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Directly observed treatment intake usefulness on the approach of drug adherence in patients with resistant hypertension

André Salgueiro[1], Loide Barbosa[2], José Alberto Silva[2], Jorge Polónia[3]

[1]USF Santa Clara, ACeS Póvoa de Varzim/Vila do Conde, Portugal
[2]Unidade Hipertensão e Risco Cardiovascular, Hospital Pedro Hispano, Matosinhos, Portugal
[3]Departamento de Medicina Faculdade de Medicina da Universidade do Porto, Porto, Portugal

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Abstract

Introduction & aim: We intend to assess the usefulness of directly observed treatment intake (DOTI) in the control of adherence to anti-hypertensive medication in patients with HTAres.

Methods: We studied 68 patients with Hres in outpatient hypertension clinic. Four were previously submitted to renal denervation. 24-h ambulatory BP (ABP) was evaluated before the procedure. In DOTI patients took all medications in the morning for 5 days under the supervision of a technician and performing on the fifth day a second ABP. In some patients a third ABP measurement was repeated 3-6 months after DOTI.

Results: Out of the 68 patients 76% were female and 21% diabetics in average ageing 62 years and BMI 30 Kg/m2. The average of antihypertensive agents was 4.6 ± 1.2 /day. After OTI casual, daytime and nighttime BP decreased significantly (24h from 149/82 + 13/13 to 131/74 +13/9 mm Hg, $p < 0.01$. In 36 patients (52.9%) there was an improvement with DOTI from the previous 24-h monitoring (i.e. the mean 24h BP was reduced to < 130/80 mm Hg or if 24h SBP and 24h DBP were both reduced by > 10%). After DOTI, 27 patients (39.7%) reported new adverse drug reactions. Out of these 36 subjects, 61% returned 3-6 months after DOTI to the previous BP values exhibited before DOTI.

Conclusions: OTI can be performed with accuracy, thereby becoming a valuable tool to identify the non-compliance to therapy as a cause of HRes.

Keywords: Direct observed treatment intake, non-adherence, resistant hypertension

Introduction

Hypertension is one of the most important risk factors for cardiovascular and renal events [1]. However the adequate control of hypertension cannot be obtained without compliance to treatment regimen recommendations. Studies have found that noncompliance rates with prescribed therapeutic regimens range more s than 30% and that 20-30% of the patients do not even initiate a new prescription [2]. Several factors influencing non-adherence to prescribed medicines have been described [3] related and nonrelated with side effects

Corresponding author: Jorge POLÓNIA
Department of Medicine/Cintesis, Faculty of Medicine,
Al. Prof. Hernâni Monteiro, 4200 - 319, Porto,
University of Porto, Portugal
E-mail address: jjpolonia@gmail.com

of medications, clinical variables, health care system issues, etc. Also, several methods have been used to assess patients' adherence to anti-hypertensive therapy but all have important limitations [4]. Moreover, overall 40% of the patients may discontinue treatment by one year after starting therapy [5]. Also adherence to treatment has been associated with better cardiovascular outcome comparing to nonadherence [6]. Resistant hypertension (HRes) is defined as un controlled hypertension in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system and a diuretic [1]. Nonadherence to prescribed antihypertensive medications must also be excluded before RH is diagnosed. Evidence exists that medication nonadherence is highly prevalent in patients with apparent RH [7]. We intend to assess the usefulness of directly observed treatment intake (OTI) in the control of adherence to anti-hypertensive medication in patients with HTAres.

Methods

The study was done in a single center i.e the ESH Excellence Centre of Blood Pressure Unit of Hospital Pedro Hispano, Matosinhos, Portugal. The study protocol was in full accordance with the guides of the Declaration of Helsinky, and all subjects followed the routine clinical procedures and gave their informed consent. For two years we enrolled all patients (1 patient per week) aging 18-75 years with Hres (office BP >= 150 90 mm Hg under with at least 3 different classes of drugs in optimal doses) who consented to be included in the protocol. Also to be included subjects had to have mean 24 hours BP systolic > 130 or diastolic > 80 mm Hg i.e. above the normalcy limits [1].

Direct Observed Treatment Intake (DOTI).

All subjects were submitted to the same DOTI protocol. After a previous 24-hours ABP, DOTI was undertaken in which patients took all medications fasting in the morning (before 09.30 AM) for 5 continuous days (monday to friday) under the supervision of a technician and performing on the fifth day a second 24 –h ABP. In some patients a third 24-ABP was undertaken 3-6 months after the DOTI without any supervision of drug adherence

Blood pressure measurement

Office BP was measured in a quiet room after 5 minutes of resting seated in the nondominant arm during the doctor´s visit with the automatic oscillometric device OMRON M10-IT with cuff and bladder size adapted to the arm circumference. The value that was considered was the average of 2 measurements 3minutes apart. 24 hours ambulatory blood pressure (ABP) studies were carried out in all subjects 1-2 month before the DOTI protocol. A second ABP was done within the 5^{th}-6^{th} day (09.00 AM friday to AM 09.00 saturday) of the DOTI protocol and in some also 3-6 months after the DOTI in that case without any supervision of drug adherence. In all cases ABP was performed with a Spacelabs 90207 (Redmond, Washington, USA), the first hour being disregarded for analysis. Readings were taken every 20 minutes during the day and every 30 minutes at night (the division between daytime and nocturnal periods was based on the patient's diary entries for rising and going to bed). Only records with >85% of valid measurements were used. On the basis of each 24 hour record, heart rate, mean 24 hour, daytime and nocturnal BP, and the absolute and percentage of the decrease in night-time systolic BP versus daytime systolic BP were analysed, as described elsewhere [8].

Statistics

For all calculations we used the package IBM SPSS software (version 24; SPSS Inc, Chicago, Continuous variables, when normally distributed were expressed as mean ± standard deviation (SD), all other categorical are reported as absolute or relative frequencies. Mean values of ABP before, during DOTI and thereafter were compared by ANOVA for repeated measurements and while significant differences were compared by Student paired t test. Mean values from different groups were compared by Student unpaired t test. All statistic tests were two-tailed. Significance was considered for p less than .05.

Results

We enrolled to the protocol 72 patients in our outpatient hypertension clinic with the diagnosis of Hres (office BP >= 150 90 mm Hg under with at least 3 different classes of drugs in optimal doses)

who also had 1-3 months before an evaluation with 24h ABP with a mean 24h systolic BP > 130 or diastolic BP > 80 mm Hg. Out of these 72 patients, four refused to participate in the protocol. Thus we were able to evaluate 68 patients, four of whom were previously submitted to renal denervation.

We analysed data from 68 patients with no previous cardiovascular events with mean age of 62 years and 71% were females, 21% diabetics who completed DOTI (Table 1). The average of antihypertensive agents was 4.6 drugs /day. Out of 68 patients, in 36 patients (52.9%) there was an improvement with DOTI from the previous 24-h monitoring (i.e. the mean 24h BP was reduced to < 130/80 mm Hg or if 24h SBP and 24h DBP were both reduced by > 10%). After DOTI, 27 patients (39.7%) reported new adverse drug reactions not reported before. Also, 5 patients who persisted with HRes after previous renal denervation were shown to have their ABP values compatible with a well hypertension after DOTI. Figure 1 shows the individual change of 23h systolic and diastolic BP before and after DOTI. Table 2 shows the average reduction of casual, 24hours, daytime and nighttime BP values from before to the end of the DOTI. As shown all these values were significantly

Table 1. Anthropometric and clinical data of the study population

BP (n=69) mm Hg *P<0.001	All N=68	Improvement with DOTI, N=36	No improvement with DOTI N=32
Age (years)	62+11	61 + 10	62 + 11
Female n (%)	48 (71)	23 (64)	25 (78)
BMI (Kg/m2)	30 + 6	29 + 4	30 + 4
Previous CV events	0	0	0
CKD (stages 1-2)	50 (74%)	26 (72%)	24 (80%)
CKD (stage 3)	18 (26%)	10 (28%)	8 (20%)
CKD (stages 4-5)	0	0	0
Dislipidemia	54 (79%)	28 (78%)	26 (81%)
Diabetes	14 (21%)	8 (22%)	6 (19%)
Drugs (anti.HT) /pt	4.5	4.4	4.6
Diuretics	68	36	32
Calcium antag	69	37	32
ACEin	30	14	16
ARBs	38	22	16
Rilmenidine	12	5	7
Spironolactone	59	31	28
Beta-blockers	24	11	13
Doxazocin	4	1	3
New ADRs	27	19	8

CKD, chronic kyddney disease; ADR, adverse drug reactions

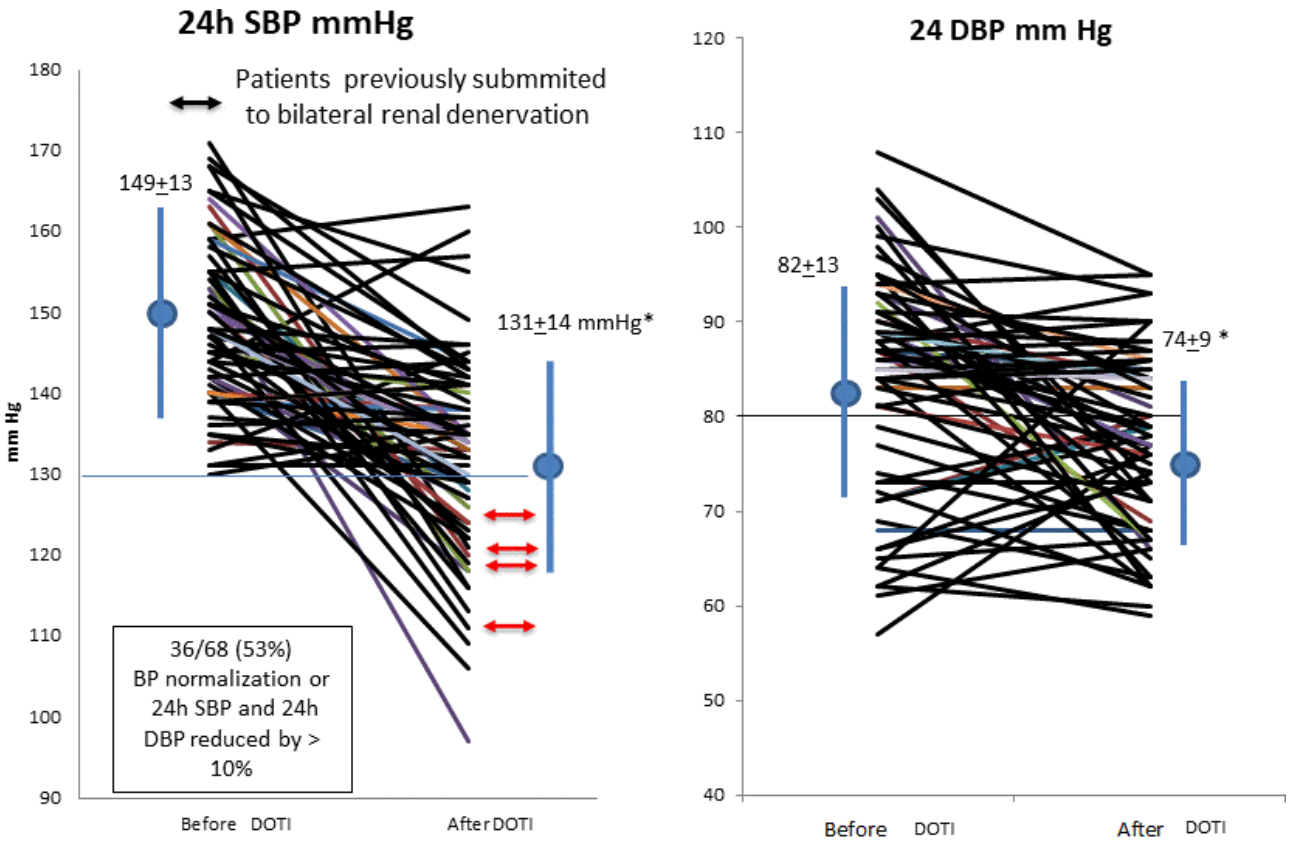

Figure 1. Values of 24-h blood pressure before and after directly observed treatment intake (DOTI) in patients with Resistant Hypertension(n = 68)
*p < 0.001

Table 2. Casual and 24-hour ambulatory BP data before and after DOTI

BP (n=68) mm Hg	Casual	24 –hour mean	Daytime	Nighttime	Nighttime fall (%)
Before DOTI	169/96 (16/20)	149/82 (13/13)	153/84 (14/15)	136/72 (17/13)	11.3 (9.3)
After DOTI	156/89 (20/13)*	131/74 (13/9)*	134/77 (14/10)*	121/65 (19/10)*	9.2 (9.4)

*P<0.001

reduced after DOTI. All 36 subjects that previously improved with DOTI were resubmitted to a new 24-hours ABP recording. As shown in Figure 2, 22 of these (61%) returned 3-6 months after DOTI to the previous BP values exhibited before DOTI.

Discussion

The diagnosis of resistant hypertension (HRes) and the efficacy of some procedures such as renal denervation ensure proper compliance with the therapy [1]. Non-compliance has been considered as one of the major challenges to the good control of hypertension [2-4] and an important contributor to the absence of prevention of cardiovascular events [6, 9]. Several methods for assessing poor adherence to antihypertensive therapy have been described [4, 10-11] as well as their advantages and inconveniences have been reported [4]. In the present study 53% of 68 patients with HRes thought to be medicated with 4.6 drugs in average were identified as not complying

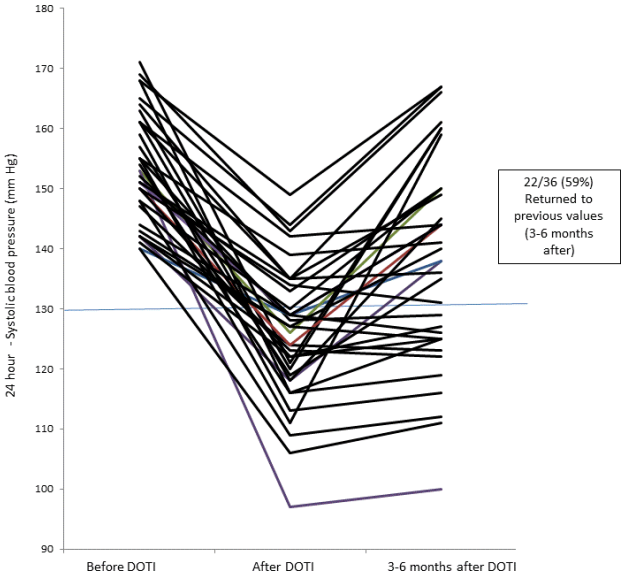

Figure 2. Evolution of systolic 24 ABPM before DOTI, during DOTI and 3–6 months after DOTI in patients with Resistant Hypertension (n = 36)

with the prescribed therapy. In these 36 patients DOTI almost normalized the 24h ambulatory BP values suggesting that if these patients had adhered to the prescribed therapeutics, the label of resistant hypertension would no longer be applied. In other words these patients did not actually have real resistant hypertension so this diagnosis was not applicable to them. In the present study we used DOTI to identify poor adherence to therapy. An ideal medication adherence measure should present low cost and be user friendly, easy to carry out, highly reliable, flexible, and practical [12]. DOTI includes interview and witnessed (supervised or observed) administration of medications followed by reliable evaluation of BP values and has been used as a non-adherence screening test prior to renal denervation [4]. At least in the conditions of the present study, DOTI helped to identify poor adherence to antihypertensive therapy in patients thought to have resistant hypertension. In favour of the fact that the patients did not comply with therapy, there was the verification that during the DOTI there was a significant number of new adverse reactions to the medication that until then were not reported. This evidence proves that there was bad adherence to therapy on the part of these patients. However, this study shows that the diagnosis of poor adherence to therapy does not guarantee that these patients will assume the need to further comply with the therapeutic. In fact 61% of the patients who normalized ABP during DOTI returned to previous uncontrolled BP 3-6 months after, suggesting that poor adherence to therapy returned back.

In conclusion

In an organized clinic, DOTI can be performed with accuracy , thereby becoming a valuable tool to identify the non-compliance to therapy as a cause of HRes and to identify false non-responders to techniques such as renal denervation due to loss of drug adherence. This study reveals that in more than half of patients with a diagnosis of HRes, the cause of the resistance is the non-adherence to therapy which can be identified with the DOTI. However it also shows that a proper diagnosis of non-adherence to therapy does not guaranty that patients will persist with prescribed therapy.

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