Comparison of alprazolam versus captopril in high blood pressure: A randomized controlled trial

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Abstract

Objective. Anxiety is an important cause of acute blood pressure (BP) elevation. However, the role of anxiolysis in this situation is still controversial. In this study, the relationship of anxiety with BP and the effect of anxiolytic treatment on BP were investigated.

Methods. Emergency department (ED) patients with an initial systolic BP (SBP) ≥ 160 mmHg or diastolic BP (DBP) ≥ 100 mmHg but no end organ damage were approached for inclusion in the study. In those consenting to participate, anxiety levels were measured using the State-Trait Anxiety Index (STAI) and Visual Analog Scale for Anxiety (VAS-A). Patients were randomly assigned to receive oral alprazolam 0.5 mg or captopril 25 mg. BP and anxiety levels were measured at baseline and at 1 and 2 h after administration of the study medication.

Results. Of 133 patients meeting inclusion criteria, 53 patients agreed to participate. Of these, 27 patients (50.9%) received captopril and 26 patients (49.1%) received alprazolam. The majority of the patients had a high-level trait (96.2%, n = 51) and state anxiety (81.1%, n = 43). The mean SBP and VAS-A values of both patient groups dropped significantly over the 2 h, with no significant difference between the two groups. A significant association between SBP and VAS-A scores was found ($F_{(2,50)} = 6.27$, $p = 0.004$). Conclusion: A significant association exists between the level of BP and anxiety in hypertensive ED patients. Alprazolam is as effective as captopril in lowering BP in ED patients with an initial SBP ≥ 160 mmHg.

Key Words: Alprazolam; anxiety; captopril; emergency department; high blood pressure

Introduction

Many patients present to the emergency department (ED) with high blood pressure (BP), but only a small proportion of these will require emergent antihypertensive therapy. The primary goal of the emergency physician is to determine which patients with acute hypertension are exhibiting symptoms of end-organ damage. In contrast, patients presenting with elevated BPs (systolic BP, SBP > 200 mmHg or diastolic BP, DBP > 120 mmHg) without symptoms, and whose BP remains high until ED discharge should begin antihypertensive therapy as an outpatient with close follow-up (1). The cause of hypertension is not known in many patients, but includes pheochromocytoma, renal artery stenosis, severe pain, cerebrovascular disease, acute renal failure, medications and illegal drugs, withdrawal of antihypertensive treatment, and panic attack or phobic anxiety (2,3).

Anxiety is known to trigger sympathetic discharge that may lead to elevated BP (2). Sympathetic activation, in addition to the elevated BP, also likely contributes to left ventricular hypertrophy and to the commonly associated metabolic abnormalities of insulin resistance and hyperlipidaemia. The mechanisms of increased long-term cardiac risk attributable to mental stress and psychiatric illness are not entirely clear, but activation of the sympathetic nervous system seems to be of prime importance (4). A meta-analysis of 2024 patients who received psycho-social treatment vs 1156 control subjects found that the psychosocially treated patients showed greater reductions in psychological distress, SBP, heart rate and cholesterol levels (5). Another meta-analysis of 37 studies found that psychoeducational (health education and stress management) programmes for coronary heart disease patients yielded lower BP, cardiac mortality and recurrence of myocardial infarction (6).

Although the above long-term studies have found treatment for anxiety to have cardiovascular benefits, studies of anxiety levels and acute BP control in ED patients have been few. In one study of 36 patients,
diazepam was as effective as captopril in treating a hypertensive episode but anxiety levels were not measured (3). If anxiolytic treatment for selected patients with severe hypertension is found to be effective without serious side-effects, our approach to treating these patients in the short- or long-term might need to be altered. Patients with high anxiety scores may benefit more from anxiolytics than antihypertensives. The present study investigated the relationship between anxiety and BP and compared the effects of alprazolam vs captopril in acutely lowering BP and anxiety levels in ED patients.

Methods

Study design

This single-blind, prospective, randomized, controlled clinical trial compared oral alprazolam with captopril in the treatment of elevated BP in ED patients without end organ damage. Our study design and implementation were approved by our university ethics committee.

Study setting

Study participants were recruited from the ED of a university hospital with an annual census of approximately 40,000 adult visits. All subjects provided written informed consent.

Selection of participants

Consecutive ED patients over 18 years old who had an initial SBP ≥ 160 or DBP ≥ 100 mmHg and repeat high BP after a 10-min resting period were approached for participation in the study (7). Exclusion criteria included a history of secondary hypertension, malignant hypertension, acute left cardiac failure, chronic renal failure, acute coronary syndrome, aorta dissection, cerebrovascular event, conditions requiring analgesics use, known allergy to captopril or alprazolam, and pregnancy. Data from patients with end organ damage, as determined by history, physical examination, electrocardiography, serum creatinine, electrolytes, urinalysis and fundoscopy, were excluded from analysis.

Interventions

The authors generated the allocation sequence using a random numbers table before the study. Participants were given details about the study. The patients were enrolled and assigned to a study group according to the previously established table by a senior resident. Following baseline measurement of BP and psychometric assessments as described below, patients received (patients blinded, medical staff unblinded) 0.5 mg alprazolam (Xanax®, Eczacıbaşi A.S., İstanbul, Türkiye) or 25 mg captopril (Kapto-ril®, Deva A.S., İstanbul, Türkiye).

Assessments and measurements

BP measurement. JNC-7 recommendations (7) for accurate BP measurement in the office were used to noninvasively (oscillometric method) measure BP with a calibrated and validated instrument (Vista® monitor, Draeger Medical Systems, Inc., Danvers, MA, USA). Before BP measurements, the patients were seated quietly for at least 5 min in a chair, with feet on the floor and arm supported at heart level. The second BP measurement was performed after 10 min. Measurement of BP was repeated at 1 and 2 h after administration of the study medication.

Psychometric assessments. The State Trait Anxiety Inventory (STAI) was used to measure the anxiety levels of the patients in both groups at baseline and 1 and 2 h after medication administration. The STAI has two subscales, 40 questions and uses a 4-point Likert scale for responses (8). One of the subscales aims to measure the current level of anxiety (STAI-S, state anxiety), the other subscale measures the characteristic or enduring level of anxiety (STAI-T, trait anxiety). This test has excellent validity (levels up to \( r = 0.80 \)), reliability (\( r = 0.77 \)) and internal consistency (0.89 for state anxiety, 0.91 for trait anxiety). The reliability and validity of the Turkish version of the test has been previously established (9). A cut off score of 39–40 was considered an abnormal state of anxiety (9,10). In addition, a self-reported 100-mm visual-analogue scale for the measurement of acute anxiety (VAS-A) was used at baseline, and 1 and 2 h after medication administration.

Outcome

The main outcome measures were BP and anxiety levels, as measured at 1 and 2 h after administration of the study medications. The secondary outcome measure was the association between anxiety and BP over the course of the study.

Data analysis

All statistical analyses were performed with SPSS version 16.0 for Windows (SPSS Inc. Chicago, USA). The Shapiro–Wilk test was used to evaluate if the data were normally distributed. Socio-demographic variables were assessed with either independent samples \( t \)-test for continuous variables or chi-square test. Yates’ corrected chi-square was used for all the other 2 \( \times \) 2 tables. After Box’s M test for equality of covariance matrices and Mauchly’s test of sphericity, a repeated-measures analysis of variance (ANOVA)
with repeated contrasts was performed on three consecutive measurements of BP to explore the differences in pattern and magnitude between the alprazolam and captopril groups. If sphericity could not be assumed, the multivariate analysis of variance (MANOVA) approach was used to test the significance of $F$ values. Following a significant global $F$ test, univariate ANOVA with Greenhouse–Geisser adjustment was then performed. In addition, a repeated measure of analysis of covariance (ANCOVA) with the same statistical procedures mentioned above was performed for evaluating the effect of baseline STAI scores as covariates on change in BP. The significance level was set at 0.05. As a measure of effect size, partial eta-squared ($\eta^2$) was also reported in the main ANOVAs.

**Results**

**Characteristics of study subjects**

Patient recruitment and flow in the study are shown in Figure 1. Demographics, clinical characteristics of patients and comparisons are shown in Table I. Of the 53 patients granting consent to participate in the study, 27 were males (50.9%); 27 patients (50.9%) received captopril and 26 patients (49.1%) received alprazolam. Treatment groups were not significantly different in gender, age and history of psychiatric disorder or hypertension. All patients had high SBP but 44 patients (83%) had concomitantly high DBP. However, baseline SBP was significantly higher in the captopril group (for alprozolam group, $187.46 \pm 18.34$; for the captopril group, $199.85 \pm 20.72$; $t = -2.30$, df = 51, $p = 0.025$), but the baseline DBP values of the two groups were similar (for alprozolam group, $106.81 \pm 12.74$; for the captopril group, $108.30 \pm 12.63$; $t = -0.43$, df = 51, $p = 0.67$). As measured by the STAI test, trait anxiety was present (a score over 40) in 96.2% ($n = 51$) of patients and 81.1% ($n = 43$) had state anxiety (a score over 40). The mean state and trait anxiety scores were not significantly different between the treatment groups. However, baseline VAS-A scores of the two groups were significantly different (Table I).

**Treatment effect on BP**

Since Mauchly's test indicated that the assumption of sphericity had been violated for the main effects of BP ($\chi^2 = 7.68$, df = 2, $p = 0.021$), we used the MANOVA approach after Box's M test (Box M = 24.38, df1 = 21, df2 = 9535.83, $p = 0.442$) for evaluating the effect of medication on BP and VAS-A. There was no significant association between change of BP and baseline STAI-T ($F(1.43, 71.29) = 0.28$, $p = 0.933$) or STAI-S ($F(1.43, 71.29) = 1.028$, $p = 0.341$) scores. As shown in Figure 2, SBP dropped significantly from baseline in both alprazolam and captopril groups ($F(1.42, 72.46) = 113.41$, $p < 0.0005$, $\eta^2 = 0.69$), but the mean change in SBP was not significantly different between the two groups ($F(1.42, 72.46) = 0.36$, $p = 0.626$, $\eta^2 = 0.007$). SBP was significantly correlated with VAS-A scores ($F(2,51) = 5.00$, $p = 0.010$). Both groups had a significant drop from baseline in VAS-A ($F(1.84, 93.87) = 86.18$, $p < 0.0005$, $\eta^2 = 0.63$), with the VAS-A scores decreasing more in the alprazolam group than in the captopril group ($F(1.84, 93.87) = 9.67$, $p < 0.0005$, $\eta^2 = 0.159$). A contrasts analysis in MANOVA found no difference in change of VAS-A score between the baseline and first hour measurements ($F(1, 51) = 2.70$, $p = 0.107$), but a

![Figure 1. Flow diagram of patient selection.](image-url)
significant difference at the second hour measurement between the treatment groups in favor of alprazolam \( F(1, 51) = 9.89, p = 0.003 \).

**Discussion**

We found that ED patients with high BP but no end organ damage have high levels of anxiety, and as anxiety is relieved, BP falls accordingly. BP falls in a similar fashion whether one uses an anxiolytic or anti-hypertensive agent, but anxiety is relieved more effectively with alprazolam. Anxiety, including panic attack and hyperventilation, has been shown to increase BP (2,10). Up to 18% of anxiety disorder patients have hypertension according to studies performed in psychiatry and/or primary healthcare units (11). However, the associations between anxiety and medical problems have not been explored in ED patients. The majority of our patients had high levels of state and trait anxiety upon presentation to the ED. The effect of anxiolytics on BP has been investigated in a few earlier studies. Grossman et al. (3) compared oral diazepam and sublingual captopril without measuring anxiety levels in ED patients with elevated BP, and found that both agents were similarly effective in lowering BP. In contrast to that study, we measured anxiety with both the STAI test and VAS-A. In addition, we used alprazolam because of its more rapid onset of action and shorter duration of activity compared with diazepam. These characteristics render it a more appropriate agent for use in ED, and we obtained results similar to the mentioned study.

Although alprazolam was found to lower anxiety levels more than captopril, the mechanism by which captopril lowers anxiety is unclear. Captopril’s ability to reduce VAS-A scores might be related to a placebo effect or a pathophysiological process. Based on the
results of our study with a small number of patients, studies with more hypertensive patients are needed in order to recommend the use of anxiolytics as standard treatment.

Limitation
The effect size of the study was high for general comparisons, but the effect size of subgroup analysis in BP was low. Our results represent those from a single institution; therefore our study should be repeated in other healthcare settings. Interviews with the patients for diagnostic purposes and detailed psychiatric measurements could enhance the interpretations of future findings when studying the relationship between BP and anxiety.

Conclusion
Patients applying to ED with moderate elevations in BP are frequently anxious. Oral captopril and alprazolam lower BP to a similar degree in these patients, but alprazolam lowers anxiety to a greater degree than captopril. Further studies with placebo and treatment groups will help clarify medical management options in these patients.

Competing interests
None to declare.

References