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Research Article

The Randomized Clinical Trial of Pentoxifylline for Reduction of Blood Pressure in Patients with Primary Hypertension

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Abstract

Background: Pentoxifylline (PTX) is a xanthine derivative with the potential cardiovascular effects. This study was done to evaluate the impact of pentoxifylline on blood pressure when added to patients' antihypertensive regimen.

Methods: A randomized control trial were carried out on 100 patients with primary hypertension for a three-month period. The intervention group received 1200 mg daily PTX in three divided doses plus the standard treatment of antihypertensive medications, whereas the control group received only the standard treatment of hypertension. Patients' blood pressure was measured at baseline, 4, and 12 weeks after intervention. Patients were also followed up for major adverse cardiac events.

Results: After 4 weeks and 12 weeks of study, no significant difference was observed in systolic blood pressure (SBP) (135 ± 16 vs. 136.2 ± 17.2 mmHg, p=.72; 134.8 ± 13.3 vs. 134.3 ± 14.7 mmHg, p=.85) and diastolic blood pressure (DBP) (81.5 ± 9.9 vs. 82.4 ± 12.9 mmHg, p=.69; 80.8 ± 9 vs. 80.4 ± 10.7 mmHg, p=.84) between two groups.

Conclusion: The result showed that PTX has not a significant effect on BP in patients with primary hypertension.

Introduction

Hypertension is one of the most important risk factors for cardiovascular disease (CVD) and associated with the higher rate of mortality and morbidity.[1-4] It was demonstrated that approximately 29% to 31% of the US adults have been diagnosed with hypertension. In spite of high prevalence of hypertension in the US, only half of hypertensive individuals have sufficient blood pressure control. Therefore, blood pressure control is a crucial issue in reducing CVD.[5]

Pentoxifylline (PTX), a methylxanthine derivative is a phosphodiesterase inhibitor (PDEI) that reduces blood viscosity by increasing leukocyte and erythrocyte flexibility and reducing thrombus formation. Furthermore, it increases tissue oxygenation and is approved for treatment of peripheral vascular disease (PVD).[6-8]

PTX also reduces tumor necrosis factor alpha and increases cyclic adenosine monophosphate (cAMP) level and leads to inhibition of nuclear factor Kappa-B and activation of protein kinase A.[7,9-11] PTX acts on circulation system via several mechanisms. Importantly by inhibition of a group of phosphodiesterase enzymes that are responsible for degradation of cAMP and cyclic guanosine monophosphate (cGMP) in a wide variety of tissues particularly in the peripheral vascular system. In the othe hand, PTX increases the level of cAMP and cGMP in the periphery and causes to vasodilation and reduction of blood pressure (BP).[10,12,13]

Moreover; PTX directly prevents the elevation of blood pressure associated with metabolic syndrome in rats via mechanisms involving in the inhibition of renin-angiotensin-aldosterone system and low-grade inflammation.[14]

Recently, it is indicated that adding PTX to captopril caused a greater reduction of BP than captopril alone in spontaneously hypertensive rats by improvement of hemorheological properties of blood and decreasing blood viscosity and peripheral vascular resistance.[15]

In the clinical setting, the effect of PTX on BP was reported in a limited number of studies with limited sample size and all of them failed to show a significant effect of PTX in primary hypertension.[16-27]

Given the potential effects of PTX on BP, we carried out the present randomized control trial (RCT) to find out whether PTX can reduce BP when combined with antihypertensive drugs. To the best of our knowledge, this is the first well-designed study with adequate sample size that investigates the effect of PTX in patients with primary hypertension.

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Materials and Methods

Study design and setting

This was a prospective, pilot, randomized control trial study that was conducted on patients with diagnosis of primary hypertension in the cardiovascular clinic of Tabriz University of Medical Science during a 12-month period from February 2016 to February 2017.

Ethics

The study was approved by the ethics committee of Tabriz University of Medical Sciences and was registered in the International Clinical Trials Registry Platform, World Health Organization (www.irct.ir, ID: IRCT201407208307N8). The approved consent form was signed by all patients. The study was done according to the 1975 Declaration of Helsinki and the later versions on ethical principles for medical research.[28]

Study population

Study population included all patients between ages of 18 and 80 years old with a confirmed diagnosis of primary hypertension (taking anti-hypertensive medications for their BP and/or BP≥140/90mmHg) who were referred to the clinic of university. The exclusion criteria included secondary hypertension, white coat syndrome, pregnancy and lactation, liver and kidney failure, heart failure and contraindication to use of PTX or anti-hypertensive drugs. Patients who could not tolerated PTX were also excluded from the study.

Randomization and study process

All patients were randomized 1: 1 into the intervention (n=56) and the control groups (n=55) using systematic randomization by an independent person. In the intervention group, all patients received 400 mg oral PTX, 3 times a day (totally 1200 mg per day) plus the standard antihypertensive therapy based on recommendation of the American Heart Association/ American College of Cardiology (AHA/ACC) guidelines on control of BP for a three-month period; while, the control group received only the standard treatment.

Patients' information including demographic data such as sex, age, weight, height, past medical history, drug history, medication use, laboratory data, and positive family history for CVD was recorded in a data collecting form.

Study endpoints and blood pressure measurement

The primary endpoint of study was measurement of office blood pressure during the study period by using a mercury sphygmomanometer (Rudolf Riester GmbH, Jungingen, Germany) as the standard device of measurement of office BP. All blood pressures were measured based on the recommendations of American heart association (AHA) for BP measurement[29] by an expert cardiologist with cuff size at least 80% covered the right arm in the sitting position. Patients seated 5 minutes before starting the measurements. Measurements were done 3 times within 2 minutes intervals. The mean of three measurements was recorded as main BP. All of the patients were asked to avoid food, caffeine, tobacco, and alcohol use at least 60 minutes before measurement. Follow-up visits were performed at one and three months after randomization.

The secondary endpoint of study was the measurement of occurrence of major adverse cardiac events (MACEs) including hospitalization due to cardiac events, heart attack, stroke, and death.

Compliance with medication regimen

Pill counting method was used to estimate patients' adherence to medication regimen. All of the participants were asked to bring their leftover medicines. The use of >90% antihypertensive medications was assumed as a compliant patient. The patients were continued the study if they have taken their medications during the previous course of treatment. All patients were allowed to call the investigators at any time during the study period.

Sample size and power calculation

The power calculation was performed with the sample size n=100, two equal groups, three times measurements of BP, and α=0.05 using G*Power (version 3.1.9.2). The power (1−βerror) for systolic BP (SBP) with partial η2 of 0.038 and calculated effect size (F) of 0.198 was calculated 0.99. Accordingly, the power for test of diastolic BP (DBP) regarding the partial η2 of 0.025 and calculated effect size (F) of 0.16 was calculated 0.94.

Statistical analysis

Data analysis was carried out using SPSS 16.0 (SPSS Inc, Chicago, Illinois, 2007). Kolmogorov-Smirnov test was performed to determine whether data had a normal distribution. To check the effect of time and groups, repeated measures analysis of variance (rANOVA) was performed with Bonferronipost-hoc test for pair wise comparisons. Paired t-test was used to compare the means within the groups before and after intervention. Independent sample t-test was used to assess the means in different groups. Chi-square and Fisher's exact tests were also applied for frequency analysis. The continuous data were presented as mean ± SD (standard deviation). P values less than .05 were regarded as significant.

Results

Demographic and baseline data

During one year of study period, a total of 137 patients with primary hypertension were screened. Among them, 26 patients were excluded from the study. Accordingly, 111patients were randomized into the intervention (n=56) and the control groups (n=55). In the intervention group, four patients were excluded due to PTX gastrointestinal adverse effects (three cases) and severe headache (one case). One patient in PTX group and two patients in the control group were excluded due to low compliance with treatment regimen. Three patients (one in PTX group

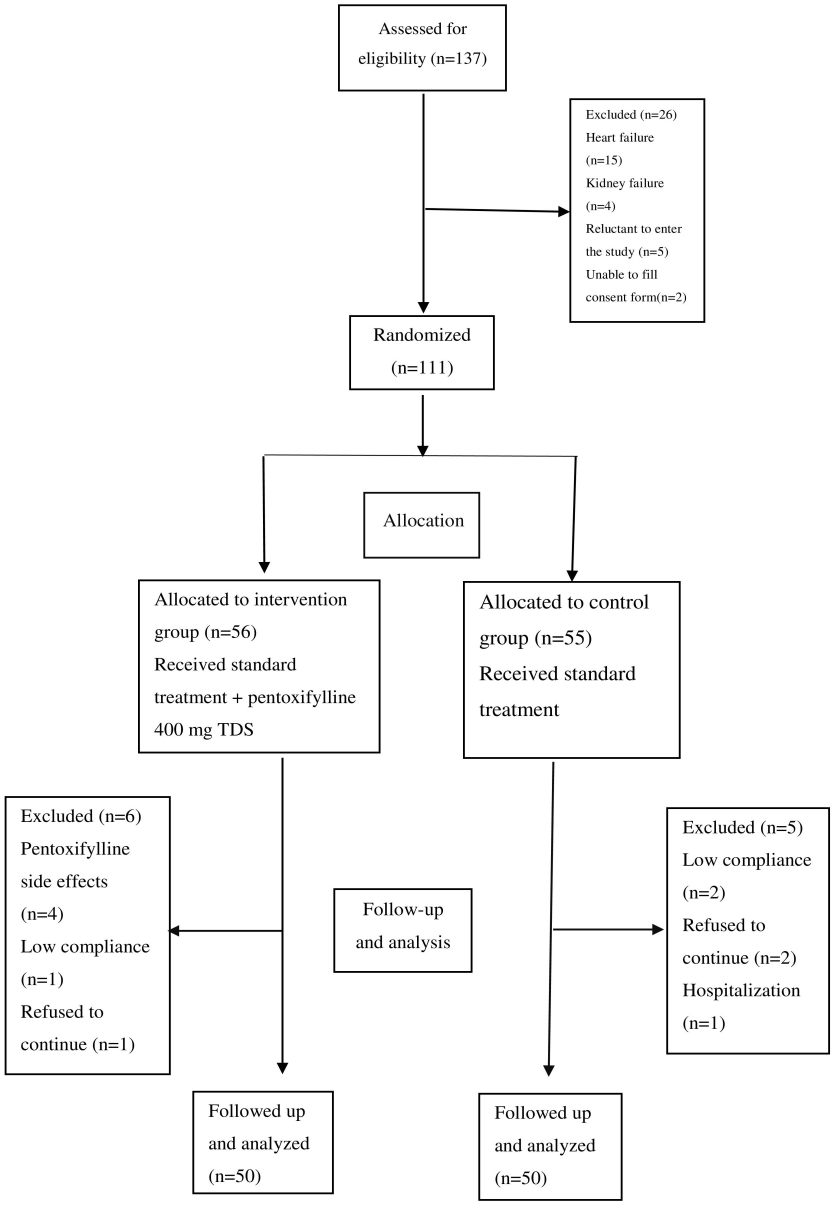

Figure 1. Literature search and review flowchart for selection of studies.

Table 1. Baseline demographic and clinical information of study population.

Characteristic	Intervention(n=50)	Control(n=50)	P value
Sex, male, n (%)	23(46)	18(36)	0.68
Age (years), mean±SD	55.5±13.3	54.7±15.1	0.78
Weight (kg), mean±SD	75.9±11.4	74.6±13.9	0.59
Serum creatinine (mg/dl), mean±SD	.98±.24	1.02±.17	0.46
Creatinine clearance (ml/min), mean±SD	66.1±19.4	70.8±34.1	0.56
LDL (mg/dl), mean±SD	121.8±27.5	124.3±32.56	0.77
HDL (mg/dl), mean±SD	50.2±7.0	48.2±6.9	0.31
Cholesterol (mg/dl), mean±SD	184.45±28.3	189.3±30.2	0.84
Fasting blood sugar (mg/dl), mean±SD	125.5±30.9	117.6±29.4	0.66
Acute coronary syndrome, n (%)	12(24)	13(26)	0.81
Hyperlipidemia, n (%)	13(26)	12(24)	0.81
Other diseases, n (%)	4(8)	9(18)	0.13
Other drugs, n (%)	14(28)	15(30)	0.82
Positive familial history for ACS, n (%)	7(14)	9(18)	0.58

ACS, acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation, TG, triglyceride.
*Fisher's exact test.

Table 2. Antihypertensive regimen.

Characteristic	Intervention (n=50)	Control (n=50)	P value
ACEI or ARB, n(%)	4(8)	7(14)	0.33
Thiazide, n(%)	2(4)	4(8)	0.67
Beta-blocker and CCB, n (%)	4(8)	1(2)	0.36*
Beta-blocker and ACEI, n (%)	8(16)	10(20)	0.60
Beta-blocker and ARB, n (%)	14(28)	9(18)	0.23
Beta-blocker and thiazide, n (%)	13(26)	9(18)	0.33
Beta-blocker and alpha 1 antagonist, n (%)	0(0)	3(6)	0.24*
Beta-blocker and nitrate, n (%)	5(10)	6(12)	0.74
CCB and ACEI, n (%)	4(8)	5(10)	1.0
CCB and thiazide, n (%)	5(10)	5(10)	1.0
ACEI and thiazide, n (%)	15(30)	7(14)	0.053
ARB and thiazide, n (%)	17(34)	11(22)	0.18
Thiazide and nitrate, n (%)	3(6)	4(8)	1.0*
Beta-blocker and ACEI and thiazide, n (%)	5(10)	4(8)	1.0*
Beta-blocker and ARB and thiazide, n (%)	7(14)	5(10)	0.53
Receiving one anti-hypertensive drug, n (%)	6(12)	11(22)	0.18
Receiving two anti-hypertensive drug, n (%)	22(44)	24(48)	0.68
Receiving three anti-hypertensive drug, n (%)	18(36)	11(22)	0.12
Receiving four anti-hypertensive drug, n (%)	4(8)	4(8)	1.0*
Number of antihypertensive drugs, mean ± SD	2.4±0.8	2.1±0.8	0.15
Adding beta blocker, n (%)	2(4)	3(6)	1.0*
Removing antihypertensive drug, n (%)	1(2)	1(2)	1.0*

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.
*Fisher's exact test.

and 2 in the control group) refused to continue the study after recruitment. One patient also was excluded because of stroke and hospitalization in the control group. Finally, 100 patients (50 patients in each group) were followed up and analyzed. The study recruitment process is shown in Figure 1.

Baseline demographic and clinical characteristics of patients in both groups were similar (Table 1). All patients were taking antihypertensive medications when entering the study. A total of 69 patients (intervention (72%, n=36); control (66%, n=33)) had a BP≥140/90 and 31 patients had their BP under control (normotensive patients).There was no significant difference between groups regarding both SBP (145.5±19.0 vs. 141.2±19.4 mmHg, p=0.26) and DBP (87.9±11.8 vs. 87.4 ±10.9 mmHg, p=0.82) at baseline.

Type and number of antihypertensive medications with all performed interventions for the control of BP during the study period are shown in Table 2. Based on the statistical analysis, no significant differences were observed regarding these variables in two groups.

Change of BP in the groups

After one month of study, no significant difference was observed regarding SBP (135 ± 16 vs. 136.2 ± 17.2 mmHg,

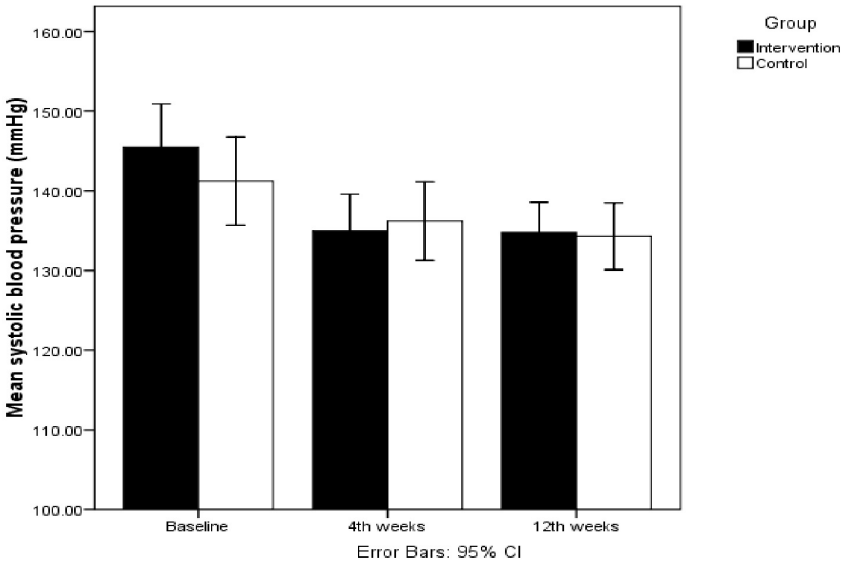

Figure 2. The changes of SBP in the groups during the study period.

Table 3. The mean blood pressure and mean difference blood pressure of patients at baseline, 1 and 3 months after study.

Blood pressure (mean ± SD)	Intervention (mmHg)	Control (mmHg)	P value
SBP (Baseline)	145.5±19.0	141.2±19.4	0.26
SBP (month 1)	135.0 ±16.0	136.2 ±17.2	0.72
SBP (month 3)	134.8 ±13.3	134.30±14.7	0.85
DBP (Baseline)	87.9±11.8	87.4 ±10.9	0.82
DBP (month 1)	81.5±9.9	82.4 ±12.9	0.69
DBP (month 3)	80.8 ±9.0	80.4 ±10.7	0.84
Mean difference for SBP (0 and 1)	10.1±13.8	4.7±7.9	0.01
Mean difference for SBP (1 and 3)	1.5 ±5.9	2.6 ±6.8	0.39
Mean difference for SBP (0 and 3)	11.6±13.8	7.3 ±10.2	0.08
Mean difference for DBP (0 and 1)	7.1 ±10.3	4.7±7.2	.0.10
Mean difference for DBP (1 and 3)	1.5±5.9	2.6±6.8	0.39
Mean difference for DBP (0 and 3)	8.6 ±10.6	5.4±7.1	0.08

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation

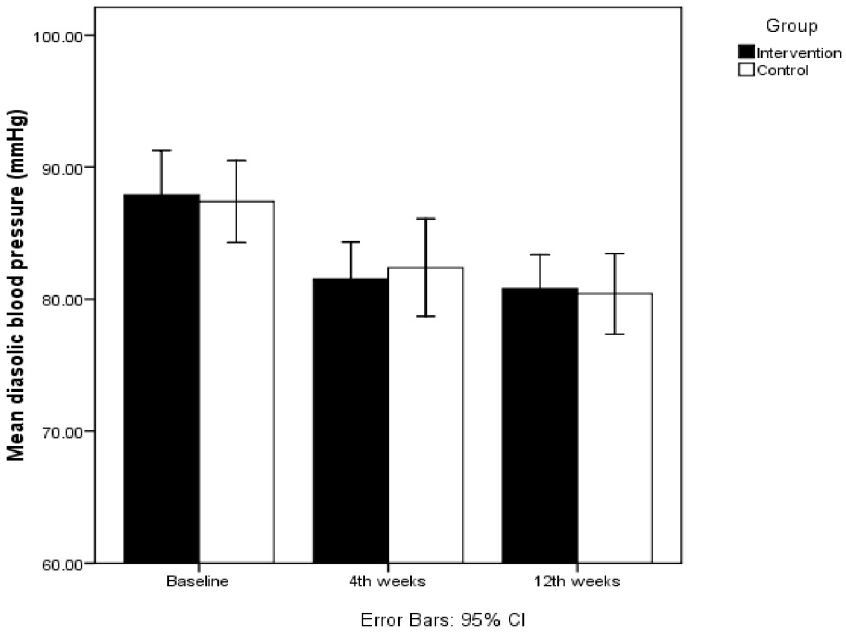

Figure 3. The changes of DBP in the groups during the study period.

p=0.72) and DBP (81.5 ± 9.9 vs. 82.4 ± 12.9 mmHg, p=0.69) between the study groups. Furthermore, no significant change was documented in both SBP (134.8 ± 13.3 vs. 134.3 ± 14.7 mmHg, p=0.85) and DBP (80.8 ± 9 vs. 80.4 ± 10.7 mmHg, p=0.84) after 3 months. The changes of BP in the groups during the study period are shown in Table 3, Figures 2 and 3.

PTX observed adverse drug reactions (ADRs) during the study period were shown in Table 4. The most commonly observed ADR was nausea (12 patients). One patient also suffered from vomiting and one had headache following the use of PTX.

Table 4. Pentoxifylline observed adverse effects.

Adverse effects	Total number (n=50)	Leading to treatment discontinuation
Nausea, n (%)	12(24)	2(4)
Vomiting, n (%)	1(2)	1(2)
Headache, n (%)	1(2)	1(2)

No significant difference was observed between the groups regarding the MACE (P>0.05). One case of stroke was observed in the control group. One case in both groups was undergone to balloon angioplasty and stent insertion.

Discussion

To the best of our knowledge, this randomized control trial is the first well-designed investigation that assessed the effect of PTX on BP in patients with primary hypertension. The present study showed that PTX could not significantly affect BP when added to antihypertensive regimen in patients with primary hypertension.

Effects of pentoxifylline on blood pressure in clinical studies

There are no significant reports of PTX on BP in the clinical studies. Except one study, all studies included a normotensive population.[16-27] For example, four double-blind, randomized placebo-control trials investigated

the effects of 1200 mg daily PTX in the setting of cardiomyopathy and heart failure during 6 months period. These studies included 41, 32, 24 and 33 participants respectively and all of patients had a BP<140/90 mmHg. No significant effect of PTX on BP was documented regarding among these normotensive population.[17, 21-23]

Some studies have also investigated the effect of PTX in the setting of diabetic nephropathy. According to Ghorbania et al. double-blind randomized control trial on 100 patients with diabetic nephropathy, PTX 400 mg daily had no significant effect on BP after 6 months.[24] Another double-blinded randomized-controlled trial was carried out on 61 patients with diabetic nephropathy with albuminuria. Data indicated that administration of 1200 mg daily PTX during a four-month did not significantly change BP.[25] Similarly, Shahidi et al. demonstrated that PTX did not change BP in patients with type 2diabetes mellitus with microalbuminuria.[26] It is important to note that all of three studies were carried out on normotensive population.

Goicoechea et al conducted a double-blind randomized-control study on a total of 70 patients with hypertensive kidney diseases. To evaluate the effect of PTX on inflammatory parameters and kidney function, the intervention group received PTX 1200 mg daily. Measurement of patients' BP after 6 and 12 months did not showed any significant effect of PTX on BP.[27] However, their study had some limitations. First, they did not only include the primary causes of hypertension but also they studied some causes of secondary hypertension such as vascular nephropathy, glomerulonephritis, interstitial nephropathy and systemic vacuities with different pathophysiologies; while, our study included only the patients with primary hypertension. Second, their study sample size was partially small and the power of study was not determined.

The result of present study may be clinically relevant in case of patients taking blood pressure lowering agents in conditions that there is a fear of hypotension. Brie et al. have conducted a systematic review and meta-analysis of RCTs on effects of PTX on inflammatory biomarkers and BP and concluded that PTX did not alter BP.[30] Excepting for Goicoechea et al [27] study they included RCTs with a normotensive population.[30]

Taken together, the present study investigated the effect of PTX in primary hypertension for a three-month period and had three strength points than the previous studies. First, in contrary to the previous reports that evaluated the effect of PTX in normotensive patients, this study was done on hypertensive patients and the mean blood pressure were >140/90 in both groups at baseline. Second, this study was done on patients with primary causes of hypertension and blood pressure was measured as primary outcome. Third, this study had partially larger sample size when compared to major previous studies importantly power calculation showed a strong power for the study samples.

Clinical applications of the study findings

As previously mentioned PTX offers a set of cardiovascular benefits. Recent meta-analysis study showed that PTX could decrease a series of inflammatory biomarkers, which are involved in the development of cardiovascular disease such as CRP or TNF-alpha.[30] Considering the key finding of present study, in normotensive or orthostatic hypotensive patients or in patients on antihypertensive therapy PTX can be administrated without fearing hypotension and such patients can benefit the anti-inflammatory effects of PTX belong the indicated background disease.

Study limitations

The result of present study should be interpreted with caution since the present study includes some limitations. First, despite the strong power of study this study has a pilot nature with a limited number of populations. Notably, the sample size and power were set to measure the primary outcome. Therefore, the study might be underpowered for measurement of secondary outcome. On the other hand, to evaluate the effect of PTX on secondary outcome (MACE) larger outcome-based studies with a longer study period are needed. Second, this study was a single center study and because of accessibility problem, we could not use placebo in the control group to minimize the potential treatment bias. Therefore, multi-center double-blind, placebo-control studies with a larger population are recommended for future studies.

Third, we had time and cost restrictions; therefore, the follow-up period may bepartially short. Importantly, the clinical significance of these findings should be confirmed by further outcome-based studies. Fourth, because of accessibility problem and limitation, we could not use a 24-hour ambulatory blood pressure monitoring (ABPM) device to measure BP. Therefore, the precise BP may not be attained during the study. However, all BPs were measured based on valid guidelines with the same conditions.

Conclusion

The result showed that PTX could not significantly reduce BP in primary hypertensive patients. Larger studies are needed to confirm these results.

Ethical Issues

The study was approved by the ethics committee of Tabriz University of Medical Sciences and was registered in the International Clinical Trials Registry Platform, World Health Organization (www.irct.ir, ID: IRCT201407208307N8). The approved consent form was signed by all patients.

Data Sharing

Applicants can obtain data by contacting the corresponding author.

Conflict of Interests

The authors claim that there is no conflict of interest.

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