**Running Head:** Effect of Carvedilol and Terazosin plus Enalapril in BPH patients

# A Randomized Crossover Pilot Study Examining the Effect of Carvedilol and Terazosin plus Enalapril on Urinary Symptoms of Patients with Hypertension and Benign Prostatic Hyperplasia

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**Abstract**

**Purpose**: The present study aims to assess and compare the effects of carvedilol and terazosin plus enalapril on lower urinary tract symptoms (LUTS), the urine flow, and blood pressure (BP) in patients with moderate hypertension (HTN) and benign prostatic hyperplasia (BPH).

**Materials and Methods**: In this randomized crossover trial, a total of 40 men with HTN and LUTS symptoms were enrolled. The first group was treated with carvedilol, and the second one received terazosin plus enalapril. After eight weeks of treatment, the patients experienced a one-month washout period, and the treatments changed and continued for eight weeks. To diagnose BPH in the study, the international prostate symptom score (IPSS) questionnaire was used. Moreover, the prostate-specific antigen (PSA), the post-void residual (PVR) urine volume, and the maximum urinary flow rate (Q-max using the uroflowmetry test) were measured.

**Results**: Effect assessment results in this crossover trial illustrated neither carryover effects nor significant treatment effects on all primary outcomes ($P > 0.05$). Moreover, the results for the period effect indicated a significant reduction in BP (systolic and diastolic), PVR, and IPSS, yet a significant raise in Qmax.

**Conclusion**: The effects of carvedilol are similar to those of the combination of terazosin and enalapril in patients with moderate HTN and BPH in controlling LUTS. Carvedilol could be used as an appropriative drug in patients with moderate HTN and cardiac problems with LUTS of BPH. Further studies are recommended to be conducted to investigate and compare the efficacy of carvedilol with that of other alpha-blockers with a larger sample size and over a longer period of time.

**Keywords**: Benign Prostatic Hyperplasia; Blood Pressure; Carvedilol; IPSS; Qmax

## INTRODUCTION

Benign prostatic hypertrophy (BPH), as a common disease in middle-aged and elderly men, imposes a large economic burden on the society every year [5], thereby affecting 50% of men over 60 years old. In addition, it is a progressive disease associated with lower urinary tract symptoms (LUTS), including frequent urination, post-void dribbling, prolonged micturition, urinary hesitancy, and incomplete urinary excretion [1-3]. Moreover, as this disease is supposed to be associated with bladder outlet obstruction (BOO) and urinary retention [2], it has a significant impact on the patient's quality of life [4].

Hypertension (HTN) causes many life-threatening complications, such as heart failure that affects more than half of the population in many countries, and like BPH, its prevalence grows with age [6]. Research shows that 20-40% of people with high blood pressure (BP) suffer from BPH as well [7]. An epidemiologic study reported an age-independent association between BPH and HTN [8].

BPH treatment involves modifications in the patient's lifestyle and administration of smooth muscle relaxant medications (alpha-1 blockers), which in turn reduce urinary retention and LUTS symptoms [9]. However, several studies have indicated that administration of alpha-blockers alone for the treatment of BPH increases the risk of heart failure [10, 11], which is not recommended for the control of blood pressure and an improvement in cardiovascular complications [11].

Carvedilol is a non-selective beta-blocker, has an alpha-1 receptor-blocking property, has an effect on α1 and β receptors, and can be an effective medical therapy in heart failure and BPH [11]. The ability of carvedilol to block α1-adrenoceptors results in vasodilatation, thereby reducing urinary disorders caused by BPH. In a study conducted in the Netherlands in 2013 on 49 patients with BPH and HTN, the positive effects of carvedilol on the maximum urinary flow rate (Q-max) and other parameters, including the international prostate symptom score (IPSS), the post-void residual (PVR) urine volume, and the prostate-specific antigen (PSA) within three months of treatment were reported [6, 7].

Terazosin is a long-acting alpha-blocker that causes a significant increase in Q-max at doses 5 and 10 mg per day, with its effects lasting for two weeks. However, it is not recommended for controlling blood pressure [12], so other drugs, such as enalapril should be taken.

Past research shows that carvedilol could be effective in improving administrative symptoms of prostate enlargement. However, effectiveness of this drug in treating BPH has not been studied yet, in contrast to other common drugs. Accordingly, this article aims to compare effects of carvedilol with those of common alpha blockers, such as terazosin, on the treatment of BPH. Due to the simultaneous alpha-blocking and beta-blocking effects of carvedilol, the present study aims to determine effects of carvedilol as well as terazosin plus enalapril on Q-max, PVR, PSA, and IPSS in patients with moderate HTN and BPH.

## MATERIALS AND METHODS

### *Study population*

The present randomized, blind, crossover clinical trial was conducted in Tabriz, Iran, using the convenience random sampling procedure, on 46 eligible male patients aged over 40, who referred to a urology clinic with moderate LUTS and HTN symptoms from March to August 2019 and were recruited for this study. Written informed consent forms were obtained from all patients at the beginning of the study. In addition, the study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.604).

### *Sample size calculation*

In an equivalence test of means using a two-period crossover design on PVR as the primary outcome of the study, a total sample size of 37 was achieved with 80% power and a 5% significance level. Accordingly, the true difference between the means and the root mean square error was considered to be 0 and 4.5, respectively. The information on the primary outcome was obtained through a pilot of 5 participants as the trial started. To consider a dropout rate of about 10%, the total sample size increased to 40 participants (20 per sequence). The sample size was estimated by PASS15 (PASS 15 Power Analysis and Sample Size Software (2017), NCSS, LLC, Kaysville, Utah, USA, ncss.com/software/pass)

***Inclusion and exclusion criteria***

Six patients who did not meet the inclusion criteria were excluded from the trial. Accordingly, two patients having an increased PSA level, one patient touching the nodule, two patients receiving medication therapy during the study, as well as one patient not willing to continue the study were dropped out of the study. In the end, 20 patients in each group participated in this study.

Accordingly, 40 eligible patients suffering from benign prostatic hyperplasia, who aged over 40, with moderate blood pressure, systolic blood pressure (SBP) between 140-150 mmHg and/or diastolic blood pressure (DBP) between 90–99 mmHg specified according to the European Society of Hypertension Guidelines, those having sustained symptoms of LUTS over the past six months as diagnosed by physical examinations and ultrasonography tests, as well as patients with IPSS > 8 and Qmax > 5 ml were recruited in the study. In addition, patients with a history of prostate surgery, urinary symptoms caused by other diseases, the PSA level > 4 ng/mL, the persistent PVR volume > 200 mL, hepatic or renal dysfunction, diabetes mellitus, and cardiovascular complications caused by hypertensive diseases were excluded from the study. Finally, the patients' eligibility was confirmed by performing medical examinations, clinical laboratory tests, and urological evaluations during clinical visits. Following the eligibility assessment, the patients experienced a four-week washout period.

***Procedure***

The first assignment of the patients to the groups treated with carvedilol as well as terazosin plus enalapril was performed. Next, the patients experienced a four-week washout period to get prepared for switching the groups (crossover) and beginning the second active intervention period. Clinical evaluations were carried out at the baseline, after eight weeks of the first active intervention period, at the end of the second washout period, and after the second active intervention period. Drugs were adjusted from the initial doses of 12.5 mg for carvedilol as well as 10 mg for terazosin plus 2.5 mg for enalapril to the doses of up to 25 mg for carvedilol as well as 20 mg for terazosin plus 20 mg for enalapril to ensure normal BP control. However, due to the orthostatic effects of all drugs, they were prescribed with dinner. In addition, BPH

symptoms were assessed using the IPSS questionnaire. Moreover, the IPSS questionnaire was completed, and PSA, PVR, as well as Q-max (using the uroflowmetry test) were measured. Systolic blood pressure and diastolic blood pressure (SBP and DBP) were assessed twice in a relaxed position after a 15-minute rest, and the mean values were recorded. In addition, SBP, DBP, PVR, IPSS, PSA, and Q-max were considered the main primary outcomes of this study and assessed at the beginning and after eight weeks.

***Statistical analysis***

All analyses were performed using data and expressed using mean and standard deviation (SD) for numeric variables and using frequency (percentages) for categorical variables. In this 2x2 crossover trial, we defined two sequences, with the first of which being 'TE_CAR' in which 20 patients received 'terazosin + enalapril' in the first period, and then they received 'carvedilol' in the second period; the second sequence was 'CAR_TE' in which 20 patients received 'carvedilol' during the first period, and then they received 'terazosin + enalapril' in the second period. Measuring effects of both treatments on the same participants allowed us to reduce the rate of variations caused by differences between the participants. In addition, the repeated measures ANOVA was used to analyze results of data comparison between the two groups at the baseline and after treatments. Statistical analyses were performed using SPSS software version 22. In addition, Mean ± Standard Error of Mean (SEM) was reported for all collected data. An independent samples t-test was used to compare the results of the quantitative data. Moreover, a paired sample t-test was used to determine mean differences before and after the treatment. In addition, a chi-square test and the Fisher's exact test were used to analyze the qualitative data. P values less than 0.05 were considered statistically significant. The three aforementioned effects were assessed using a single model and represented by both tests at a significant level of 5% and a 95% confidence interval (CI) for the effects.



**RESULTS**

Table 1 shows the patients' baseline characteristics. A total of 20 patients in each group received the treatment, and the mean age of terazosin plus enalapril and carvedilol groups was 61.25 ± 8.86 and 60.62 ± 9.31 years, respectively, which indicates no significant difference between the two intervention groups in

age. Moreover, there were no statistically significant differences between the two intervention groups in terms of demographic variables ($P > 0.05$). Table 2 shows the number of adverse events and dropouts from the treatment.

Interestingly, a significant reduction was observed in SBP values compared to the baseline values in both carvedilol and terazosin plus enalapril intervention groups ($P<0.05$) as shown in Table 3. Table 4 shows comparison results for the mean and standard deviation of SBP, DBP, PVR, PSA, Q-max, and IPSS between the two intervention groups. However, DBP values significantly decreased compared to the baseline values in both intervention groups ($P < 0.05$). Moreover, carvedilol therapy was more effective than terazosin plus enalapril therapy in lowering DBP values during the eight-week period ($P < 0.05$). In addition, in contrast to baseline values, PVR and IPSS scores indicate a remarkable decline in both carvedilol and terazosin plus enalapril groups ($P < 0.05$). In contrast, PSA values did not decrease significantly in comparison to baseline values in any of the intervention groups and had a large amount of data loss, which made the calculation of this parameter became impossible. Furthermore, treatments with carvedilol and terazosin plus enalapril significantly increased Q-max values compared to the baseline values ($P < 0.05$). As the last column of Table 3 shows, the interactions between sequence and time were not significant for all parameters; thus, one could conclude that the time effect was equal on both groups.

As comparisons show in Table 4, the mean and standard deviation of the variables between the two groups were just divided by time. Accordingly, the presented mean values for time 2 decreased for all variables except for Q-max.

## DISCUSSION

HTN and BPH are both chronic disorders that commonly coexist; therefore, it is better to consider an effective therapy for both of these disorders to improve patients' quality of life. The present study was conducted to show efficacy of carvedilol as against terazosin plus enalapril in patients with moderate HTN and BPH. The original dataset of this study confirmed that carvedilol, at hypotensive doses, might improve

urological indices and reduce BPH-related annoying symptoms; thus, it could improve quality of life in patients with LUTS due to BPH.

A BPH treatment based on lifestyle modifications and administration of smooth muscle relaxants ($\alpha_1$ blockers) [12] has been proved to reduce high BP [13]; however, its efficacy in optimal management of HTN has not been verified. Patients with BPH and concomitant HTN may require a distinctive treatment for high BP [13]. Therefore, carvedilol, a β-blocker (β1 and β2 blockers) with selective α-adrenoceptor antagonist activity, was used in treating hypertension and heart failure, which seemed to be a reasonable alternative [6].

The results of the current investigation revealed that carvedilol effectively improved BPH symptoms (LUTS). To the best of our knowledge, this is the first randomized study to have evaluated efficacy of carvedilol (α and β blockers) as against terazosin plus enalapril in patients with BPH and HTN. In 2013, in a double-blind randomized crossover study, Lewandowski et al evaluated effects of carvedilol on urologic indices in patients with HTN and BPH. They prescribed 12.5 mg/d carvedilol or 10 mg/d enalapril for three months and found out that carvedilol, as against enalapril, had a positive effect on LUTS associated with BPH in patients with HTN [6]. Our study had some similarities to this trial, yet terazosin was used along with enalapril as a treatment for high BP in the present study.

The results of this study indicated no significant difference in the treatment effect between terazosin and carvedilol in terms of BP, but a significant period effect was observed for BP. In the same vein, Ayashi reported that treatment with carvedilol reduced systolic and diastolic BP in patients with mild to moderate HTN (40 and 160mmHg) [14]. In Lewandowski's study, the mean difference between systolic and diastolic BP was not significantly different [6]. In addition, Ostergren et al showed that the mean value of diastolic BP was similar in both groups after five months of maintenance treatment with carvedilol and enalapril [10].

Lewandowski et al.'s study showed a significant reduction in PVR after carvedilol therapy as against enalapril therapy. In contrast, no significant treatment effect was shown on the PVR value in both treatments as against a significant reduction in the PVR value in terms of the time effect in the present study.

Similarly, no significant treatment effect was observed on the Q-max value in patients receiving terazosin plus enalapril and carvedilol in the present study. Considering the mentioned findings, it is implied that findings about alpha-blocking effects are consistent with the results obtained in the present study. Lewandowski et al reported that Q-max values increased significantly after treatment in the carvedilol group.

Based on the results of this study, no significant treatment effects were observed on the PSA variable in both groups. Similarly, Lewandowski's study [6] reported that there were no significant changes or differences in the PSA levels between the two groups in the study.

The results of the present study indicated no significant differences between the two groups in terms of IPSS. Accordingly, the percentage of the IPSS reduction in patients with LUTS using alpha-1 blockers was between 35-40% in a randomized clinical trial [15]. In another study, it was reported that both terazosin and tamsulosin could lead to statistically significant improvements in subjective and objective variables of symptomatic benign prostatic hyperplasia in Japanese patients [16]. In addition, Lewandowski reported that the percentage of the reduction in prostate symptoms (IPSS) was 32% in the carvedilol group, which led to a significant difference between the mean values of the IPSS reduction in the two intervention groups as against the placebo group [6]. Our study shows that treatment with carvedilol reduced the values of SBP, DBP, PVR, and IPSS, but it increased the value of Qmax. In addition, treatment with carvedilol in patients of this study was safe and well-tolerated, and no major adverse effects were reported by the patients. However, tolerance to carvedilol in normotensive patients with BPH requires further investigations.

**LIMITATIONS**

A crossover design was used to reduce the number of patients required for performing the study. As the crossover design necessitates a larger number of observations and higher estimation precision with less number of patients, it can be considered more advantageous than a parallel group design. One of the major limitations of the present study was its smaller number of patients with hypertension and BPH, who were preselected according to inclusion and exclusion criteria. Hence, the obtained findings could not be easily

generalized to other groups of patients, such as those with congestive heart failure or severe hypertension treated with multidrug regimens. Furthermore, the short period of treatment with carvedilol could be regarded as another limitation of the present study.

## CONCLUSION

The obtained results indicated that carvedilol, similar to terazosin plus enalapril was effective in treating urinary tract symptoms in patients with hypertension and benign prostatic hyperplasia. However, further studies are required to investigate efficacy of carvedilol treatment compared to that of other alfa blockers with larger sample sizes to propose carvedilol as a single-drug treatment for patients with BPH and HTN to prevent polypharmacy.


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## CONFLICT ON INTEREST

All authors declared that they have no conflict of interest.


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**Table 1;** Participants' baseline characteristics

| Variables | Terazosin + Enalapril (n=20) | Carvedilol (n=20) | P value |
|---|---|---|---|
| Age, year; mean ± SD | 61.25 ± 8.86 | 60.62 ± 9.31 | 0.15 |
| BMI, kg/m$^2$; mean ± SD | | | 0.66 |
| Hypertension history (mo.); mean ± SD | 80.5 ± 7.1 | 87.2 ± 5.3 | 0.23 |
| BPH history (mo.); mean ± SD | 39 ± 4.2 | 36 ± 6.1 | 0.46 |
| The last dose of study drug(mg); mean ± SD | 11.2 ± 3.1 | 14.6 ± 5.3 | 0.32 |
| First laboratory tests | | | |
| Creatinine (mg/ld.); mean ± SD | 1.28 ±0.1 | 1.19 ± 0.2 | 0.58 |
| PSA (µg/mL); mean ± SD | 2.39 ± 2.86 | 2.63 ± 2.12 | 0.64 |
| First IPSS; mean ± SD | 16.0 ± 2.86 | 15.80 ± 3.25 | 0.07 |
| First PVR (ml), mean ± SD | 35.55 ± 16.85 | 37.30 ± 26.52 | 0.34 |
| First Qmax (ml/s), mean ± SD | 10.18 ± 3.45 | 10.08 ± 3.25 | 0.85 |
| First systolic BP (mmHg), mean ± SD | 149.75 ± 8.95 | 148.5 ± 9.47 | 0.75 |
| First diastolic BP (mmHg); mean ± SD | 92.50 ± 5.50 | 93.75 ± 5.82 | 0.17 |

BPH: benign prostatic hyperplasia, PSA; prostate-specific antigen, IPSS; international prostate symptom score, PVR; post void residual urine volume, Qmax; maximum urinary flow rate.

P-values were not significant for all comparisons made between groups.

**Table 2;** Withdrawals from the treatment and the number of adverse events

| | **Terazosin + Enalapril** | **Carvedilol** |
|---|---|---|
| Withdrawals | | |
| All causes | 0 | 0 |
| Due to adverse events | 0 | 0 |
| Dizziness | 2 | 0 |
| Symptoms of hypo tony | 2 | 0 |
| Asthenia/ fatigue | 0 | 0 |
| Headaches | 2 | 0 |
| Impotence | 0 | 0 |
| Bradycardia | 0 | 0 |

**Table 3: The results of Period and treatment effects for Urologic markers and Systolic and diastolic blood pressures after 8 weeks of treatment**

| Variables | | Period 1 | | Period 2 | | **P Value** |
|---|---|---|---|---|---|---|
| | Sequence | Mean | SD | Mean | SD | Sq. vs. Time |
| SBP (mmHg) | TE_CAR | 149.75 | 2.06 | 132 | 2.13 | 0.29 |
| | CAR_TE | 148.5 | 2.06 | 133.25 | 2.13 | |
| DBP (mmHg) | TE_CAR | 92.50 | 1.27 | 85.75 | 3.35 | 0.16 |
| | CAR_TE | 93.75 | 1.27 | 80 | 3.35 | |
| PVR (ML) | TE_CAR | 35.55 | 4.97 | 15.45 | 2.78 | 0.29 |
| | CAR_TE | 37.30 | 4.97 | 11.10 | 2.78 | |
| IPSS (points) | TE_CAR | 16.00 | 0.69 | 9.10 | 0.84 | 0.99 |
| | CAR_TE | 15.80 | 0.69 | 8.90 | 0.84 | |
| Qmax (ml/s) | TE_CAR | 12 | 2.85 | 17.50 | 2.57 | 0.29 |
| | CAR_TE | 13.50 | 2.85 | 20 | 2.57 | |

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PVR: Post-Void Residual; IPSS: International Prostate Symptom Score; PSA: Prostate-Specific Antigen; Qmax: Maximum Urinary Flow Rate; CI: Confidence Interval; SD: Standard Deviation

**Sequences*:***

**"TE_CAR"**: wherein first period, 20 patients received "Terazosin + Enalapril" and then in the second period these patients received "Carvedilol"

**"CAR_TE"**: wherein first period, 20 patients received "Carvedilol" and then in the second period these patients received "Terazosin + Enalapril".

**Table4: Mean and standard deviation comparisons of SBP, DBP, PVR, PSA, Q-max, and IPSS between two groups**

| **Variables** | **Period 1** | | | **Period 2** | | |
|---|---|---|---|---|---|---|
| | Mean | SD | CI | Mean | SD | CI |
| **SBP** | 149.13 | 1.46 | (146.18, 152.08) | 132.63 | 1.5 | (129.58, 135.67) |
| **DBP** | 93.13 | 0.90 | (91.31, 94.34) | 82.88 | 2.37 | (78.08, 87.67) |
| **PVR** | 36.43 | 3.51 | (29.32, 43.53) | 13.28 | 1.96 | (9.3, 17.25) |
| **IPSS** | 15.9 | 0.49 | (14.92, 16.88) | 9 | 0.60 | (7.79, 10.21) |
| **QMAX** | 12.75 | 2.02 | (4.08, 21.42) | 18.75 | 1.82 | (10.92, 26.58) |

**Figure 1;** Diagram of the patients