Original Research

CARDIOLOGY

Cardiology 2013;125:235–241
DOI: 10.1159/000350955

Received: December 30, 2012
Accepted after revision: March 26, 2013
Published online: June 26, 2013

The Effect of Combined Antihypertensive Treatment (Felodipine with Either Irbesartan or Metoprolol) on Erectile Function: A Randomized Controlled Trial

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For editorial comment see p. 232

Key Words
Combination therapy · Felodipine · Hypertension · Oxidative stress · Sexual function

Abstract
Objectives: This study aimed to determine whether combining a calcium channel blocker with either an angiotensin II receptor blocker or a β-blocker would have similar effects on sexual function in men with hypertension. ***Methods:*** This prospective, randomized study (ClinicalTrials.gov: NCT01238705) included 218 male participants with untreated hypertension. Patients were randomized to treatment with felodipine combined with irbesartan or metoprolol for 48 weeks. Sexual function was evaluated at baseline and after 48 weeks of therapy. The levels of serum sex hormones and markers of oxidative stress were measured at the same time. ***Results:*** There was no significant difference in the prevalence of erectile dysfunction before and after treatment in either group ($p > 0.05$). There were also no differences in the levels of serum testosterone, sex hormone-binding globulin or 4-hydroxynonenal before and after treatment in either group ($p > 0.05$). In the felodipine-irbesartan group, sexual desire scores rose after treatment ($p = 0.022$) and the concentrations of serum 8-hydroxy-2′-deoxyguanosine and malondialdehyde declined ($p < 0.001$ and $p = 0.002$, respectively). The between-group differences for 8-hydroxy-2′-deoxyguanosine and malondialdehyde were not significant ($p > 0.05$, respectively). ***Conclusion:*** The results suggest that felodipine-irbesartan may be more beneficial to the sexual desire of hypertensive male patients than felodipine-metoprolol. This effect was possibly relevant to irbesartan, which prevents oxidative stress to some extent.

Introduction

Hypertension and erectile dysfunction (ED) share a number of risk factors, such as obesity, smoking, diabetes mellitus, aging, hyperlipidemia, and certain medications. A significant association between hypertension and ED has been reported by several authors [1–6]. Oxidative stress is involved in the pathophysiology of ED [7–9], and several studies have shown that certain forms of genetic or acquired hypertension are associated with oxidative stress [10, 11]. We hypothesize that oxidative stress may be involved in the pathophysiology of both hypertension

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and ED via the enhancement of oxidation and the inactivation of nitric oxide (NO). Antihypertensive drugs can impact many aspects of sexual function [12, 13], including orgasm, overall satisfaction with sexual intercourse and sexual desire [14–18]. Regimens of either calcium channel blockers (CCBs) combined with angiotensin II receptor blockers (ARBs) or CCBs combined with β-blockers are recommended as effective therapies for hypertension. The effects of combined antihypertensive therapy on oxidative stress and sexual function are unclear.

Testosterone can regulate male sexual function, including sexual reflexes and the corpus cavernosum. Serum testosterone plays a vital role in maintaining male sexual function; however, the exact mechanism has been debated. Studies have shown that the serum testosterone level in patients with ED is insufficient [19]. When bound to sex hormones, sex hormone-binding globulin (SHBG) participates in the transportation and regulation of sex hormones in the blood and testicular spermatogenic activity. A previous study showed that serum SHBG levels were reduced in ED patients.

8-Hydroxy-deoxyguanosine (8-OHdG) is the product of DNA oxidation by reactive oxygen species. Its concentration in the urine and blood is indicative of the extent of oxidative damage; thus, it is considered to be an indicator and biomarker of oxidative DNA damage and oxidative stress [20, 21]. Total and free malondialdehyde (MDA) are end products of lipid oxidation and are used as indexes of oxidative damage [22]. 4-Hydroxynonena (HNE) is one of the end products of lipid oxidation in the human body and is an important indicator of lipid peroxidation/oxidative stress [23].

The purpose of this study was to compare the effects of a felodipine-irbesartan combination and a felodipine-metoprolol combination on sexual function and oxidative stress in male patients with hypertension.

Methods

Participants

This was a prospective, randomized, parallel, active-controlled, open-label study (ClinicalTrials.gov: NCT01238705) conducted from January 2008 through December 2011. Participants were unpaid volunteers recruited from the outpatient department of Lanzhou University Second Hospital in Lanzhou, China. The study protocol was approved by the Ethical Committee of Lanzhou University Second Hospital. Informed consent was obtained from all individual participants before they were enrolled. All interviews were conducted privately and confidentially. The anonymity of the participants was maintained.

Inclusion Criteria

Male patients aged 25–60 years with previously untreated essential hypertension were included. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mm Hg and/or a diastolic BP (DBP) ≥90 mm Hg. A stable sexual relationship for the previous 6 months was required.

Exclusion Criteria

The key exclusion criteria included malignant hypertension, a history of syncope, bradycardia (heart rate <45 beats/min), atrioventricular block (or degree), congestive heart failure, serious hepatic and kidney dysfunction, secondary hypertension and the use of any form of treatment for ED within the 4 weeks preceding enrollment, the presence of any genital deformity or sexual disturbance that precluded sexual intercourse and patients who had participated in any other studies involving investigational drugs.

Intervention

The randomization procedure included the generation of a randomization list by a validated system that automates the random assignment of treatment groups. Eligible patients were assigned the lowest available number on the randomization list. Patients were randomly assigned to receive either felodipine (5 mg/day) plus irbesartan (F+I group; 150 mg/day, n = 113) or felodipine (5 mg/day) plus metoprolol (F+M group; 47.5 mg/d, n = 105). The dosage of felodipine was titrated to 10 mg/day in the 4th week if the patient's BP was ≥140/90 mm Hg. Patients were instructed to take the tablets at 6–8 a.m. each day on an empty stomach. Felodipine extended-release tablets (Plendil) and metoprolol succinate extended-release tablets (Betaloc ZOK) were manufactured by AstraZeneca, England. Irbesartan (Aprovel) was synthesized by Sanofi-Aventis, France.

The primary outcome was the effect of treatment on the international index of erectile function (IIEF) score. The secondary outcomes included the effects of treatment on SBP, DBP, serum testosterone, SHBG, serum 8-OHdG, 4-HNE, and MDA.

Assessment of Sexual Function

Sexual function was evaluated with the IIEF questionnaire. The IIEF, a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function, was developed by Rosen et al. [24] in 1997. Patients were asked to complete the IIEF within 1 h. Assistance was given by the research staff to patients during the completion of the IIEF if help was requested. The responses to each of the five questions of erectile function (EF) were rated on a 0- to 5-point scale, and the total EF score ranged from 0 to 25. A higher score of 22–25, indicating better sexual function, placed patients in the category of having no ED. Patients with scores ranging from 12 to 21 were considered to have mild ED, and patients with a score of 1–7 were considered to have severe ED [24].

BP Measurement

BP measurements were performed three times on the right upper limb of sitting patients by a trained staff member using an appropriately sized cuff with a validated mercurial desk model sphygmomanometer. At each assessment, three readings, taken at intervals of 1–2 min, were averaged to obtain the BP. To further minimize the confounding influence of alerting reaction BP, measurements were performed in a noise-protected room with a constant temperature (23°C) that was not associated with usual patient care.

Table 1. Baseline characteristics of participants assigned to the F+M group and the F+I group at entry

Characteristics	F+M group (n = 105)	F+I group (n = 113)	p value
Age, years	46.25±6.65	47.49±6.76	0.174
BMI, kg/m^2	24.86±2.52	24.31±2.38	0.097
DBP, mm Hg	149.37±8.83	149.96±8.43	0.612
SBP, mm Hg	99.56±8.40	98.48±9.63	0.378
Smoking	71	75	0.480
Alcohol consumption	41	42	0.442
Plasma glucose, mmol/l	5.08±0.61	4.94±0.60	0.067
Total cholesterol, mmol/l	4.18±0.86	4.18±0.88	0.985
TG[1], mmol/l	1.28±0.36	1.266±0.37	0.561
HDL, mmol/l	1.51±0.33	1.51±0.33	0.944
LDL, mmol/l	2.29±0.55	2.25±0.50	0.627
Duration of hypertension, years	6.48±5.06	7.40±6.11	0.670
BUA[1], mmol/l	326.71±49.28	335.29±43.84	0.177

p values are calculated by the Mann-Whitney test. BMI = Body mass index; TG = triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BUA = blood uric acid.

[1] Data are not normally distributed.

Laboratory Analysis

Blood samples were collected from participants at 8–9 a.m. after an overnight fast. The serum was obtained by immediate centrifugation at 3,000 *g* for 15 min at 4°C between 1 and 2 h after collection. The samples were stored at –80°C until analysis. Fasting serum levels of total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, fasting blood sugar and uric acid were determined using standard laboratory methods at the Lanzhou University Second Hospital. Serum HNE, 8-OHdG and MDA were measured using an enzyme-linked immunosorbent assay from R&D Systems (Minneapolis, Minn., USA). Serum testosterone and SHBG were measured using a radioimmunoassay (Beijing North Institute of Biological Technology, Beijing, China).

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows (SPSS Inc., Chicago, Ill., USA). The results are presented as rates or means ± SD, as appropriate. The score distributions were evaluated by the Shapiro-Wilk normality test. Following this evaluation, differences between groups were tested for significance using Student's t test and a one-way analysis of variance for normally distributed variables and non-parametric statistical tests (Kruskal-Wallis) for non-normally distributed variables. Differences between treatment and baseline were tested for significance using paired-sample t tests. The χ^2 test and Fisher's exact test were used for categorical variables. A p value <0.05 was considered significant.

In this study, published data were used to estimate the effect of sample size. A previous study reported that the prevalence of ED in patients with hypertension was 35.2% [12], whereas it was 65.9% in patients taking β-blockers [25]. The minimum sample size required to determine whether sexual function was affected by the drug treatments was determined using the following formula:

$N_1 = N_2 = f(\alpha, \beta)\ [\pi_1 (1 - \pi_1) + \pi_2 (1 - \pi_2)] / (\pi_2 - \pi_1)^2$ (significance level $\alpha = 0.05$; type II error $\beta = 0.10$; power $1 - \beta = 0.9$; $f(\alpha, \beta) = 10.5$).

A minimum sample size of 51 individuals in each group was calculated. Assuming a 20% loss to follow-up, a total of 128 patients was required in this study.

Results

Participants

In total, 373 male hypertensive patients were screened, which included medical history, physical examination and laboratory parameters; 59 individuals did not meet the eligibility criteria (35 patients with uncontrolled BP taking 2 antihypertensive drugs, 19 patients without a stable sexual relationship and 5 patients with renal dysfunction). After presenting the informed consent form, 55 patients declined to participate. The remaining 259 patients were randomized to either the F+M group (n = 130) or the F+I group (n = 129). In the F+M group, 21 patients were lost to follow-up, and 4 patients were found to be taking sildenafil and were excluded. In the F+I group, 14 patients were lost to follow-up, and 2 were excluded for taking sildenafil. A total of 218 participants (105 in the F+M group and 113 in the F+I group) completed the study and were included in the study protocol analysis. The characteristics of the participants in the two groups were well balanced at baseline (table 1). According to the participant self-reports and the results of the phys-

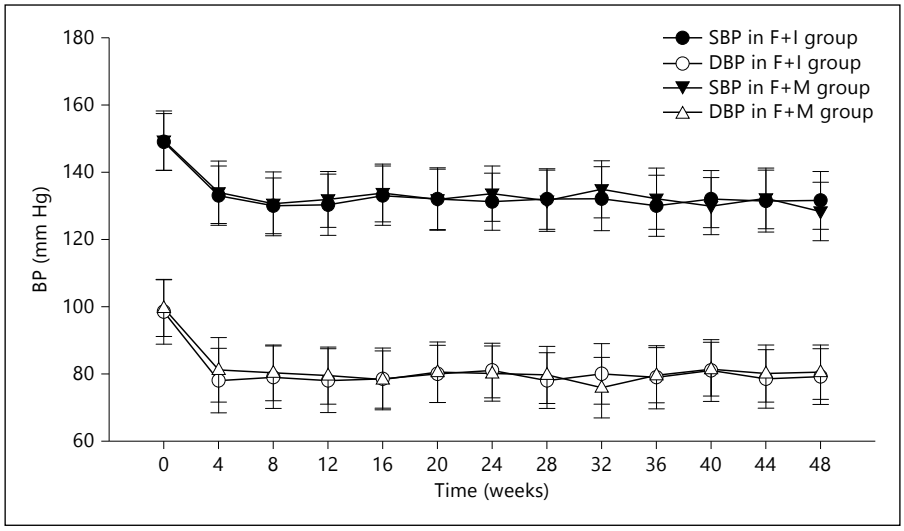

Fig. 1. Effects of treatment on SBP and DBP between the two groups. The trends of BP decline were similar during the administration period.

Table 2. Changes in sexual function of participants during medication

	F+M group		p value	F+I group		p value
	week 0	week 48		week 0	week 48	
EF						
Total score	20.50±6.48	20.53±6.61	0.758	20.46±6.67	20.81±6.44	0.236
Score of ED						
None (22–25)	24.25±0.98	24.51±0.86		24.45±0.87	24.51±0.93	
Mild (12–21)	18.33±2.50	19.14±2.48		17.67±3.24	17.46±2.76	
Moderate (8–11)	9.90±0.87	10.10±0.99		9.78±1.09	10.00±0.87	
Severe (1–7)	6.30±0.82	6.45±0.69		6.33±0.89	6.73±.65	
Proportion of ED, %	27	30	0.384[1]	23	20	0.386[1]
OF	9.33±1.20	9.45±0.93	0.158	9.73±0.72	9.79±0.67	0.052
SD	9.60±0.69	9.65±0.62	0.459	9.66±0.68	9.82±0.45	0.022
IS	13.90±2.03	14.09±1.72	0.084	14.23±1.29	14.16±1.34	0.379
OS	9.53±0.95	9.62±1.07	0.412	9.548±0.74	9.62±0.69	0.088

OF = Orgasmic function; SD = sexual desire; IS = intercourse satisfaction; OS = overall satisfaction.
[1] Pearson's χ^2 test.

ical examination and the laboratory parameters, no serious adverse events related to the study medicines were reported in either treatment group. Most of the adverse events that occurred during the study were transient and mild.

BP Measurements through 48 Weeks

Compared with baseline, SBP and DBP had decreased progressively in the 2 groups by the 4th week. The BP reductions remained stable in both groups from the 4th to the 48th week. The trend in BP decline was similar in both groups (fig. 1).

Effects of Treatment on Sexual Function

In the F+I group, the total IIEF score did not differ significantly at week 48 of follow-up compared to baseline ($p = 0.236$), but the scores of sexual desire were increased ($p = 0.022$). The results were similar in an intent-to-treat analysis ($p = 0.040$). Scores for other domains did not significantly differ from the baseline scores ($p > 0.05$ for all; table 2).

The total IIEF score in the F+M group did not differ significantly at week 48 of follow-up compared to baseline ($p = 0.758$). No significant changes were observed in

Table 3. Changes in biomarker of participants during the administration period

	F+M group		p value	F+I group		p value
	week 0	week 48		week 0	week 48	
Marker of OS						
8-OHdG, ng/l	132.62±42.83	134.16±40.16	0.069	133.47±32.31	130.70±31.25	<0.001
HNE, ng/l	10.83±4.18	11.08±3.86	0.315	10.75±4.08	10.74±4.16	0.942
MDA, nmol/ml	6.78±1.35	6.84±1.29	0.384	6.82±1.17	6.59±1.14	0.002
Sex hormone						
T, ng/dl	1,108.60±419.75	1,122.25±383.46	0.192	1,177.66±405.07	1,179.88±350.62	0.902
SHBG, nmol/l	36.44±6.30	36.66±6.36	0.096	35.82±6.92	36.22±7.32	0.096

p values are calculated by paired 2-tailed t test. OS = Oxidative stress; T = testosterone.

the scores of the domains for EF, orgasmic function, sexual desire, sexual intercourse satisfaction or overall satisfaction in the F+M group ($p > 0.05$ for all; table 2).

Sexual Hormones and Markers of Oxidative Stress

In the F+I group, significant decreases in 8-OhdG and MDA were observed after 48 weeks of follow-up ($p < 0.001$, $p = 0.002$). The results were similar in the intent-to-treat analysis ($p = 0.025$, $p = 0.036$). There were no significant differences in the other items within the two groups ($p > 0.05$; table 3).

Discussion

This study demonstrated that felodipine combined with irbesartan or metoprolol had the same effect on lowering BP. Previous studies have reported variable and inconclusive results for the sexual side effects of antihypertensive medications in men. Long-acting CCBs are regarded as having a neutral effect on the sexual function of male patients with hypertension, but there are differing opinions regarding the effects of metoprolol and irbesartan.

ARBs have not been generally associated with impairment of sexual activity and have even been associated with improvements compared to other antihypertensive agents [14–16, 26–28]. The activation of oxidative stress can be induced by angiotensin II through the angiotensin II type 1 receptor. O^{2-}, one component of reactive oxygen species, reacts with NO to form $ONOO^-$. The NO → cGMP → PGK pathway, which plays an important role in the maintenance of EF, is impaired by the decline in NO concentration. However, this process could be prevented by ARBs by blocking the angiotensin II type 1 receptor. This mechanism may explain why the EF score was elevated during the administration of ARBs in these previous studies. In this study, decreased concentrations of 8-OHdG and MDA were observed, suggesting that the process of oxidative stress was depressed to a certain extent. At the same time, the sexual desire values were increased following 48 weeks of treatment in the F+I group. This result is consistent with previous research [29, 30]. However, the scores for the other domains and the total IIEF scores showed no improvement compared with baseline.

Most previous studies have reported that β-blockers are associated with a negative impact on male sexual function [13]. Fogari et al. [28] suggested that these drugs might cause a further decrease in androgen. However, testosterone and SHBG did not significantly differ after treatment in the F+M group in our study. The possible explanation for this outcome is that, unlike short-acting and less selective β-blockers such as atenolol and carvedilol, which act on and block the β_2-receptors of the sexual organs, metoprolol succinate extended-release tablets are long acting and highly selective β_1-blockers, and they may not cause a significant decrease in androgen, which would further affect sexual function in hypertensive men. Excluding the sexual desire score, other aspects of sexual function did not significantly differ between the two groups after drug administration. This suggests that selective β-blockers do not have a negative impact on the sexual function of patients with hypertension.

The impact of metoprolol on oxidative stress is inconsistent. Cicek et al. [31] suggested that serum MDA decreased following metoprolol administration after coronary angioplasty and that this was accompanied by an

increase in the total antioxidant capacity. By contrast, another study showed that metoprolol had no effect on oxidative stress [32]. In the present study, the indicators of oxidative stress in the F+M group did not differ before and after treatment. Therefore, it is difficult to draw a conclusion regarding the relationship between metoprolol and oxidative stress based on the present evidence.

Compared with previous studies, our trial used metoprolol succinate extended-release tablets; metoprolol is a highly selective β_1-receptor blocker that theoretically does not act on β_2-receptors in the penis. This distinction may also explain the lack of a difference between these two combination therapies on some items of the IIEF and the prevalence of ED. Similar results were observed in another study on female hypertensive patients in which felodipine-metoprolol had no influence on the total score of the female sexual function index [33].

Our study has some limitations. The participants were not blinded to the interventions, which is an inherent problem and included the risk of expectation bias. This study primarily focused on the evaluation of EF using the IIEF. Male sexual dysfunction can be expressed as a series of complex symptoms, such as sexual desire disorder (e.g., low sexual desire, eroticism), ED or abnormal erection, ejaculation disorder (e.g., premature ejaculation, no ejaculation) and sensory disturbances, which all involve complex mechanisms. However, the IIEF does not evaluate ejaculation disorders. Additionally, the 48-week follow-up period is relatively short to observe changes in symptoms, sexual function and oxidative stress due to the combination therapy.

Conclusions

This study indicates that felodipine plus irbesartan may be more beneficial than felodipine plus metoprolol for the sexual desire of patients with hypertension and that the benefits may be related to decreased oxidative stress. Because of the limited sample size and the short observation period, more research is required to improve our understanding of sexual function, BP and oxidative stress.

Acknowledgements

This study was supported by the Specific Project of Technological Research and Development in Gansu Province of China (0709TCYA068).

We express our deep appreciation to Xuehong Chen and Guangdi Li from the Nuclear Medicine Clinic and the Center of Clinical Laboratory of Lanzhuo University Second Hospital, Lanzhuo, Gansu, China.

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