#163 Impact of low dose tadalafil, phosphodiesterase-5 inhibitor, on adverse events after low dose rate brachytherapy for prostate cancer - a multi center randomized open label trial-

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Hypothesis / aims of study

Low-dose rate brachytherapy (LDR) has become a popular treatment option for localized prostate cancer. However, lower urinary tract symptoms (LUTS) often occur following the implantation. Erectile dysfunction(ED) is thought to be lower incidence rather than prostatectomy but still problem after implantation. Nowadays, prophylactic use of alpha 1-adrenergic receptor antagonist (α1ARA) is the most common treatment or prevention for LUTS after LDR. For ED, taking phosphodiesterase-5 inhibitors on demand is one of the choice. On the other hand, usefulness of tadalafil was established as a treatment for male LUTS with benign prostatic hyperplasia and ED. (Ref #1 and #2) Although tadalafil may be theoretically useful for management of LUTS and ED after LDR, the role of tadalafil after LDR has not been established yet. We herein investigated the efficacy of tadalafil to attenuate adverse events after LDR comparing tamuslosin, alpha 1-adrenergic receptor antagonist.

Study design, materials and methods

This study was conducted as a multicenter randomized open-label trial. The ethical committee approved this study in both Shinshu University and Nagano Municipal hospital.Informed Consent was obtained from each participants. Localized prostate cancer patients (80 years less, T2 or less, PSA 10ng/ml or less, Gleson score 3+4 or less) without LUTS were enrolled in this trial. International prostate symptom score (IPSS) and overactive bladder symptom score (OABSS) were used for subjective evaluation for LUTS. And, uroflowmetry (Qmax and voided volume) and residual urine volume were measured for objective evaluation for LUTS also. Sexual health inventory for men (SHIM) were used for evaluation of ED. Each clinical parameter was evaluated at baseline,1, 3, 6, 9, 12months after LDR.

Results

Figure1

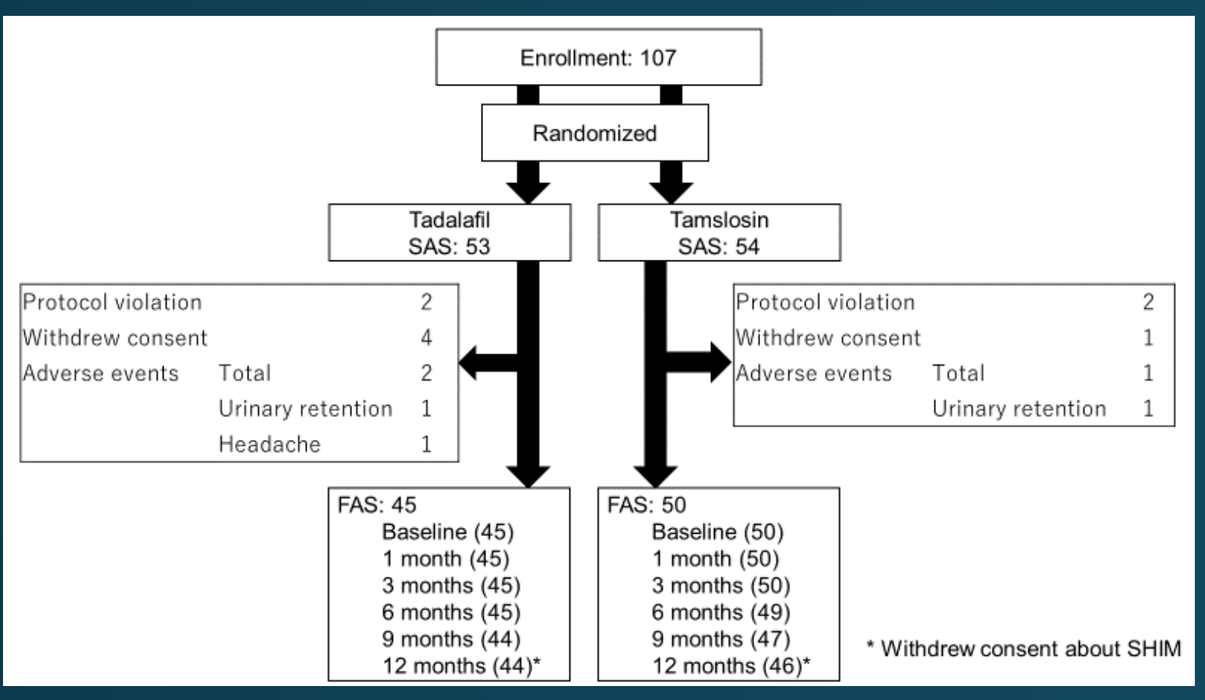


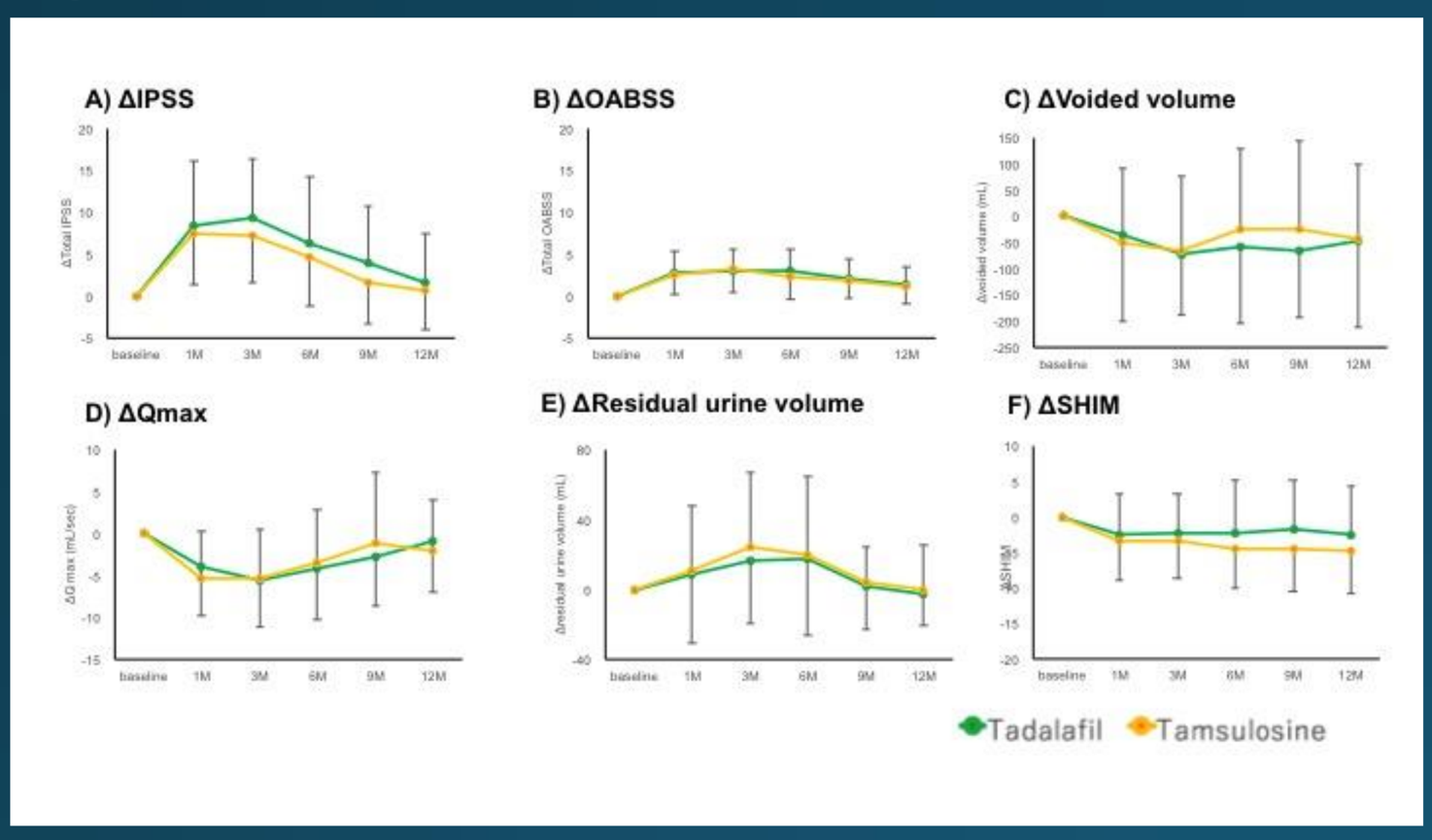
Table1

		Total	Tadalafil group	Tamsulosin group	
N		95	45	50	
Age		66.1 ± 6.8	66.7 ± 6.8	67.2 ± 6.7	N.S.
Initial PSA		5.9 ± 2.8	6.0 ± 2.8	5.7 ± 2.8	N.S.
Gleason score	3+3	43	19	24	
	3+4	52	27	26	
Pre-LDR hormone therapy		7 (7.3%)	1 (1.8%)	6 (11.1%)	
T staging	T1c	39	18	21	
	T2a	52	25	27	
	T2b	0	0	0	
	T2c	4	2	2	
Prostate volume (cm3)		24.6 ± 7.3	25.1 ± 8.1	24.2 ± 6.4	N.S.
UrD30% (as Gy)		205.0 ± 18.2	208.1 ± 16.5	202.5 19.3	N.S.
IPSS	Total	10.0 ± 4.6	9.9 ± 4.7	10.2 ± 4.6	N.S.
QoL index		2.6 ± 1.3	2.6 ± 1.3	2.5 ± 1.3	N.S.
OABSS		3.1 ± 2.1	3.3 ± 2.2	3.0 ± 1.9	N.S.
Uroflowmetry	Voided volume (mL)	252.6 ± 154.4	258.0 ± 168.9	266.6 ± 139.8	N.S.
	Qmax (mL/sec)	16.9 ± 6.9	17.0 ± 7.0	16.9 ± 6.9	N.S.
	Residual urione (mL)	14.1 ± 20.8	12.3 ± 20.1	15.8 ± 21.3	N.S.
SHIM	Total	95	45	50	
	SHIM 0-7	42	18	24	
	SHIM 8-16	27	15	12	
	SHIM ≧ 17	26	12	4	
	Mean ± SD	10.6 ± 7.5	10.8 ± 7.2	10.4 ± 7.8	N.S.

A total of 107 patients were enrolled in this study.
Finally, 96 patients were analyzed.

There was no significant difference in the patient background among the groups.

FigureA-I



The results of LUTS were shown in Figure(A-E). Means of total IPSS in tamsulosin group at baseline, 1, 3, 6, 9, 12 months after LDR are 10.2, 17.6, 17.3, 14.7, 11.6, and 10.9 respectively. And, those in tadalafil group are 9.9, 18.4, 19.1, 16.2, 13.8, and 11.4 respectively. There are no statistical differences about subjective findings besides total and storage subscore of IPSS 9 months after LDR. Moreover, there are no statistical differences in all of the objective findings of bladder function during 1 year follow up. The results about ED were shown in Figure(F) . Means of SHIM in tamsulosin group at baseline, 1, 3, 6, 9, 12 months after LDR are 10.4, 7.0, 7.0, 6.1, 6.4, and 6.2 respectively. And, those in tadalafil group are 10.8, 8.3, 8.5, 8.6, 8.9, and 8.1 respectively. SHIM of tadalafil group were statistically higher than SHIM of tamsulosin group on 6, 9, and 12 months after LDR($p<0.05$).

Interpretation of results

Edema after seed implantation and circulatory impairment due to radiation provoke LUTS. LUTS got worse in 3 months and gradually naturally improve. Circulatory impairment and neurogenic disorder after radiation sometimes cause sexual dysfunction too. Previous study already showed the efficacy of tamsulosin or silodosin for LUTS after LDR. There is a study which reports anticholinergic agent could relieve OAB symptoms. Tadalafil affect blood smooth muscle and dilate blood vessels and improves bladder tissue damage which lead to improve LUTS on BPH. Tadalafil affect internal urethral sphincter (= bladder neck smooth muscle), external urethral sphincter, and prostate smooth muscle causes improvement of bladder outlet obstruction in BPH.It also inhibits afferent nerve activity enhanced by bladder hyperextension, bladder blood flow disorder, inflammation, and oxidative stress. Although tadalafi has different mechanisms on LUTS from tamsulosin, tadalafil was effective on LUTS after LDR as well as tamuslosin was in this trial. Tadalafil equally attenuated the effect of LDR on LUTS. And, the effect of tadalafil on ED after LDR is statistically superior to tamuslosin in this trial. Tadalafil might improve blood flow in urinary bladder and prostate, and attenuated symptoms.

Concluding message

Tadalafil can be a prophylactic option for management of LUTS and ED after LDR. Especially, tadalafil is a treatment option about ED after LDR better than tamuslosin.

References
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2. Wang, Y., Bao, Y., Liu, J. et al.: Tadalafil 5 mg Once Daily Improves Lower Urinary Tract Symptoms and Erectile Dysfunction: A Systematic Review and Meta-analysis. Low Urin Tract Symptoms, 10: 84, 2018

COI: None to declare
This research was approved at ethical committee of Shinshu University and Nagano Municipal Hospital.
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