few studies have focused on treating the progression of LUTS following LDR brachytherapy through combined therapy with an alpha blocker and a phosphodiesterase type 5 inhibitor (PDE5I). In the present study, tamsulosin monotherapy and tamsulosin with low-dose sildenafil combination therapy for LUTS following brachytherapy in prostate cancer patients with a Gleason score equal to or less than 7 were prospectively designed for clinical analysis.

Materials and methods

From March 2008 to June 2014, 212 biopsy-proven prostate cancer patients with a Gleason score equal to or less than 7 who underwent ^{125}I seeds implantation LDR brachytherapy with an implant prescription dose of 145 Gy were studied at CHA Bundang Medical Center. The implants were preplanned using transrectal ultrasound (TRUS) mapping and were subsequently performed under spinal anesthesia using TRUS and fluoroscopy guidance. One urologist and one radiation oncologist, using a modified peripheral iso-dose plan, performed all of the implantations. Among the patients, 80 patients who had a prostate volume equal to or less than 35 cc according to the TRUS and with at least 6 months of follow-up and medical therapy due to progressed LUTS following the implantation were randomly selected and analyzed. The LUTS were evaluated at baseline using the International Prostate Symptom Score (IPSS) questionnaire and at each follow-up visit.

All 80 patients did not receive any alpha blocker treatment before brachytherapy, and they were treated with tamsulosin 0.4-mg monotherapy until 1 month after the implantation. Then, the patients were divided into two groups: 45 patients received tamsulosin 0.4-mg monotherapy and the other 35 patients received tamsulosin 0.4-mg plus sildenafil 25-mg combination therapy until 3 months post-implantation due to the presence of erectile dysfunction (ED). Anti-inflammatory drugs and anticholinergics were not administered to any patients in both groups.

Initially, sexual function was evaluated in all the patients of combination therapy group who complained of ED before the brachytherapy using the simplified International Index of Erectile Function (IIEF-5) questionnaire, and ED was defined as an IIEF-5 score of less than 22. Later, IIEF-5 was analyzed again at 1 and 3 months post-implantation for the corresponding ED patients. Between the two groups, improvement in the LUTS was determined using the total IPSS, mean maximum flow rate (Q_{max}) and pre-implantation post-voiding residual (PVR) volume at 1 and 3 months after the implantation. Moreover, IPSS was also separately analyzed for the voiding (intermittency, weak stream, and straining) and storage (frequency, urgency, and nocturia) sub-scores. All clinical values were presented as mean ± standard deviation (SD). The statistical significances of the intergroup differences of the total IPSS and sub-scores between baseline and each post-implantation follow-up time were analyzed using an unpaired *t* test. The statistical significances of changes in potency and urinary symptom-related measurements, such as the total IPSS, Q_{max}, and PVR, were analyzed using a one-way ANOVA followed by Turkey's multiple comparison test. All statistical tests were performed using the SPSS package version 15.0 (SPSS Inc., Chicago, IL, USA), and P values <0.05 were considered significant.

Results

The implant prescription dose was 145 Gy using 71–83 ^{125}I seeds with a seed activity of 0.382 mCi, and supplemental external beam radiation was not used. The mean pre-implantation IIEF-5 score of the combination therapy group was 14.36 ± 4.51. Then it decreased to 9.17 ± 3.82 at 1 month post-implantation ($P = 0.003$). At 3 months post-implantation, the combination therapy group had a statistically significant recovery in potency by showing IIEF-5 score increased to 11.03 ± 3.54 ($P = 0.04$) (Table 1; Fig. 1).

The pre-implantation total IPSS for the monotherapy group was 14.0 ± 6.7, while that of the combination therapy group was 15.3 ± 5.6. During the pre-implantation evaluation, the monotherapy group had a Q_{max} and PVR of 14.3 ± 3.2 ml/s and 36.3 ± 16.7 ml, respectively, whereas the combination therapy group had values of

Table 1 Erectile function changes in tamsulosin + sildenafil combination therapy group ($n = 35$)

	IIEF-5 (mean ± SD)	*P*
Pre-implantation	14.36 ± 4.51	
		0.003
1 Month post-implantation	9.17 ± 3.82	
		0.04
3 Months post-implantation	11.03 ± 3.54	

13.7 ± 4.5 ml/s and 39.0 ± 23.4 ml, respectively. In the pre-implantation IPSS sub-scores, both the tamsulosin monotherapy group and the tamsulosin plus combination therapy group showed a higher voiding score compared with the storage score, and the IPSS V/S were 2.1 ± 2.0 and 2.2 ± 1.7 for the monotherapy and combination therapy groups, respectively. Moreover, no statistically significant differences were observed in the IPSS sub-scores and IPSS V/S between the two groups (voiding score: $P = 0.192$, storage score: $P = 0.083$, IPSS V/S: $P = 0.115$). At 1 month post-implantation, both groups showed an increase in the total IPSS and PVR, but no statistically significant differences were observed between the two groups.

The IPSS sub-scores, voiding score and storage score, as well as IPSS V/S, increased in both the monotherapy group and the combination group, and no statistically significant differences were observed between the two groups (voiding score: $P = 0.162$, storage score: $P = 0.07$, IPSS V/S: $P = 0.099$). At 3 months post-implantation, the monotherapy group had a total IPSS of 18.2 ± 4.5, a Q_{max} of 12.1 ± 2.9 ml/s, and a PVR of 49.2 ± 26.2 ml, whereas the combination therapy group had a total IPSS, Q_{max} and PVR of 15.9 ± 3.6, 11.8 ± 4.2 ml/s and 45.4 ± 37.8 ml, respectively. The combination therapy group showed a greater decrease in the total IPSS compared with the monotherapy group ($P = 0.035$). The Q_{max} and PVR were improved in both the monotherapy and combination therapy groups, but the results were not statistically significant between the two groups. Compared with 1 month post-implantation scores, decreases in both the voiding and storage scores were observed at 3 months after implantation. In addition, the combination therapy group exhibited a statistically significant difference only in the storage score ($P = 0.047$), but not in the voiding score ($P = 0.061$) or IPSS V/S ($P = 0.076$) (Table 2; Fig. 2).

Discussion

Most patients who receive brachytherapy for early localized prostate cancer develop some degree of acute urinary morbidity (AUM) for approximately 1 year. Stone and Stock [14] reported that AUMs include urinary retention (1.5–22 %) and increased IPSS in nearly all patients at 1 month post-implantation, and significant LUTS persist in 10 % of patients at 1 year. Moreover, Mallick et al. [15] reported that patients with prostate brachytherapy had a high incidence of acute urinary symptoms, such as a weak stream, dysuria and both obstructive and irritative LUTS, at 1 month post-implantation, which substantially improved by 6 months. The IPSS provides no information on dysuria, but it is commonly used post-brachytherapy. Tsui et al. stated that 78 % of patients who underwent brachytherapy were still using tamsulosin for the management of LUTS at 6 months, and this percentage decreased to 55 % at 1 year and 27 % at 2 years.

AUM is caused by acute radiation exposure, as well as the invasiveness of the procedure. Transperineal needle insertion during brachytherapy can cause a subcutaneous hematoma and perineal swelling. If the needles are implanted adjacent to the bladder neck or the urethra, significant urinary bleeding can occur, which may result in clot retention. In addition, Gelblum et al. [16] reported a

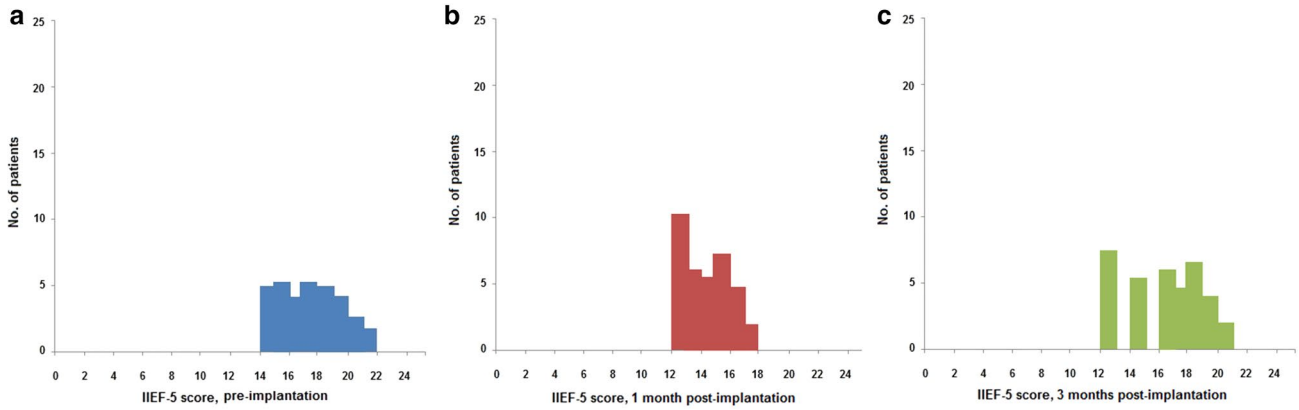

Fig. 1 International Index of Erectile Function (IIEF)-5 distribution for tamsulosin + sildenafil combination treatment group

Table 2 Characteristics of LDR brachytherapy patients, stratified by treatment method total number of patients ($n = 80$)

	Group 1 (mean ± SD)	Group 2 (mean ± SD)	*P*
No. of patients	45 (56.25 %)	35 (43.75 %)	
Mean age (year)	65.3 ± 7.9	67.4 ± 5.4	0.127
Prostate volume (cc)	25.7 ± 5.7	28.3 ± 3.4	0.084
Pre-implantation			
Total IPSS	14.0 ± 6.7	15.3 ± 5.6	0.15
Voiding score	8.9 ± 5.2	9.2 ± 4.8	0.192
Storage score	5.1 ± 3.9	6.1 ± 3.5	0.083
IPSS V/S	2.1 ± 2.0	2.0 ± 1.7	0.115
Q_{max} (ml/s)	14.3 ± 3.2	13.7 ± 4.5	0.09
PVR (ml)	36.3 ± 16.7	39.0 ± 23.4	0.31
Post-implantation (1 month)			
Total IPSS	20.0 ± 6.8	21.0 ± 5.3	0.078
Voiding score	12.4 ± 5.7	12.9 ± 5.8	0.162
Storage score	7.6 ± 4.5	8.1 ± 3.9	0.07
IPSS V/S	2.4 ± 1.9	2.4 ± 0.9	0.099
Q_{max} (ml/s)	11.2 ± 2.4	10.5 ± 2.7	0.171
PVR (ml)	75.1 ± 25.8	83.2 ± 33.6	0.23
Post-implantation (3 months)			
Total IPSS	18.2 ± 4.5	15.9 ± 3.6	0.035
Voiding score	11.3 ± 4.1	10.8 ± 3.0	0.061
Storage score	6.9 ± 3.6	5.5 ± 1.9	0.047
IPSS V/S	2.2 ± 1.7	2.3 ± 2.1	0.076
Q_{max} (ml/s)	12.1 ± 2.9	11.8 ± 4.2	0.085
PVR (ml)	49.2 ± 26.2	45.4 ± 37.8	0.143

Group 1: tamsulosin monotherapy

Group 2: tamsulosin + sildenafil combination therapy

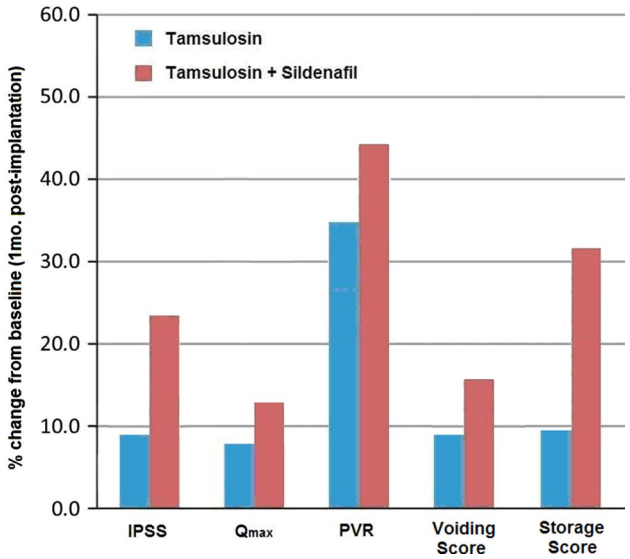

Fig. 2 3 Months post-implantation changes of IPSS, Q_{max}, PVR, voiding score, storage score in tamsulosin and tamsulosin + sildenafil groups (% changed from 1 month post-operative.)

greater risk of AUM in patients with prostates >35 cc. Chronic urinary morbidities due to brachytherapy include irritative voiding symptoms and urethral scarring, which cause obstruction and incontinence. The timing of LUTS improvement and IPSS recovery varies between studies; some studies have reported recovery times as early as 2–4 months post-implantation [17], whereas others have reported recovery after 12 months.

In the present study, because the prostate volumes of the selected patients during pre-implantation were <35 cc, it is assumed that the pre-implantation prostate volume will not be correlated with AUM. Moreover, the peripheral seed insertion technique was applied during the implantation to minimize urethral injury resulting in AUM. Because the follow-up duration of this study was relatively short, long-term IPSS recovery was not confirmed.

Radiation-induced ED likely represents a multifactorial process, including neurogenic compromise, vascular insufficiency, local trauma, and psychogenic causes, with microvascular damage representing the most dominant factor [18]. Early administration of phosphodiesterase-5 (PDE-5) inhibitors in patients with ED may help in restoring erectile function [19]. The majority of patients with brachytherapy-induced ED respond favorably to sildenafil citrate [20, 21]. Moreover, Merrick et al. [20] reported brachytherapy-induced erectile dysfunction for more than 50 % of patients at 3 years post-implantation. In this study, all of the patients who had been potent before implantation retained their potency even after implantation, but IIEF-5 score decreased significantly. This result is similar to the short-term potency outcomes reported in other studies, and further researches with a longer follow-up period are undergoing for the analysis of potency preservation under the influence of low-dose sildenafil administration in the present study.

Many studies have reported the relationship between LUTS and ED, and it is supported by four leading theories [22]: the autonomic hyperactivity and metabolic syndrome hypothesis [23], changes in the nitric oxide synthetase/nitric oxide (NOS/NO) cyclic-guanine monophosphate (cGMP) pathway in the prostate and penis [24], the Rho-kinase activation/endothelin pathway [25], and the physiopathological consequences of pelvic atherosclerosis [26]. In addition, Kaplan et al. reported that combination therapy of the PDE-5 inhibitor sildenafil with an alpha blocker significantly improved the IPSS, Q_{max} and PVR compared with alpha blocker monotherapy [27, 28]. In this study, the result of combination therapy with tamsulosin and sildenafil was similar to previous reports, as the total IPSS of the combination group was significantly improved at the 3-month follow-up. In addition, compared with 1 month post-implantation, the combination therapy group showed a significant improvement in the storage score at 3 months after implantation, and this result is probably derived from

the smooth muscle relaxation effect of the PDE-5 inhibitor, which was mentioned earlier in the report. The uroflowmetry parameters, Q_{max} and PVR, were improved in both the monotherapy and combination therapy groups at the 3-month follow-up, but these improvements were not statistically significant. It is assumed that the lack of statistically significant improvements in the uroflowmetry parameters was due to the small number of patients and the relatively short follow-up period rather than the post-implantation status. Since most of the patients receiving brachytherapy had Q_{max} and PVR parameters that returned to baseline at 1 year after implantation [11, 12], the uroflowmetry parameters of the patients in this study might be improved significantly if the follow-up period was over 1 year. Moreover, the methodological aspects of the study should be discussed. In this study, the placebo effect was not taken into account, although the placebo effect is particularly high in men with LUTS [29]. Furthermore, the dose of sildenafil used (25 mg OD) was experimental. Higher doses (50–100 mg OD) have been shown to have a significant effect on LUTS compared with a placebo [30]. Combination therapy with tamsulosin and high-dose sildenafil may be more effective on post-brachytherapy LUTS and ED. Therefore, a large-scale study with a longer follow-up period testing the optimal dose of sildenafil to be administered with 0.4 mg of tamsulosin should be conducted to further confirm the value of this combination therapy in post-brachytherapy patients with urinary morbidities. In addition, the data on co-morbidities and lifestyle variables that could influence negatively on erectile function were not collected in the present study and it is recommended those factors to be included in future analysis.

Conclusion

To manage the development of LUTS following LDR brachytherapy, tamsulosin plus low-dose sildenafil combination therapy was applied; a significant improvement in the total IPSS but insignificant changes in the Q_{max} and PVR were observed. The results of this study indicate that the use of tamsulosin and low-dose sildenafil to treat LUTS following brachytherapy leads to LUTS improvement and ED enhancement. In addition, a large-scale study with a long-term follow-up period is necessary to confirm the clinical advantage of this combination therapy.

Author's contribution YD Yu was involved in project development, data collection, data analysis, manuscript writing and manuscript editing. MH Kang was involved in data collection and data analysis. CI Choi was involved in data collection. HS Shin was involved in data management. JJ Oh was involved in data analysis and manuscript editing. DS Park was involved in project development, data analysis, and manuscript editing.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest with any institutions or products. No financial support was received by any author.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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