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Dilcy Morgana Barros Maciel Cabral Davino, Rosileide Zeferino Da Silva,
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Alfredo Dias de Oliveira-Filho
Improving blood pressure control in patients with pseudoresistant hypertension – A pilot randomized trial

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This study aims to evaluate the effect of an intervention focused on medication adherence to improve blood at three basic health units in Maceió, Brazil. Patients were followed-up for three months. Primary outcomes were pressure control in patients with pseudoresistant hypertension. A randomized controlled clinical trial was conducted mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP). 185 patients were included, 145 of whom were randomly assigned to the experimental group, while 40 were allocated to the control group. After three months of follow-up, SBP did not change significantly in any of the groups; however, there was a significant reduction in DBP in the group submitted to intervention. Similar interventions given to patients with hypertension, without suspicion of resistant hypertension have focused exclusively on SBP.

Key words: Resistant hypertension to conventional therapy, medication adherence, blood pressure.

INTRODUCTION

Resistant hypertension (RHTN) is defined as blood pressure that remains above goal (less than 140/90 mm Hg for the overall population, and less than 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic. Patients whose blood pressure is controlled with four or more medications are considered to have resistant hypertension (Alessi et al., 2018; Calhoun et al., 2008).

Initially, the prevalence of RHTN was estimated in up to 30% of patients with hypertension (Calhoun et al., 2008). Such estimates were revised when studies began to adopt the definition of pseudoresistant hypertension - a false resistance to blood pressure control caused by 1) inadequate measurement of BP; 2) inappropriate choice of antihypertensive and/or doses; 3) low adherence to prescribed therapy or; 4) white coat effect - to diagnose RHTN. Since then, the prevalence of RHTN has been decreasing. Currently, resistant hypertension is known to reach 12 to 15% of hypertensive patients (Pimenta et al., 2012; Brazilian Society of Cardiology, 2012).

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In a study to determine the association between adherence to antihypertensive treatment and BP control in hypertensive outpatients, it was observed that 62.4% of the patients with uncontrolled BP despite appropriate antihypertensive therapy (including 3 or more antihypertensives) were non-adherers, and could be diagnosed as resistant hypertensive patients (Oliveira-Filho et al., 2014a, b, c). Although other studies to determine the impact of the four causes of pseudoresistance have not yet been performed, it is estimated that medication adherence plays one of the most important roles in achieving blood pressure control (Abegaz et al., 2017; Hedegaard et al., 2015).

Interventions to improve blood pressure control in hypertensive patients through medication adherence have been tested with different degrees of success (Xu et al., 2018; Conn et al., 2016). However, no studies evaluating the effect of such interventions on BP control in patients with RHTN or pseudo-resistant hypertension have been published yet. Given the importance of medication adherence, its identification and management is essential to rule out the diagnosis of resistant hypertension. Thus, the present study aims to assess the effect of an intervention focused on therapeutic adherence to improve blood pressure control in patients with pseudo-resistant hypertension.

MATERIALS AND METHODS

This randomized controlled trial was conducted at three health facilities in Maceió, Brazil, from April 2014 to October 2015. A computer program - Software package PEPS – randomized patients by minimization with a random element to ensure that the 2 trial arms are not significantly different on 1 variable: age. Blinded allocation occurred via means of sealed envelopes which were opened by the pharmacists which provided the intervention.

Inclusion criteria: All patients who had a diagnosis of hypertension with uncontrolled BP at the baseline, and who were on an unchanged antihypertensive drug treatment for at least three months were recruited.

Exclusion criteria: Patients were excluded if they reported they were already using any tool to improve adherence. The patients in the control group received primary care units' usual care, while an informational and behavioral intervention protocol focused on medication adherence - based on the Morisky-Green-Levine scale (1986) and adapted from a previously tested protocol - was delivered to the participants in the intervention group (Morisky et al., 1986; Oliveira-Filho et al., 2014a, b, c). Medication adherence protocol consisted of 2 distinct parts: patients centered verbal instructions and written material about prescribed medications. While Oliveira-Filho et al. (2014a, b, c) tested it in post-discharge patients with cardiovascular diseases. The present study delivered the intervention on patients with hypertension treated in primary care facilities affiliated to the Brazilian unified health system. The main elements of the protocol were: a) information about disease process/prognosis; b) information about prescribed drugs (e.g., therapeutic goals; how to monitor drug treatment, especially the consequences of abrupt cessation of antihypertensive treatments and adverse drug reactions that may be causes of withdrawal; and how to handle inaccurate dosing systems or unusual dosage forms). Additional information (e.g., dosage schedule) was written on a drug treatment card adapted as a refrigerator magnet.

Patients were recruited after they had been registered into the outpatient clinic and were waiting to see a physician. All individuals were followed up for three months, the same duration of the intervention. Primary outcome was mean difference in BP between groups. Medication adherence was assessed using the Morisky-Green-Levine Scale (1986), while the Medication Appropriateness Index (MAI) was used to identify and revise inappropriate antihypertensive prescriptions (Hanlon et al., 1992). In Brazil, some blood pressure lowering drugs of different classes are freely distributed at the public health system, including a thiazide diuretic, 2 beta-blockers, 2 angiotensin-converting enzyme inhibitors, and an angiotensin receptor blocker.

Data collection was performed through interviews and determinations of outcomes, as well as data on prescriptions and records first in the health units (at the baseline) and then in two home visits (after 1 and 3 months). In a trial carried out by the authors of this study to assess the effect of a similar intervention on hypertensive outpatients it was observed that SBP and DBP decreased significantly after 1 and 3 months, respectively (Oliveira-Filho et al., 2014a,b,c). The values of systolic (SBP) and diastolic (DBP) blood pressure were obtained by the mean of two blood pressure measurements using calibrated mercury sphygmomanometers, carried out by the research team, according to the guidelines established in the JNC-8 Hypertension Guidelines, with a minimum interval of 10 min between each measurement (James et al., 2014). Primary endpoints were mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP).

It was estimated that a sample size of at least 34 patients in each group would provide 80% power to detect a 6 mmHg (SD=10) difference in SBP, by using a t-test with a one-sidened significance level of 0.05. However, considering the low prevalence of medication adherence among the target population and the positive results of the aforementioned intervention on post-discharge adherence levels of patients with cardiovascular diseases in the present study, patients were allocated in a 4:1 ratio to receive intervention or usual care, respectively (Oliveira-Filho et al., 2014a,b,c). Informed consent was obtained from each patient and the Federal University of Alagoas institutional review board approved the study protocol and consent form.

Ethical approval and informed consent

The study was submitted to the Research Ethics Committee of the Federal University of Alagoas under the protocol number CAAE 39336714.8.0000.5013 and approved under opinion 1,899,672. All participants signed the Informed Consent Form (ICF), after explaining their participation in the study.

Statistical analysis

Analysis was performed on a treatment basis using SPSS version 20.0. Baseline characteristics are presented as mean + SD and frequencies (%) or median (for skewed variables). Independent t test was used to examine the mean difference among variables. Efficacy of the intervention on the outcomes (between-group differences) was analyzed using changes in outcome variables. All tests were two sided and statistical significance was set at p <0.05.

RESULTS

A total of 185 patients were included in the study, 145 of
Table 1. Baseline characteristics of patients by group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group (n = 145)</th>
<th>Control group (n = 40)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (28.5)</td>
<td>10 (25)</td>
<td>0.780a</td>
</tr>
<tr>
<td>Female</td>
<td>103 (71.5)</td>
<td>30 (75)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>59.17 (10.39)</td>
<td>60.88 (10.47)</td>
<td>0.811b</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>19 (13.1)</td>
<td>6 (15)</td>
<td>0.917a</td>
</tr>
<tr>
<td>Regular alcohol consumption (%)</td>
<td>14 (9.7)</td>
<td>3 (7.5)</td>
<td>0.772a</td>
</tr>
<tr>
<td>Physical Activity (%)</td>
<td>17 (11.7)</td>
<td>6 (15)</td>
<td>0.249a</td>
</tr>
<tr>
<td>No. of prescribed antihypertensives, mean (SD)</td>
<td>1.70 (0.485)</td>
<td>1.55 (0.504)</td>
<td>0.549b</td>
</tr>
</tbody>
</table>

*Chi-square test  *ANOVA

Figure 1. Systolic Blood Pressure Values at 3-Months Follow Up.

Chances in SBP (mmHg) in patients with pseudoresistant hypertension during 3 months in the intervention group versus control group.

DISCUSSION

In the present study, an intervention designed to improve medication adherence in patients with hypertension did not affect the systolic blood pressure values of patients with pseudoresistant hypertension. On the other hand, patients in the intervention group showed significantly lower BPD values after three months. In a study to
determine medication adherence through Therapeutic Drug Monitoring (TDM) in 50 patients with RHTN, Avataneo et al. observed a significant association between low adherence and high diastolic blood pressure (Avataneo et al., 2018). However, in their study, the authors did not identify patients with pseudoresistant hypertension (pRHTN). In the present study, for patients with pRHTN, a similar association between medication adherence and DBP was observed. Considering the difficulty of differentiating pRHTN from RHTN and the fact that patients with resistant hypertension should be necessarily adherent to antihypertensive therapy, it can be assumed that the relationship between low adherence and low DBP control should occur exclusively in pseudoresistant patients. Although Avataneo et al. (2018) have suggested that this association is due to low adherence to beta-blockers and antihypertensives with central BP action, the CAFE15 study, a sub-study of the ASCOT16 study (Williams et al., 2006; Sever et al., 2003), compared the effects of different classes of antihypertensive drugs on peripheral and central BP - using the applanation tonometry of the radial artery together with a transfer function - and observed that the reduction of central BP leads to a greater decrease in cardiovascular risk when compared to similar values of peripheral arterial BP obtained via brachial artery. In addition, in the present study, less than 15% of the patients used beta-blockers and/or antihypertensives with central BP action. Although the relationship between medication adherence and SBP is well known in the literature - due to the focus on lowering SBP and its association with effective antihypertensive therapy, and consequently medication adherence - the influence of adherence to antihypertensive treatment on DBP has been poorly reported (Black, 2004; James et al., 2014; McNaughton et al., 2017; Cummings et al., 2016; McNaughton et al., 2017; Cummings et al., 2016). The present study reinforces the findings found in the study of Avataneo et al., although they evaluated patients with resistant hypertension (Avataneo et al., 2018). Finally, similar interventions given to hypertensive patients without suspicion of resistant hypertension have focused exclusively on SBP (McNaughton et al., 2017; Cummings et al., 2016). Thus, diastolic blood pressure and medication adherence should be investigated in subsequent studies involving patients with resistant and pseudo-resistant hypertension.

**Conclusion**

In the present study, it was observed that an intervention targeted on medication adherence improvement reduced diastolic blood pressure values in patients with pseudo-resistant hypertension, but it did not change the mean values of systolic blood pressure.

**STUDY LIMITATIONS**

Sample size may be a limitation of the study, as well as the different sizes of the two groups. Although fewer
patients could have been enough to answer the question, the risk of "over-treatment" was not considered as a potential consequence of the tested intervention. The classification of patients with uncontrolled hypertension according to the pseudo-resistant or resistant type is also subjected to interpretation bias, due to the lack of diagnosis of this clinical condition through ABPM, which is considered as one of the most important tools for the diagnosis of RHTN.

CONFLICT OF INTERESTS
The authors have not declared any conflict of interests.

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