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ORIGINAL ARTICLE

Evaluation of the efficacy of adrenergic neurons inhibition through various surgical and therapeutic regimens on controlling blood pressure and circadian rhythm in patients with uncontrolled hypertension

Hany A. Al-Hussaniy [1,3] **Ali Anwar Al-kuraishy** [2] **Husam Jamal Jalil** [3]

[1]Faculty of Pharmacy, Bilad Alrafidain University College, Diyala, 32001, Iraq
[2]Department of Surgery, Al-Karama Hospital, Baghdad Health Department, Karkh, Iraq
[3]Dr. Hany Akeel Insitute, Iraqi Medical Research Center, Baghdad, Iraq

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Correspondence:

Al-Hussaniy HA, Faculty of Pharmacy, Bilad Alrafidain University College, Diyala, 32001, Iraq.

e-mail:
hany_akeel2000@yahoo.com

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Abstract

Objective: Resistant hypertension treatment is one of the most challenging medical issues that are difficult to treat, even nowadays with advanced medical techniques and advances, even combination therapy is not effective for resistant hypertension treatment or uncontrolled hypertension surgeons may give the resolving for this issue. Such a treatment is also Renal denervation – the technique developed ten years earlier that includes interrupting the renal adrenergic fibers efferent and afferent with radiofrequency energy. Using this technique, we wanted to know the effectiveness of blocking the adrenal activity by various therapeutic regimens in decreasing the variability of blood pressure and circadian diurnal profile in patients with resistant hypertension.

Materials and methods: A total of 80 patients with resistant HTN without comorbidities were enrolled in the study, these patients undergo surgical treatment of hypertension.

Results: The pathological profile "non-dipper" for NOCTURNAL blood pressure was documented in most patients at the initial stage: in group I -20 (80%), in group II -17 (68%), and in group III -19 (76%). After 3 months of evaluation, the number of subjects with this pathological profile increases in the treatment groups with Clonidine (21 (84%) patients) and Bisoprolol (19 (76% patients)) due to their rebound from the more aggressive profiles "night-picker" and "over-dipper", in the group treated by Renal denervation there was a reduction in this number (18 (72%) patients).

Conclusions: The data obtained have illustrated the antihypertensive efficacy of both medical and surgical treatment; however, renal denervation has a clearly superior effect.

Keywords: Adrenergic blockers, renal denervation, uncontrolled hypertension.

Introduction

Hypertension (HTN) is the main risk factor for preventable premature death and disability worldwide (1,2). HTN makes an important contribution to the structure of cardiovascular mortality, which in 2015 up to 53% in Europe in both sexes and up to 64% in men in Central Europe. In Iraq, it is responsible for 64.2% of CV deaths in men and 65.2% in women (3,4). There is a continuous linear correlation between blood pressure values and the risk of stroke or myocardial infarction (5). Despite the extensive availability of antihypertensive drugs on the pharmacological market, approximately 10% of patients on therapy remain with uncontrolled blood pressure, thus being at high risk for fatal cardiac and vascular events (6,7). Due to the recent publication of the results of second-generation studies in the last 3 years, renal denervation has positioned itself as an effective and safe therapeutic pathway in patients with HTN (8,9).

Our aim was to compare the impact of renal denervation versus pharmacological treatment on variability and circadian diurnal profile of hypertension in patients with resistant HTN.

Materials and methods

A total 80 patients with resistant HTN without comorbidities were enrolled in the study. During the course of three weeks, all patients received standardized treatment with Losartan, Amlodipine, and Indapamide. After confirmation of resistant HTN, subjects were randomly assigned to three equal groups of 25 patients depending on the medication supplemented with the one previously administered: group I – Clonidine, group II - Bisoprolol, and group III – Renal denervation. Ambulatory monitoring of blood pressure was carried out using the device "Monarch Meditech Varachha Surat, Gujarat, India. Evaluation of patients was carried out initially, at 3 and 6 months. The research was conducted under ethical regulations and was received an ethical approval number 1007/ 2020, Iraqi medical research center Baghdad, Iraq. Patient consent was obtained.

Statistical analysis

SPSS-15 software (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. According to whether the distribution is normal or not, the mean value and standard deviation or median value and minimum and maximum values are used in numerical data. Frequency and percentage values were used for categorical data.

Results

Systolic blood pressure variability analysis m/day recorded increased values of this parameter in all servation groups at the initial stage: 18.13±0.46 mmHg in group I compared to 17.62±0.32 mmHg in bisoprolol group (II) and 17.98±0,28 mmHg in group III ($p > 0,05$). Its statistically significant reduction ($p<0.001$ for all groups) has already been observed at 3 months of monitoring in the three research groups, the beneficial effect being maintained throughout the period of conduct of the study. Therefore, at 3 months of evaluation in group I, blood pressure night/day constituted blood pressure of 15.05±0.42 mmHg, demonstrating a reduction of 3,06±0,33 mmHg from baselines; in bisoprolol group (II) 15.27±0.30 mmHg, with a reduction of - 2.233±0.23 mmHg; group III had a superior potency in the improvement of this parameter reaching normal values 14.35±0.29 mmHg (a decrease of -3.74±0.20 mmHg). The comparative analysis of resistant hypertension in m/day variability between groups at this stage did not demonstrate statistical differences between them ($p>0,05$), but the dynamics had a high statistical difference ($p<0,001$).

At 6 months of monitoring, the maximum effect of improving the variability of blood pressure m/day is manifested, recording its normal values in all three groups: 11.73±0.43 mmHg in the I group in comparative to 12.92±0.36 mmHg in bisoprolol group (II) and 11,62±0,33 mm Hg in group III ($p<0,05$). The dynamics of the reductions at this stage constituted 6.39±0.31 mmHg in clonidine group (I) in comparative -4.71±0.30 mmHg in bisoprolol group (II) and -6.36±0.25 mmHg in group III, with Clonidine and Renal denervation treatment groups demonstrating a superior effect compared to the group of patients treated with Bisoprolol ($p<0,001$) (Table 1).

Variability of M/night blood pressure also experienced a favorable dynamic in all three applied schemes, reaching reference values of this parameter already at 3 months, the beneficial effect is maintained up to 6 months of monitoring. Thus, increased at the enrollment stage in the study (16.80±0.23 versus 16.73±0.17 and 17.02±0.16 mmHg in lots I, II, and III, respectively), the variability at 3 months of observation recorded the following values: in the clonidine group (group 1) -14.12±0.24 mmHg, in the bisoprolol group (2) -14.90 ± 0.12 mmHg and in the group III- 13,70±0,27 mmHg. Comparative analysis of STD blood pressure m/night values between groups, homogeneous at the initial stage, at this stage, observed

Table 1: Evolution of variability of blood pressure m/day depending on the treatment applied, mmHg

Variables	Group I Clonidine	Group II Bisoprolol	Group III	P	F
Originally	18.13±0.46	17.62±0.32	17.988±0.28	> 0.05	0,52
3 months	15.05±0.42	15.27±0.30	14.35±0.29	> 0.05	3,09
6 months	11.733±0.43	12.92±0.36	11.63±0.32	**< 0.05**	3,25
95% CI	10,79-12,71	12,16-13,64	12,95-13,27		
Dynamics 3 months	- 3.05±0.32	- 2.23±0.23	- 3.75±0.21	**< 0.001**	8,67
Dynamics 6 months	- 6.39±0.31	- 4.71±0.28	- 6.36±0.25	**< 0.001**	11,62

the appearance of a significant statistical difference (p<0,01) from the account of the diverse rate of their decrease under the action of treatment schemes: -2,65±0,160 mmHg in group I group versus -1,82±0,11 mmHg in the bisoprolol group and -3.21±0,24 mmHg in group III (p<0,001). The dynamics of the changes in each group at 3 months of monitoring were statistically authentic.

The variability of the blood pressure m/night continued to decrease until 6 months, constituting at this stage 11.90±0.31 mmHg in group I in comparison to 13.20±0.20 mmHg in group II and 11.62±0.28 mmHg in the group III, lots not being comparable according to this parameter, p<0,001. From the moment of inclusion in the study to the end of the monitoring period, the reduction in blood pressure variability m/night was -4,85±0,25 mmHg in group I, -3,51±0,18 mmHg in group bisoprolol (II), and -5,44±0,24 mmHg in group III (p<0,001). Although the treatment supplemented with Clonidine demonstrated a superior effect to that with Bisoprolol, and Renal denervation - an absolute superiority over both, all three schemes had superiority to that Bisoprolol, and Renal denervation - an absolute superiority both, all three

Table 2: Evolution of variability of blood pressure m/night depending on the treatment applied

Variables	Group I Clonidine	Group II Bisoprolol	Group III	P	F
Originally	16.80±0.23	16.73±0.17	17.02±0.16	> 0.05	0,51
3 months (95%CI)	14.12±0.24	14.90±0.12	13.70±0.27	**< 0.01**	7,09
	12,62-12,60	14,69-15,10	13,20-14,30		
6 months (95%CI)	11.90±0.31	13.20±0.20	11.56±0.29	**< 0.001**	10,69
	11.38-12.58	12,85-13,61	10,98-12,14		
Dynamics 3 months	- 2.65±0.16	- 1.82±0.10	- 3.21±0.24	**< 0.001**	15,66
Dynamics 6 months	- 4.84±0.26	- 3.52±0.19	- 5.44±0.24	**< 0.001**	17,39

Table 3: Evolution of resistance hypertension variability m/day depending on the treatment applied

Variables	Group I Clonidine	Group II Bisoprolol	Group III	P	F
Originally	15.87±0.16	15.78±0.09	15.65±0.11	> 0.05	0,91
3 months 95% CI	13.51±0.121	14.18±0.11	12.98±0.25	**< 0.001**	12,4
	13,26-13,74	13,96-14,40	12,48-13,48		
6 months 95% CI	11.70±0.16	12.45±0.19	11.13±0.26	**< 0.001**	10,25
	11.38-12.02	12,07-12,83	10.61-11.65		
Dynamics 3 months	- 2.37±0.12	- 1.61±0.08	- 2.68±0.23	**< 0.001**	12,54
Dynamics 6 months	- 4.18±0.16	- 3.34±0.18	- 4.53±0.23	**< 0.001**	9,81

schemes had statistically significant dynamics in the improvement of the resistant hypertension m/ night at 6 months of evaluation (p<0,001) (Table 2).

The resistance hypertension variability m/day increased at the initial stage (15,87±0,16 mmHg in group I versus 15,79±0,08 mmHg in group II and 15,65±0,11 mmHg in group III (p>0,05) at 3 months of the evaluation was statistically significantly reduced in the three observation groups so that it reached normal values in group I - 13,51±0,121 mmHg and III -12,98±0,25 mmHg, in group II are slightly above the limit -14,18±0,11 mmHg (p<0,001). The dynamics of the reduction of variability at this stage were inhomogeneous between groups, demonstrating a comparable beneficial effect in groups I (-2.36±0.11 mmHg) and III (-2.68±0.23 mmHg), which is superior to group II (-1.61±0.08) (p<0.001).

At 6 months of monitoring, the variability of resistant hypertension m / day was observed in all evaluation groups I -11,71±0,12 mmHg, group II -12,45±0,19 mmHg, and group III -11.13±0.26 mmHg (p<0.001). The dynamics of the changes produced had, as in the previous stage, veracity with high statistical significance in each group (p<0,001). Comparative analysis of the reduction in resistant hypertension variability m/day between groups found the presence of a statistically significant difference with a predilection for the group treated by Renal denervation: -4,18±0,16 mmHg in group I in comparison - 3,34 ± 0,18 mmHg in group II and - 4,53±0,23 mmHg in group III, (p<0,001) (Table 3).

The evolution of hypertension variability m/night noted authentic statistical beneficial effect starting with 3 months of observation: 11.70±0.13 mmHg in the I group

Table 4: Evolution of hypertension variability m/night depending on the treatment applied

Variables	Group I Clonidine	Group II Bisoprolol	Group III	P	F
Originally	13.89±0.141	13.52±0.12	13.61±0.10	>0.05	2,43
3 months 95% CI	11.71±0.12	11.96±0.12	11.29±0.16	<0.01	6,33
	11.46-11.94	11.72-12.20	10.97-11.61		
6 months 95% CI	10.89±0.10	11.16±0.10	10.10±0.16	<0.001	20,15
	10.69-11.09	10.96-11.36	9,78 -10,42		
Dynamics 3 months	- 2.18±0.12	- 1.57±0.09	- 2.31±0.17	<0.001	9,21
Dynamics 6 months	- 3,00±0,14	- 2.36±0.11	- 3,50±0,19	<0.001	14,41

Table 5: Distribution of patients by type of circadian diurnal profile in venous nectarial blood pressure

		Group I Clonidine N (%)	Group II Bisoprolol N (%)	Group III N (%)	χ^2	P
Originally	Night-picker	3.0 (12%)	2.0 (8%)	3.0 (12.0%)	3,10	>0.05
	Non-dipper	20.0 (80%)	17.0 (68%)	19.0 (76.1%)		
	Dipper	1.0 (4%)	3.0 (12%)	1.0 (4.3%)		
	Over-dipper	1.0(4%)	3.0 (12%)	2.0 (8.2%)		
3 months	Night-picker	2.0 (8%)	1.0 (4%)	1.0 (4.1%)	3,91	>0.05
	Non-dripper	21.0 (84%)	19.0 (76%)	18.0 (72.0%)		
	Dipper	1.0 (4%)	3.0 (12%)	5.0 (20.2%)		
	Over-dipper	1.0 (4%)	2.0 (8%)	1.0 (4.2%)		
6 months	Night-picker	1.0 (4%)	-	-	6,28	>0.05
	Non-dipper	19.0 (76%)	21.0 (84%)	15.0 (60.1%)		
	Dipper	5.0 (20%)	4.0 (16%)	10.0 (40.1%)		
	Over-dipper	-	-	-		

in comparative 11.95± 0,13 mmHg in the bisoprolol group and 11,30±0,15 mmHg in group III, p<0,01. The improvement of this parameter continued for 6 months, resulting in 10.89±0.10 mmHg versus 11.160±0.11 mmHg and 10.11±0.160 mmHg in groups I, II, and III, respectively (p<0.001). Comparative analysis of the reduction dynamics demonstrated the presence of the statistical difference between the lots at both 3 moths (-2.18±0.12 mmHg in the I group versus -1.56±0.08 mmHg in group II and -2.31±0.17 mmHg in group III), as well as 6 months of monitoring (-3.0±0.140 mmHg in group I versus -2.36±0.11 mmHg in group II and -3.51±0.18 mmHg in group III). Although the reduction in hypertension variability m/night was statistically authentic in all three groups at all stages of evaluation, the Bisoprolol treatment group noted a more modest effect in the improvement of this parameter, the clearly superior effect being manifested by the group of patients subject to Renal denervation (Table 4).

MAATA also allowed the completion of the diurnal profile of the circadian rhythm for blood pressure and resistant hypertension at each monitoring stage to assess the modulation efficacy of the SNS activity, either medicinally or through renal denervation, in improving this indicator.

Thus, the appreciation of the diurnal pattern of the resistant hypertension circadian rhythm at the enrollment stage in the study noted the presence of pathological profiles "night-picker", "non-dipper" and "over-dipper" in most conditions: 24 (96%) subjects in the group I, 22 (88%) - in the II group and 24 (96%) - in the III group, the distribution of patients being homogeneous between the groups (p>0,05). The pathological profile "night-picker" was initially observed in 3 (12%) patients in the I group, 2 (8%) patients in the II group, and 3 (12%) in the III group. At 3 months of medication, the treatment of subjects with this type of profile was reduced to 2 (8%) in the I group, 1 (4%) in the II group, and 1 (4%) in the III group. By the 6th month of treatment, the presence of the pathological diurnal profile "night-picker" was found only in 1 (4%) patient from the group treated with Clonidine, not registered in patients in the bisoprolol and Renal denervation treatment groups (Table 5).

The pathological profile "non-dipper" for NOCTURNAL blood pressure was documented in most patients at the initial stage: in group I -20 (80%), in group II -17 (68%), and in group III- 19 (76%). After 3 months of evaluation, the number of subjects with this pathological profile increases in the treatment groups with Clonidine (21 (84%) patients) and Bisoprolol (19 (76% patients)) due to their rebound from the more aggressive profiles "night-picker" and "over-dipper", in the group treated by Renal denervation there was a reduction in this number (18 (72%) patients) due to the return of patients to the physiological profile "dipper". This "migration" of patients from a more nefarious profile to a less negative or normal one continued until the end of the study when the treatment of patients with the diurnal profile "non-dipper" for nocturnal BP made up 76% (19) in group I, 84% (21) in group II and 60 % (15) in group III.

The physiological profile of the dipper for nocturnal BP was estimated at the initial stage only in 3 (12%) patients from group II and 1 (4%) patient from groups I and II. This number remained constant at 3 months of

Table 6: Distribution of patients by type of circadian diurnal profile in arterial nectarial pressure

		Group I Clonidine N (%)	Group II Bisoprolol N (%)	Group III N (%)	χ^2	P
Originally	Night-picker	5 (16%)	2.0 (8%)	2.0 (8%)	3,15	> 0.05
	Non-dipper	18 (72%)	16.0 (64%)	19.0 (76%)		
	Dipper	2 (8%)	5 (20%)	3.0 (12%)		
	Over-dipper	1.0 (4%)	2 (8%)	1.0 (4%)		
3 months	Night-picker	2.0 (8%)	-	1.0 (4%)	5,11	> 0.05
	Non-dripper	20.0 (80%)	19 (76%)	18.0 (72%)		
	Dipper	2.0 (8%)	5 (20%)	6.0 (24%)		
	Over-dipper	1.0 (4%)	1 (4%)	-		
6 months	Night-picker	-	-	-	0,91	> 0.05
	Non-dipper	19.0 (76%)	18 (72%)	16 (64%)		
	Dipper	6.0 (24%)	7.0 (28%)	9.0 (36%)		
	Over-dipper	-	-	-		

monitoring in groups I and II and increased in group III D, being appreciated in 5 (20%) subjects. By the 6th month, the maximum effect of improvement of the pathological diurnal profiles was reached, thus the physiological profile "dipper" being registered in 5 (20%) patients from the I group, 4 (16%) patients from the II group, and 10 (40%) from the III group, the latter showing absolute superiority over the pharmacological treatment groups.

At the initial stage, the pathological profile "over-dipper" for blood pressure was registered in 1 (4%) patient from the I group, 3 (12%) patients from the II group, and 2 (8%) patients from the III group. At 3 months of evaluation, this number remained constant in the I M group and decreased in the II and III groups, being recorded in 2 (8%) and 1 (4%) patients, respectively. Toward the end of the study, this type of pathological diurnal profile was not appreciated in any group.

The evaluation of the diurnal profile for diastolic (NOCTURNAL DIASTOLICE) at the enrollment stage noted the presence of pathological profiles in most of the enrolled patients: 92% (23 patients) from the I group, 80% (20 patients) from group II and 88% (22 patients) of group III, the distribution between the groups being homogeneous (p>0,05).

The pathological profile "night-picker" was recorded at the initial stage at 16% (4), 8% (2), and 8% (2) patients from the I, II, and III groups, respectively. After 3 months of monitoring, the rate of subjects with this type of profile decreased considerably in the group treated with Clonidine, constituting 8% (2), and in the group of patients subjected to Renal denervation - 4% (1), at the same time disappeared among patients the scheme of treatment of which was supplemented with Bisoprolol. At the end of the surveillance period, the "night-picker" profile was not recorded in any group (Table 6).

Most of the patients at the initial stage had a pathological diurnal profile for "non-dipper" DIASTOLICE: in the I group – 72% (18), in the II group – 64% (16), and 76%

(19) in group III, $p > 0,05$, $\chi^2 = 3,16$. By the third month of monitoring, the rate of patients with this type of diurnal profile increased in groups I and II due to the migration of patients from more aggressive "nightpicker" and "over-dipper" profiles, thus constituting 80% and 76% (19), respectively. Group III recorded a reduction of the share of patients with a "non-dipper" profile (72% (18) patients) by recovering the physiological "dipper" profile. At the end of the surveillance period, the presence of only two types of diurnal profiles was noted - physiologically "dipper" and pathologically "non dipper", the last recorded in 76% (19) of patients in the Clonidine-treated group, 72% (18) of the Bisoprolol-treated group and 64% (16) of patients undergoing renal denervation.

The physiological profile "dipper" at the initial stage was appreciated in 8% (2) patients from the I group, 20% (5) of group II and 12% (3) of group III. Recovery of the physiological profile lasted slower in the treatment groups with Clonidine and Bisoprolol, so at 3 months of evaluation the rate of patients with a dipper profile remains unchanged compared to the initial stage, the dynamics being recorded only at 6 months of continuous treatment – 24% (6) and 28% (7) patients in groups I and II, respectively. The group of patients undergoing Renal

denervation has demonstrated, in this respect, a much superior effect, the dynamics being noted already 3 months after the procedure, when the number of subjects with physiological profile doubled compared to the pre-hypo-hypo-cultural stage, constituting 24% (6 subjects). At 6 months of evaluation, group III D was made up of 36% (9) patients with a "dipper" profile.

The pathological diurnal profile " overdipper" for resistant hypertension was recorded in 4% (1), 8% (2), and 4% (1) patients in groups I, II, and III, respectively. At 3 months of monitoring, it was noted the improvement of the pathological diurnal profile by the recoil of the patients in the profile "over-dipper" in "non-dipper" in the treatment group with Bisoprolol (4% (1)) and Renal denervation, in which it disappeared completely the "over-dipper" profile.

Discussion

Because of the importance of sympathetic nerves in controlling blood pressure, we developed a new minimally invasive technique that may decrease the activity of adrenergic neurons at the peripheral and renal levels, which results in decreased renin production and decreased blood pressure with a reduction of referral vascular resistance. Such a treatment is also called Renal denervation – the technique developed ten years earlier that includes interrupting the renal adrenergic fibers efferent and afferent with radiofrequency energy (10-12).

Using this technique, we wanted to know the effectiveness of blocking the adrenal activity by various therapeutic regimens in decreasing the variability of blood pressure and circadian diurnal profile in patients with resistant hypertension. The data obtained have illustrated the antihypertensive efficacy of both medical and surgical treatment; however, renal denervation has a clearly superior effect (14,15).

Our study is augmented and agrees with the previse studies (11-13). Furthermore, the Clonidine treatment group did not experience dynamics at this stage. At the end of the study, no group had an "over-dipper" diurnal profile for resistant hypertension was not noted in any group. We observed that improvement of the diurnal profile was achieved under the influence of all three administered treatment schemes, Renal denervation presents quantitative and qualitative changes superior to the pharmacological treatment in restoring the physiological circadian pattern. Thus, the physiological profile "dipper" towards the end of the study was recorded for blood pressure in 20% versus 16% and 40% of patients and for diastolic in 24% versus 28% and 36% of the treatment groups with Clonidine, Bisoprolol and completed with Renal denervation, respectively. So we observe that renal denervation is one of the best strategies to treat resistant hypertension.

Conclusions

The patient expected from doctor to treat his disease even in difficult cases such as resistant hypertension, which is a situation where hypertension is difficult to treat even if they take 2 antihypertension medications or more such as ACE inhibitors and/or beta-blockers and thiazide for that it is important to manage and treat this disease, in our research several variabilities of the hypertension being initially increased in all the observation groups, it was statistically significantly reduced under the influence of all three treatment schemes, thus it was observed the improvement of this parameter at different stages of evaluation depending on the medication administered. Renal denervation in this context has demonstrated a clear superiority over pharmacological treatment. Is several types of patients with resistant hypertension and this surgery may offer the best treatment plan for hypertension.

Conflict of interest:

The authors report no conflict of interest.

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Ethical approval:

The research was conducted under ethical regulations and was received an ethical approval number 1007/ 2020, Iraqi medical research center Baghdad, Iraq. Patient consent was obtained.

Contributions

Research concept and design: **HAA, AAA, HJJ**
Data analysis and interpretation: **AAA, HJJ**
Collection and/or assembly of data: **HAA, AAA**
Writing the article: **HAA, HJJ**
Critical revision of the article: **AAA, HJJ**
Final approval of the article: **HAA, AAA, HJJ**

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