The Efficacy of L-Arginine for Benign Prostatic Hyperplasia

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Objective : Recent studies have demonstrated the effectiveness of phosphodiesterase type 5 (PDE5) inhibitor, a known drug for erectile dysfunction, for treating lower urinary tract symptoms (LUTS) of benign prostatic hyperplasia (BPH). Smooth muscle relaxation mediated by the nitric oxide (NO) pathway has been considered to improve urinary symptoms. Hence, we examined whether the administration of L-arginine as a precursor of NO could improve urinary conditions via the NO pathway. We also studied whether the combination of tamsulosin hydrochloride (tamsulosin), a known therapeutic drug for prostatic hyperplasia, and L-arginine administered as therapeutic agents can provide synergistic effects on BPH.

Materials and Methods : The study subjects comprised 21 patients who visited our hospital with the complaint of LUTS diagnosed as BPH, for which the patients received L-arginine at 1,200 mg/day. First, the changes in urinary symptoms associated with the L-arginine administration were evaluated. After a washout period, 0.1-mg/day tamsulosin was administered. Next, a combination of 0.1-mg/day tamsulosin and 1,200-mg/day L-arginine was administered to determine whether the combination therapy has a synergistic effect against LUTS. International Prostate Symptom Score (IPSS), quality of life (QOL) score, maximum urinary flow rate ($Q_{\max}$), and residual urine volume were measured before and after the administration of each dose of L-arginine. Furthermore, to determine the role of L-arginine in LUTS, we examined the changes in serum cyclic guanosine monophosphate (cGMP) levels associated with the administration of L-arginine.

Results : The mean values at baseline versus those after the administration of L-arginine alone were as follows : IPSS, 17.8 ± 5.5 vs. 15.8 ± 7.0 ; QOL score, 4.9 ± 1.2 vs. 4.2 ± 1.7 ; $Q_{\max}$, 13.9 ± 6.9 ml/s vs. 15.6 ± 6.6 ml/s ; and residual urine volume, 74.5 ± 78.6 ml vs. 37.1 ± 61.2 ml, respectively. Those of tamsulosin versus the combination therapy were as follows : IPSS score, 10.9 ± 6.1 vs. 11.3 ± 6.4 ; QOL score, 4.1 ± 2.0 vs. 3.6 ± 1.9 ; $Q_{\max}$, 17.5 ± 7.7 ml/s vs. 17.8 ± 10.0 ml/s ; and residual urine volume, 43.8 ± 51.6 ml vs. 35.5 ± 60.9 ml, respectively. L-Arginine alone significantly improved the IPSS for "weak stream" ($p = 0.027$), QOL score ($p = 0.047$), and residual urine volume ($p = 0.003$). No significant difference was observed between tamsulosin therapy and the combination therapy. However, the differences between the serum cGMP levels before and those after L-arginine administration indicated significant increases ranging from 2.8 ± 0.9 to 3.4 ± 0.9 pmol/ml ($p = 0.011$). Regarding the correlation of the IPSS with the serum cGMP levels, significant differences were observed in the "Intermittency" ($r = -0.464$, $p = 0.034$) and "Irritable" IPSS subscores ($r = -0.441$, $p = 0.045$).

Conclusions : We suggest that L-arginine alone might mitigate BPH symptoms.

Key words : benign prostatic hyperplasia, L-Arginine

Introduction

For benign prostatic hyperplasia (BPH), medical therapies such as α_1 -receptor antagonists that induce smooth muscle relaxation, 5 α -reductase inhibitors, antiandrogens, and herbal medicines have been used. Recent studies have demonstrated the effectiveness of the phosphodiesterase type 5 (PDE5) inhibitor for treating lower urinary tract symptoms (LUTS). The suggested mechanism underlying the effect of the PDE5 inhibitor is as follows : the nitric oxide (NO) pathway, one of the

pathways for smooth muscle relaxation, elevates cyclic guanosine monophosphate (cGMP) levels and activates cGMP-dependent protein kinase (PKG) to ensure smooth muscle relaxation and reduce urethral resistance. L-Arginine, a precursor of NO, is included as an ingredient in health drinks or supplements and is widely used in daily life. In this study, we examined whether L-arginine administration could improve urinary symptoms, and we have evaluated its correlation with urinary symptoms. Furthermore, we assessed whether a combination therapy of tamsulosin and L-arginine

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Figure-1 Study schedule
 US : Ultrasonography
 IPSS : International Prostate Symptom Score
 QOLs : Quality of life score

provides a synergistic effect on BPH.

Materials and Methods

Among the 23 patients with BPH that was clinically diagnosed at the Department of Urology, Juntendo University Urayasu Hospital, between February 2007 and June 2008, 21 were included in this study, as 2 patients dropped out. We excluded patients who had prostate-specific antigen levels > 4.0 ng/dl ; undergone surgery for BPH ; a history of central nervous system disorder ; undergone pelvic surgery ; received α -receptor antagonists, nitrites, or anticholinergic drugs ; and undergone self-catheterization or catheter drainage. The present study was approved by the ethical review board of our hospital. Written consent was obtained from each subject before participation in this study. The patients underwent treatment in the following schedule : (1) 1,200-mg/day L-arginine (Ajinomoto Pharma Co., Ltd), (2) washout period, (3) 0.1-mg/day tamsulosin, and (4) 0.1-mg/day tamsulosin plus 1,200-mg/day L-arginine. At weeks 0, 2, 6, and 8, we measured the IPSS, QOL score, $Q_{\max}$, and residual urine volume and performed subjective and objective evaluations (Figure-1). At week 2, serum cGMP levels were measured, and their correlation with urinary symptoms was examined. At 2 weeks after administration, hematological tests were performed to evaluate the safety of L-arginine. Each end point was analyzed using the JMP software and tested using the Wilcoxon signed-rank test and Spearman rank correlation coefficient.

Results

The mean age was 60.6 ± 6.0 years (range, 47–71 years), and the mean prostate volume was 35.2 ± 20.1 ml (range, 25–116.6 ml). As shown in Figure-2, at week 0, the mean values for IPSS was 17.8 ± 5.5 ; QOL, 4.9 ± 1.2 ; $Q_{\max}$, 13.9 ± 6.9 ml/s ; and residual urine volume, 74.5 ± 78.6 ml. At week 2, the patients were treated with L-arginine alone, which improved all the mean results as follows : IPSS, 15.8 ± 7.0 ; QOL score, 4.2 ± 1.7 ; $Q_{\max}$, 15.6 ± 6.6 ml/s ; and residual urine volume, 37.1 ± 61.2 ml. In particular, the IPSS for “weak stream” ($p = 0.027$; Figure-3), QOL score ($p = 0.047$), and residual urine volume ($p = 0.003$; Figure-2) significantly improved. Among the 21 patients, 12 (57%), 7 (33%), 16 (76%), and 13 (62%) showed improvement in IPSS, QOL score, residual urine volume, and $Q_{\max}$, respectively. Furthermore, the “Irritable” subscore pertaining to storage symptoms tended to improve ($p = 0.058$; Figure-4). At week 6, the patients were treated with tamsulosin alone, and the mean values obtained for all the parameters are as follows : IPSS, 10.9 ± 6.1 ; QOL score 4.1 ± 2.0 ; $Q_{\max}$, 17.5 ± 7.7 ml/s ; and residual urine volume, 43.8 ± 51.6 ml (Figure-5). At week 8, the patients were treated with tamsulosin combined with L-arginine. No significant differences were found in the following results : IPSS, 11.3 ± 6.4 ; QOL score, 3.6 ± 1.9 ; $Q_{\max}$, 17.8 ± 10.0 ml/s ; and residual urine volume, 35.5 ± 60.9 ml (Figure-5). Serum levels of cGMP increased significantly after the administration of

Figure-2 QOL score and residual urine volume were improved significantly. Serum cGMP was significantly elevated with L-arginine.

Figure-3 IPSS items (0-2W)
Q1 : Incomplete emptying ; Q2 : Frequency ; Q3 : Intermittency ; Q4 : Urgency ; Q5 : Weak stream ; Q6 : Straining ; Q7 : Nocturia

Figure-4 Irritable subscore · Obstructive subscore (0-2W)
Obstructive subscore, Q3 : Intermittency ; Q5 : Weak stream ; Q6 : Straining Irritable subscore, Q1 : Incomplete emptying ; Q2 : Frequency ; Q4 : Urgency ; Q7 : Nocturia
Irritable subscore tended to improve ($p=0.058$).

Figure-5 Tamsulosin combined with L-arginine did not improve the parameters, significantly.

Figure-6 The correlations of IPSS “Intermittency” and “Irritable subscore” with the serum cGMP
Regarding the correlation with serum cGMP, significant differences were observed in the IPSS “Intermittency” and “Irritable subscore”.

Table-1 The correlations between each items of the IPSS and the serum cGMP. Significant differences were observed in the IPSS “Intermittency” and “Irritable subscore”.

	2w-0w	r	p
I-PSS Q1		-0.022	0.926
I-PSS Q2		0.073	0.754
I-PSS Q3		-0.464	0.034*
I-PSS Q4		0.121	0.603
I-PSS Q5		-0.254	0.266
I-PSS Q6		-0.336	0.136
I-PSS Q7		0.103	0.657
I-PSS total score		-0.223	0.331
I-PSS Irritable subscore		-0.441	0.045*
I-PSS Obstructive subscore		0.149	0.519

L-arginine, from 2.8 ± 0.9 to 3.4 ± 0.9 pmol/ml ($p = 0.011$; Figure-2). Regarding the correlation of the IPSS with the cGMP levels, significant differences were observed in the “Intermittency” ($p = 0.034$) and “Irritable” IPSS subscore ($p = 0.045$; Figure-6, Table-1).

Discussion

Elevated urethral resistance is the primary cause of LUTS of BPH. The factors that regulate this urethral resistance are as follows: (1) the form and contraction of the prostate, (2) the contraction of the outer and inner areas of the musculus sphincter

of the urethra, and (3) the smooth muscle that constitutes the area from the bladder neck to the proximal urethra. For BPH, α_1 -receptor antagonists such as tamsulosin that induce smooth muscle relaxation have been used. Recent studies demonstrated the effectiveness of the PDE5 inhibitor in treating LUTS. Furthermore, the NO pathway, which is one of the pathways for smooth muscle relaxation, elevates cGMP levels and activates PKG, thereby contributing to smooth muscle relaxation. The suggested mechanism underlying smooth muscle relaxation via the NO pathway is as follows: (1) antagonizing inositol 1,4,5-trisphosphate receptor and reducing Ca^{2+} release from the myoplasmic reticulum, (2) promoting Ca^{2+} to be reabsorbed into the myoplasmic reticulum, (3) inhibition of the voltage dependency channel, and (4) dephosphorylation of the myosin light chain (MLC) through the activated MLC phosphatase (Figure-7)^{1~3)}. Moreover, oxidative stress increases owing to impaired vascular endothelial function and impaired blood flow associated with arteriosclerosis in the pelvis or various other complications (e. g., diabetes mellitus, hypertension, hyperlipidemia, or heart disease); thus, NO may be consumed or the levels of the endothelial NO synthase inhibitor may increase, resulting in a reduction in the amount of NO used in the cGMP system, leading to insufficient relaxation of the

Figure-7 The contraction systems of the smooth muscle
 L-Arginine induces smooth muscle relaxation via the NO pathway.

prostate^{4) 5)}. In the prostatic glandular tissues, PDE4, PDE5, and PDE11A are produced, particularly in the tissues of patients with prostatic hyperplasia, with qualitatively reduced nitrinergic innervation. Consequently, the PDE5 inhibitor is considered to increase cGMP activity, inducing relaxation in the smooth muscles of the prostate and improving LUTS^{6~9)}. Furthermore, we examined whether administration of L-arginine can improve urinary conditions via the NO pathway.

L-Arginine alone improved the mean QOL score and residual urine volume with significant differences. In addition, the "Irritable" IPSS subscore indicated a tendency toward improvement. The following mechanism may provide an interpretation of the results: the functional urinary storage capacity was increased by the reduced residual urine levels associated with improved urination, leading to improved QOL score. Mulhall *et al.*¹⁰⁾ administered 100 mg of sildenafil to 48 patients with erectile dysfunction who had LUTS and reported that of the patients, 60% had improved IPSS and 45% experienced improvement in IPSS by 4 or more points at week 12. Furthermore, according to Stief *et al.*¹¹⁾ and McVary *et al.*¹²⁾, in randomized controlled trials using tadalafil and vardenafil, the PDE5 inhibitor significantly improved the IPSS and

QOL score in comparison with placebo administration. However, the Q_{max} indicated no significant improvement in both trials. It is supposed that the mechanism of the PDE5 inhibitor is different from that of the α_1 -receptor antagonist and includes bladder smooth muscle relaxation¹³⁾. Therefore, the PDE5 inhibitor may be considered to contribute to the improvement of subjective rather than objective symptoms. Kaplan *et al.*¹⁴⁾ reported that a combination of 10 mg of alfuzosin and 25 mg of sildenafil markedly improved the IPSS compared with the administration of alfuzosin or sildenafil alone. Conversely, our study did not demonstrate that tamsulosin combined with L-arginine improved any parameters, significantly. Therefore, despite some patients showing improvement in urinary symptoms, we could not conclude that the combination treatment was effective and a large-scale study is required to obtain conclusive findings. Regarding the correlation of the IPSS with the serum cGMP levels, significant differences were observed in the "Intermittency" and "Irritable" IPSS subscore, suggesting that L-arginine administration might improve LUTS via the cGMP pathway. Furthermore, it was suggested that a more definite correlation might be achieved by increasing the dosage of L-arginine or measuring tissue or urine cGMP

levels. Moreover, we recommend that a study using other biomarkers such as oxidative stress markers should be conducted. L-Arginine is classified as a healthy food ingredient, which is often included in health drinks and supplements and widely used in daily life. In our study, no patient showed any adverse effects, suggesting that L-arginine can be used safely.

Conclusions

We propose L-arginine therapy via the NO pathway may be a new treatment method for LUTS of BPH.

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