

ORIGINAL ARTICLE

Sexuality and the management of BPH with alfuzosin (SAMBA) trial

B-H Chung¹, J-Y Lee², C-I Kim³, C-S Kim⁴, C-Y Oh⁵, S-W Lee⁶, J-S Lee⁷ and S-J Yoo¹

¹Department of Urology, Yonsei University Health System, Seoul, Korea; ²Department of Urology, The Catholic University of Korea, Seoul, Korea; ³Department of Urology, Keimyung University, Daegu, Korea; ⁴Department of Urology, Ulsan University, Seoul, Korea; ⁵Department of Urology, Hallym University, Chuncheon, Korea; ⁶Department of Urology, Eulji University, Seoul, Korea and ⁷Department of Urology, Mizmedi Hospital, Seoul, Korea

The sexuality and the management of benign prostatic hyperplasia (BPH) with alfuzosin (SAMBA) trial evaluated the effect of alfuzosin on sexual function in men treated for BPH using two sexual function scales: male sexual health questionnaire (MSHQ) and international index of erectile function (IIEF-15). A total of 148 patients with BPH were treated with alfuzosin for 24 weeks. The patients were followed at baseline, 4, 12 and 24 weeks after medication with alfuzosin. MSHQ was collected at every visit, whereas Q_{max} , IPSS and IIEF-15 were checked at baseline and end point. At the end point, Q_{max} (+4.7 ml s⁻¹, $P < 0.01$) and IPSS (-5.3, $P < 0.01$) had improved significantly. Alfuzosin also significantly improved the total MSHQ (19.2%, 79.1–94.3, $P < 0.01$) and the MSHQ ejaculatory scores (26.0%, 22.3–28.1, $P < 0.01$) versus baseline. Alfuzosin for the treatment of patients with BPH is effective in improving sexual function, as well as lower urinary tract symptoms (LUTSs) and quality of life, and is well tolerated.

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Introduction

Benign prostatic hyperplasia (BPH) and sexual dysfunction are common medical conditions that increase with advancing age and may have a negative impact on the quality of life of aging men.^{1,2} Lower urinary tract symptoms (LUTSs) and sexual dysfunction often occur concomitantly, and recent studies have shown a significant association between the LUTSs caused by BPH and sexual dysfunction not only from the epidemiological perspective but also in their pathophysiological mechanisms. Theoretically, many aspects of the pathophysiology of LUTSs and sexual dysfunction are still unclear and most urologists agree that these medical conditions are the results of multiple and complex pathological mechanisms.^{3,4} However, there is much established evidence indicating that

increased α -adrenergic activity is the common pathophysiological mechanism underlying LUTSs and sexual dysfunction. Therefore, it is widely accepted that blocking α -adrenergic activity in the lower urinary tract may improve both the LUTSs associated with BPH and sexual dysfunction.^{5,6}

Alfuzosin, a uroselective α -1 adrenergic blocker, is distributed preferentially in the smooth muscle of the bladder neck and prostate gland rather than in other cardiovascular tissues. Therefore, it improves the symptoms associated with BPH and LUTSs with minimal adverse effects on blood pressure, and this may be associated with its low incidence of sexual adverse effects.^{7–9} Earlier reports concerning the clinical efficacy of alfuzosin in the treatment of symptomatic BPH and its concomitant effect on sexual function have suggested that the improvement in LUTSs is strongly associated with the improvement in sexual function.^{10,11} Most of the earlier studies used changes in the Danish prostate symptom sex score (DAN-PSSsex) or the international index of erectile function (IIEF) questionnaire score as the parameter of improvement in sexual function. However, sexual function is complex and includes multiple domains, including sexual desire and erectile and ejaculatory functions. Some studies have reported that sexual dysfunction predominantly

Correspondence: Professor BH Chung, Department of Urology, Yongdong Severance Hospital, Yonsei University Health System, Eonju 612, Dogok-dong, Gangnam-gu, Seoul 135-720, Republic of Korea.

E-mail: chung646@yuhs.ac

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associated with BPH and LUTSs is related to the ejaculatory and erectile domains rather than to the other domains. In the 'sexuality and the management of BPH with alfuzosin' (SAMBA) trial, we used the recently developed male sexual health questionnaire (MSHQ), which includes seven items on the ejaculatory domain, with the aim of focusing not only on erectile function but also on the ejaculatory domain of sexual dysfunction. The aim of this trial was to assess the effect of alfuzosin (10 mg once daily), a uroselective α -1 adrenergic blocker, on the sexual function in patients with BPH, using the MSHQ, with especial focus on the detailed aspects of sexual functional domains.

Patients and methods

Study design

The SAMBA trial was an open, noncomparative study conducted in four urology centers in Korea from June 2006 to October 2007. The enrolled patients were followed at baseline and at 4, 12 and 24 weeks after medication with alfuzosin. In addition to the routine evaluations of BPH, such as transrectal ultrasound of the prostate, uroflowmetry, the international prostatic symptom score (IPSS) and prostate-specific antigen, the patients were asked to complete the MSHQ and IIEF-15 for the baseline evaluation of their erectile function. The MSHQ was collected at every visit, whereas uroflowmetry, IPSS and IIEF were checked at baseline and at the end point of the study. In addition to checks of their clinical parameters, all patients were interviewed by the investigator to evaluate any adverse effects related to the treatment or any other changes in health-related issues. The alfuzosin treatment was taken once daily immediately after the evening meal or before sleep. The study protocol was reviewed and approved by the institutional review board of each participating institution, and the study was performed in accordance with good clinical practice guidelines. Each patient provided a written informed consent before the enrollment in the trial.

Patients

Patients eligible to enroll in the study were men who met the following criteria at the initial visit (day 1): ≥ 50 years of age, moderate-to-severe LUTSs associated with BPH for ≥ 6 months, a total IPSS of ≥ 8 points and ongoing sexual activity. In the SAMBA trial, the definition of 'sexually active men' was those patients who reported that they had experienced at least one episode of sexual activity (for example, intercourse, caress, foreplay or masturbation) in the previous 4 weeks. All 'sexually inactive' patients were excluded from the trial. Patients were also excluded from the trial if they had neurogenic

bladder dysfunction, confirmed prostate cancer, acute or chronic urinary retention status, acute or chronic prostatitis within the previous 3 months, a history of recurrent urinary tract infection or bladder stones, or earlier transurethral resection of the prostate or other surgical intervention related to BPH. The exclusion criteria related to the medication included known hypersensitivity to any kind of α -adrenergic blocker, a poor response history to previous α -blocker treatment and the use of anticholinergics, antidepressants, plant extracts (herbal medications) or other investigational drugs within 1 month of enrollment in the trial. A personal history of myocardial infarction or other severe cardiovascular disease, syncope related to postural hypotension or active renal or liver disease was also included in the exclusion criteria. The medications that could influence sexual function, such as 5- α reductase inhibitors and phosphodiesterase-5 inhibitors, were also considered to exclude the probable bias. Patients who had been administered 5- α reductase inhibitors and phosphodiesterase-5 inhibitors within 1 month of screening were excluded from the trial, and the use of these drugs was prohibited in this study after the enrollment.

Statistical analysis

Efficacy was analyzed at the end point in the intent-to-treat population (that is, all patients who received at least one dose of alfuzosin (10 mg), and had had at least one evaluation at baseline and afterward with IPSS, MSHQ and IIEF-15). Repeated measures analysis with the 'last observation carried forward' method was also used. Linear regression analysis was used to evaluate the relationships between the MSHQ, IPSS and IIEF-15 scores. Changes from baseline in the scores for the IPSS, IIEF-15 and each scale of the MSHQ were analyzed using a paired Student's *t*-test. Safety was analyzed in the exposed population (patients who received at least one dose of alfuzosin). All statistical tests were two sided.

Results

Of the 148 men, 123 (83.1%) completed enough of the trial to be evaluated. Of the 25 patients who were excluded from the final analysis, 21 patients were lost to follow-up or the collected clinical data were incomplete, and the other four patients retracted the written consents after they enrolled in this trial. However, the reason for the retraction was not related to the adverse events. The patients' clinical characteristics at baseline are shown in Table 1. The mean age of the patients was 57.8 years and their mean total IPSS and 'bother' scores were 17.4 ± 6.2 and 3.9 ± 1.1 , respectively. The mean total MSHQ and the IIEF-15 scores were 79.1 ± 2.1 and 34.4 ± 5.1 , respectively. The other parameters, such as prostate

volume, uroflowmetry and serum prostate-specific antigen level, indicated that the enrolled patients generally had moderate-to-severe LUTS-associated BPH. Although there was a negative correlation between the severity of LUTSs/BPH represented by the IPSS and the degree of sexual dysfunction measured with the MSHQ, it was not statistically significant in this study ($P > 0.05$; Pearson correlation coefficient = -0.24 ; Table 1).

The effects of alfuzosin (10 mg) on LUTSs/BPH and sexual function from baseline to the end point are summarized in Table 2. There was a definite improvement in the severity of LUTSs/BPH in these patients, as reflected by the statistically significant decrease at the end point in the total IPSS (-5.3 , 30.5% , $P < 0.05$) and the bother scores (-1.7 , -43.6% , $P < 0.05$) relative to baseline. In addition to the subjective improvement in LUTSs/BPH represented by the IPSS questionnaires, there was also objective improvement in LUTSs/BPH reflected in the improvement in the maximal flow rate (Q_{\max} ; $+4.7$, $+43.1\%$, $P < 0.05$).

The data from this study indicate that there was a general improvement in sexual function during the

study. The total MSHQ score was increased statistically significant from baseline to the end point ($79.1-94.3$, $P < 0.05$). The improvement in sexual function, reflected by the changes in the IIEF-15 score, was also statistically significant ($34.4-41.2$, $P < 0.05$), and the degree of improvement in the total MSHQ score was correlated with the degree of improvement in the IIEF-15 score (Pearson correlation coefficient = 0.54 , $P < 0.05$). The individual MSHQ scores (erection, ejaculatory and satisfaction) at the end point were also increased relative to those at baseline (18.9 , 26.0 and 12.1% , respectively). However, the improvement in the MSHQ satisfaction scale was not statistically significant (Table 2, Figure 1).

Alfuzosin (10 mg once daily) was well tolerated in men with BPH/LUTSs. The proportion of patients who experienced treatment-associated adverse events was 22.5% ($28/124$ patients). The most commonly reported adverse events were dizziness (8.0% , 10 patients) and headache (4.0% , five patients). No serious adverse events related to treatment were reported, and most of the adverse events were self-limited and controlled by conservative management and patient education.

Nonserious treatment-associated adverse events that led to the patient withdrawal from the study were reported in two patients, who experienced dizziness. However, there were no more patients who experienced the adverse events and were withdrawn from the trial due to adverse events not being drug related.

Discussion

Sexual dysfunction is often perceived by physicians to be of secondary concern to patients with LUTSs/BPH because of incorrect preconceptions about the sexual activity of aging men. However, this conventional opinion should definitely be reconsidered in

Table 1 Baseline characteristics of the patients

Variable	Mean (s.d.)
Mean age (years)	57.8 (3.5)
IPSS total	17.4 (6.2)
Bother score	3.9 (1.1)
Q_{\max} (ml s ⁻¹)	10.9 (4.3)
Prostate volume (ml)	34.4 (5.4)
PSA (ng ml ⁻¹)	1.84 (1.1)
MSHQ total	79.1 (11.4)
MSHQ erection score	7.4 (2.1)
MSHQ ejaculatory score	22.3 (3.2)
MSHQ satisfaction score	23.4 (5.3)
IIEF-15	34.4 (5.1)

Abbreviations: IIEF, international index of erectile function; IPSS, international prostatic symptom score; MSHQ, male sexual health questionnaire; PSA, prostatic specific antigen.

Table 2 The efficacy of alfuzosin therapy on LUTS/BPH and sexual function at the end point

Mean (s.d.) variable	Baseline	End point	Δ (%)	P-value versus baseline
LUTS/BPH				
IPSS total	17.4 (6.2)	12.1 (6.3)	-5.3 (-30.5%)	$P < 0.05$
Bother score	3.9 (1.1)	2.2 (1.0)	-1.7 (-43.6%)	$P < 0.05$
Q_{\max} (ml s ⁻¹)	10.9 (4.3)	15.6 (5.1)	4.7 (43.1%)	$P < 0.05$
Sexual function				
MSHQ total	79.1 (11.4)	94.3 (13.5)	15.2 (19.2%)	$P < 0.05$
MSHQ erection	7.4 (2.1)	8.8 (2.0)	1.4 (18.9%)	$P < 0.05$
MSHQ ejaculatory	22.3 (4.2)	28.1 (4.8)	5.8 (26.0%)	$P < 0.05$
MSHQ satisfaction	19.4 (5.3)	21.8 (6.4)	2.4 (12.1%)	$P = 0.14$
IIEF-15 total	34.4 (5.1)	41.2 (4.5)	6.8 (19.8%)	$P < 0.05$

Abbreviations: BPH, benign prostatic hyperplasia; IPSS, international prostatic symptom score; LUTS, lower urinary tract symptoms; MSHQ, male sexual health questionnaire.

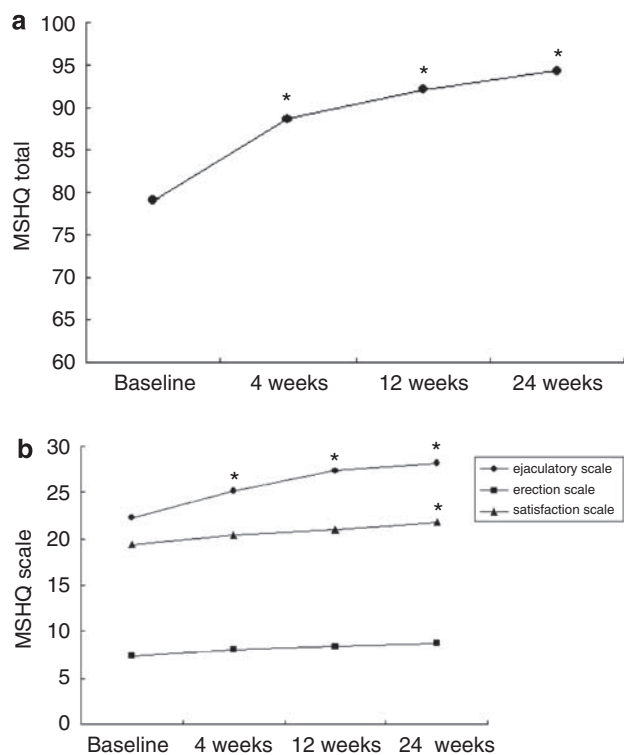


Figure 1 The changes from baseline in total MSHQ (a) and individual MSHQ scale scores (b) over 24 weeks of treatment with alfuzosin 10 mg once daily (* $P < 0.05$ versus baseline). MSHQ, male sexual health questionnaire.

view of the results of recent epidemiological studies, which revealed that the level of sexual activity in aging men was higher than the predicted level. According to the multinational survey of the aging men-7, which surveyed 12 815 men aged 50–80 years, 71% of the respondents reported at least one episode of sexual activity in the previous 4 weeks. Moreover, 83% of the respondents believed that they were still ‘sexually active’.¹² When we consider the high prevalence of concomitant BPH and sexual dysfunction in aging men, the strong desire for a sexual life in aging men may be an important factor, which should not be dismissed in the management of patients with BPH/LUTS. In this study, we only included patients with BPH/LUTS who reported that they had experienced at least one episode of sexual activity in the previous 4 weeks and excluded all ‘sexually inactive’ patients. These unique inclusion and exclusion criteria are very important and must be considered before the results are discussed. In most of the earlier studies concerning the relationship between BPH and sexual dysfunction, the surveys of patients with BPH were conducted regardless of their baseline sexual activity.^{10,11,13} However, an improvement in sexual function may be influenced by baseline sexual activity before treatment. It could simply be expected that the improvement in sexual function in

patients with active sex lives may be more significant than in patients who are not sexually active. The results of this study are important and differ from those of earlier similar studies that reflect the improvement in sexual function in ‘sexually active’ patients. These differences may affect the results of the trial. The baseline IIEF-15 score was higher than those of earlier similar studies. This is logical when the inclusion criteria are considered, because the enrolled patients were limited to sexually active men. In addition to the higher baseline scores of IIEF and MSHQ, the degree of improvement in sexual function was more significant and more rapid than those of earlier studies. In this study, the improvement in sexual function at 24 weeks, reflected in the MSHQ and IIEF scores, was 19.2 and 19.8%, respectively, and a significant improvement in the MSHQ score was also observed at the first visit after medication (79.1–88.7). The greater degree of improvement in sexual function and the more rapid onset of efficacy than those observed in earlier studies may be partially attributable to the differences in our patient group, which comprised only sexually active patients. When considering earlier reports of BPH and sexual function, we can assume that the improvement in sexual function, brought about by the medical treatment of patients with BPH, will differ according to the original degree of sexual dysfunction.

In this study, there was a negative correlation between the voiding symptoms reported by the IPSS and the sexual function reported by the MSHQ scores. However, the correlation was not statistically significant ($P > 0.05$, Pearson correlation coefficient = -0.24). Our results are not consistent with those of earlier studies,^{3,5,14} which confirmed a strong correlation between the voiding symptoms of BPH/LUTS and sexual dysfunction. We assume that the characteristics of the patients enrolled in this study excluded patients with severe sexual dysfunction, which may also have contributed to our different results. However, there has been no confirmative report about the severity of BPH and of the sexual dysfunction reflected by the MSHQ (or by the IIEF-15 or DAN-PSSsex). Further studies using the MSHQ to evaluate sexual function in patients with BPH and concomitant sexual dysfunction are required.

Although the previously mentioned questionnaires that evaluate sexual function, such as the IIEF-15 or DAN-PSSsex, have been used in various clinical trials, there are some limitations to those questionnaires, which predominantly focus on erectile function and are unsuited to the assessment of the detailed aspects of sexual function. For example, the question on ejaculatory function in the IIEF-15 only assesses the presence or absence of ejaculation and does not provide any information on delayed or retrograde ejaculation, the strength of ejaculation or the satisfaction related to ejaculation.

In this study, the MSHQ was used to assess sexual function. The MSHQ was developed and validated to assess, in detail, different aspects of male sexual function, such as ejaculation, orgasm and satisfaction, in addition to erectile function.¹⁵ The MSHQ consists of a self-administered 25-item questionnaire, and addresses three major domains (erection, ejaculation and satisfaction with sexual life) and additional items related to sexual activity, desire and the 'bother' related to sexual dysfunction. In the ejaculation domain, seven items are related to the detailed aspects of ejaculation, which cannot be evaluated with the IIEF-15 or DAN-PSSsex. Thus, the MSHQ has many benefits in the detailed evaluation of sexual dysfunction according to the various domains related to sexual function. The validity and reliability of the Korean version of the MSHQ, which was used in this study, have been confirmed in an earlier report.¹⁶ Although it has advantages in evaluating sexual function in detail, there is a paucity of literature that evaluates sexual dysfunction using the MSHQ. This is mainly because of the complexity of the questionnaire and the difficulty in maintaining the compliance of the patients during the study period. To the best of our knowledge, the SAMBA trial is the first clinical trial concerning the medical treatment of patients with BPH and the improvement in sexual dysfunction assessed by the MSHQ.

The finding that alfuzosin treatment improved the ejaculatory function of patients with BPH is one of the unique and remarkable points of this study. A serial improvement in the score for the ejaculatory scale was observed over the whole period of the trial and was statistically significant (22.3–28.1; $P < 0.05$, relative to baseline). This may be an advantage of alfuzosin treatment over some other α -blockers commonly prescribed for the treatment of BPH/LUTSs. For example, tamsulosin, a typical α -1 blocker that competes commercially with alfuzosin, had a greater incidence of adverse effects related to ejaculation, regardless of its positive effects on overall sexual function.¹⁷ When we consider the major role of ejaculation in overall sexual function and the high prevalence of ejaculatory disorders in patients with BPH/LUTSs, the relatively strong positive effect of alfuzosin treatment on ejaculatory function may give it a dominant position in the treatment of BPH/LUTSs with concomitant sexual dysfunction. The improvement in the ejaculatory function produced by alfuzosin in this study is consistent with the results of earlier studies that evaluated the effects of alfuzosin on sexual function with respect to ejaculatory function.^{10,11,18} Those studies suggested that there was a significant improvement in ejaculatory function with alfuzosin treatment of BPH/LUTSs after the analysis of the changes in DAN-PSSsex questionnaire scores. By using the MSHQ questionnaire, we have provided more concrete and detailed evidence of the

improvement in ejaculatory function caused by alfuzosin treatment in patients with BPH/LUTSs with concomitant sexual dysfunction.

The mechanism by which alfuzosin or any other α -blocker improves sexual function in patients with BPH/LUTSs remains unclear and is under investigation. One possible explanation is that the increased sympathetic tone may play a major role in the common pathophysiological mechanism of BPH/LUTSs and erectile dysfunction. The stimulation of the α 1-receptors of the human corpus cavernosum is related to penile detumescence and flaccidity. Thus, the elevated baseline adrenergic activity that is commonly observed in patients with BPH has a negative effect on erectile function.^{19,20} According to the theoretical background of BPH/LUTSs and erectile dysfunction related to elevated sympathetic tone, the blocking of the α 1-receptors with alfuzosin is believed to affect not only voiding symptoms but also erectile function. The ejaculatory function is suggested to be mainly related to the α -1A receptor subtype rather than to the other α -1 receptor subtypes (α -1B and α -1D). This hypothesis is supported not only by a clinical trial that revealed the relatively higher prevalence of ejaculatory disorders in patients treated with tamsulosin (selective α -1A receptor blocker), but also by a recent animal study that provided evidence of a relationship between tamsulosin and ejaculatory disorder, through a reduction in seminal vesicle pressure.^{17,21} In this study, the erectile score on the MSHQ increased independently during serial evaluations from baseline to the end point (7.4–8.8, $P < 0.05$ versus baseline). However, there was no significant improvement in the satisfaction score on the MSHQ (19.4–21.8, $P > 0.05$ versus baseline). Multiple factors may have influenced this result, such as selection bias or the small size of the patient sample. In addition to these unexpected factors, we believe that the characteristics of the questionnaire itself are responsible for the result. The satisfaction domain of the MSHQ addresses not only the satisfaction of the patient himself but also that of the relationship with the main partner. Two questions are related to the response of and communication with the main partner. Moreover, the last question is related to the general aspects of the relationship, distinct from the sexual aspects. Because of these characteristics of the satisfaction domain of the MSHQ, any improvement on the satisfaction scale could be relatively independent of the improvement in the sexual function of the patient himself. The relationship between alfuzosin and the patient's satisfaction with his sexual life cannot be concluded from a single study. Further studies on a larger scale are required to evaluate the effect of alfuzosin treatment on the satisfaction aspect of sexual function.

This study also confirms the clinical efficacy of alfuzosin in the treatment of patients with BPH/LUTSs. All the clinical parameters related to

voiding symptoms, such as Q_{max} , total IPSS score and bother score, improved significantly from baseline. The clinical tolerability related to treatment-associated adverse effects was also confirmed in this study, as has already been shown in earlier studies.⁷⁻⁹

Conclusions

Alfuzosin (10 mg once daily) for the treatment of patients with BPH is effective in improving sexual function, as well as LUTSs and quality of life, and is tolerated well. There was an especially significant improvement in ejaculatory function after the treatment of patients with LUTSs and BPH with alfuzosin. The MSHQ, a newly developed questionnaire that provides detailed access to the individual domains of sexual function, allowed the more accurate and in-depth evaluation of male sexual function. The degree of improvement in sexual function determined by the MSHQ correlated with that determined by the IIEF-15.

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