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CLINICAL TRIAL REPORT

Effect of Sequential Nephron Blockade versus Dual Renin-Angiotensin System Blockade Plus Bisoprolol in the Treatment of Resistant Hypertension, a Randomized Controlled Trial (Resistant Hypertension on Treatment - ResHypOT)

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Introduction: Hypertension is the most important modifiable risk factor for cardiovascular disease and a leading public health concern.

Objectives: The primary aim was to compare sequential nephron blockade (SNB) versus dual renin-angiotensin system blockade (DRASB) plus bisoprolol in patients with resistant hypertension to observe reductions in systolic and diastolic blood pressure (SBP and DBP) levels after 20 weeks of treatment.

Material and Methods: This trial was an open-label, prospective, randomized, parallel-group, clinical study with optional drug up-titration. Participants were evaluated during five visits at 28-day intervals.

Results: The mean age was 55.5 years in the SNB and 58.4 years in the DRASB + bisoprolol group (p=NS). Significant office BP reductions were observed in both groups. SNB group, SBP decreased from 174.5±21.0 to 127.0±14.74 mmHg (p<0.0001), and DBP decreased from 105.3±15.5 to 78.11±9.28 mmHg (p<0.0001). DRASB group, SBP decreased from 178.4±21.08 to 134.4 ± 23.25 mmHg (p<0.0001) and DBP decreased from 102.7±11.07 to 77.33±13.75 mmHg (p<0.0001). Ambulatory blood pressure monitoring (ABPM) showed also significant SBP and DBP reductions in both groups (p<0.0001).

Conclusion: In patients with RHTN adherent to treatment, SNB and DRASB plus bisoprolol showed excellent therapeutic efficacy, although SNB was associated with earlier SBP reduction.

Keywords: resistant hypertension, natriuretic agents, dual blockade of the renin-angiotensin system, bisoprolol

Introduction

Hypertension (HTN) is the most important modifiable risk factor for cardiovascular disease and a leading public health concern. This condition is associated with functional and structural damage to target organs (heart, brain, kidneys, and blood vessels)[1,2] along with metabolic abnormalities, increasing the risk of fatal and nonfatal cerebrocardiovascular events.[3]

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Resistant HTN (RHTN) is defined as the maintenance of BP values persistently above the recommended target values despite the use of three antihypertensive agents of different classes, including one renin-angiotensin system (RAS) blocker (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin II receptor blocker [ARB]), one long-acting calcium-channel blocker (CCB), and one long-acting thiazide diuretic (TZD) at the maximum recommended and tolerated doses, administered with appropriate frequency and with proven adherence.[4,5] The definition above includes a subgroup of patients with RHTN whose BP is controlled with four or more antihypertensive medications, known as controlled RHTN (C-RHTN).[6]

In a meta-analysis of studies evaluating individuals with treated hypertension, Achelrod et al[7] found a prevalence of RHTN of 13.72% in 20 observational studies and 16.32% in four randomized controlled trials. In Brazil, a multicenter study (ReHOT), using the ambulatory BP monitoring (ABPM), reported a prevalence of RHTN of 11.7%.[8]

Management of RHTN is further challenged by patients' failure in adhering to treatment. Medical inertia hampers the physician's ability to adjust medications due to the interference of pharmacokinetics and pharmacodynamic factors hindering treatment effectiveness.[9]

The pathophysiological mechanisms of RHTN remain uncertain but are clearly multifactorial. According to Taler et al, persistent fluid retention, increased sodium sensitivity, excessive salt intake, hyperaldosteronism, renal dysfunction, and sympathetic hyperactivity are common underlying causes contributing to the hypervolemic state found in patients with RHTN.[10–14]

In patients with RHTN, the addition of mineralocorticoid receptor blockers to hypertension therapy reduces BP and volume overload, further supporting the claim that fluid retention is a major contributor to the RHTN pathophysiology.[15]

Additional mechanisms involved in the RHTN pathophysiology include vascular smooth muscle tone, intensified sympathetic system activity, and RAS hyperactivity.[16,17]

Bobrie et al[18] compared the efficacy and safety of two stepped care strategies, namely, sequential nephron blockade (SNB) and dual RAS blockade (DRASB) added to triple standardized antihypertensive therapy of TZD, ARB, and CCB during 3 months in patients with RHTN.

Considering the above and the lack of Brazilian studies in patients with RHTN undergoing treatment with SNB or DRASB, the aims of the present study were to demonstrate the therapeutic efficacy of SNB compared with DRASB plus bisoprolol in patients with RHTN and to assess the side effects and adherence to treatment over 20 weeks.

Materials and Methods

Study Design

Detailed information about the study protocol was published previously.[19] Briefly, the ResHypOT (Resistant Hypertension on Treatment) trial of SNB versus DRASB plus bisoprolol in the treatment of resistant hypertension was an open-label, prospective, randomized, and parallel-group study with optional drug up-titration (ClinicalTrials.gov, identifier, NCT02832973, registered on 18 July 2016). Two therapeutic regimens for RHTN were compared, namely, SNB versus DRASB plus bisoprolol. Initially, all patients received standardized triple antihypertensive treatment. This research followed the ethical guidelines of the 1975 Declaration of Helsinki, and the study protocol was evaluated and approved by the Research Ethics Committee of the institution (CAAE nº 33943014.6.0000.5415, nº 870.093). All participants signed a written informed consent before random allocation to the SNB or the DRASB plus bisoprolol group.

Participants

The study, conducted between September 2016 and September 2019, included 72 patients with RHTN undergoing treatment with losartan (100–200 mg), chlorthalidone (25 mg), and amlodipine (5 mg) at the Hypertension Outpatient Clinic of the university hospital. The inclusion criteria were patients with RH on treatment with three antihypertensive drug classes at maximum tolerated doses for at least 6 months, after excluding causes of pseudo resistance, and both genders aged between 18 and 75 years. The exclusion criteria were chronic renal failure with dialysis or creatinine clearance <40 mL/min, coronary artery disease including unstable angina or recent myocardial infarction, atrial fibrillation or atrioventricular block, secondary hypertension, contraindication or intolerance to the drugs used in the study, and

refusal or failure to follow the treatment regimen. The First Brazilian position on resistant hypertension[20] and the Scientific Statement of American Heart Association[5] were used to define RHTN.

Two comparison groups were generated using simple randomization and equal allocation ratio based on a table of random numbers. The study coordinator organized, and sequentially numbered opaque and sealed envelopes allocated to the patients in order of enrollment. The allocation process was developed and monitored to preserve concealment, and the envelopes were opened sequentially after irreversibly assigned to the participant. The flowchart in Figure 1 shows the process of selection of the participants. Participants in both groups were evaluated during five visits at 28-day intervals over 20 weeks. In addition to maintaining the baseline therapy, the participants in the SNB group (n=35) received sequentially (A) spironolactone 25 mg, (B) spironolactone 25 mg plus furosemide 20 mg, (C) spironolactone 25 mg plus furosemide 40 mg, and (D) spironolactone 25 mg plus furosemide 40 mg plus amiloride 5 mg, while participants in the DRASB group (n=37) received sequentially (A) ramipril 5 mg, (B) ramipril 10 mg, (C) ramipril 10 mg plus bisoprolol 5 mg, and (D) ramipril 10 mg plus bisoprolol (10 mg).

Randomization and Follow-Up

Protocol

The flowchart in Figure 1 shows the process of randomization and treatment follow-up of the participants.

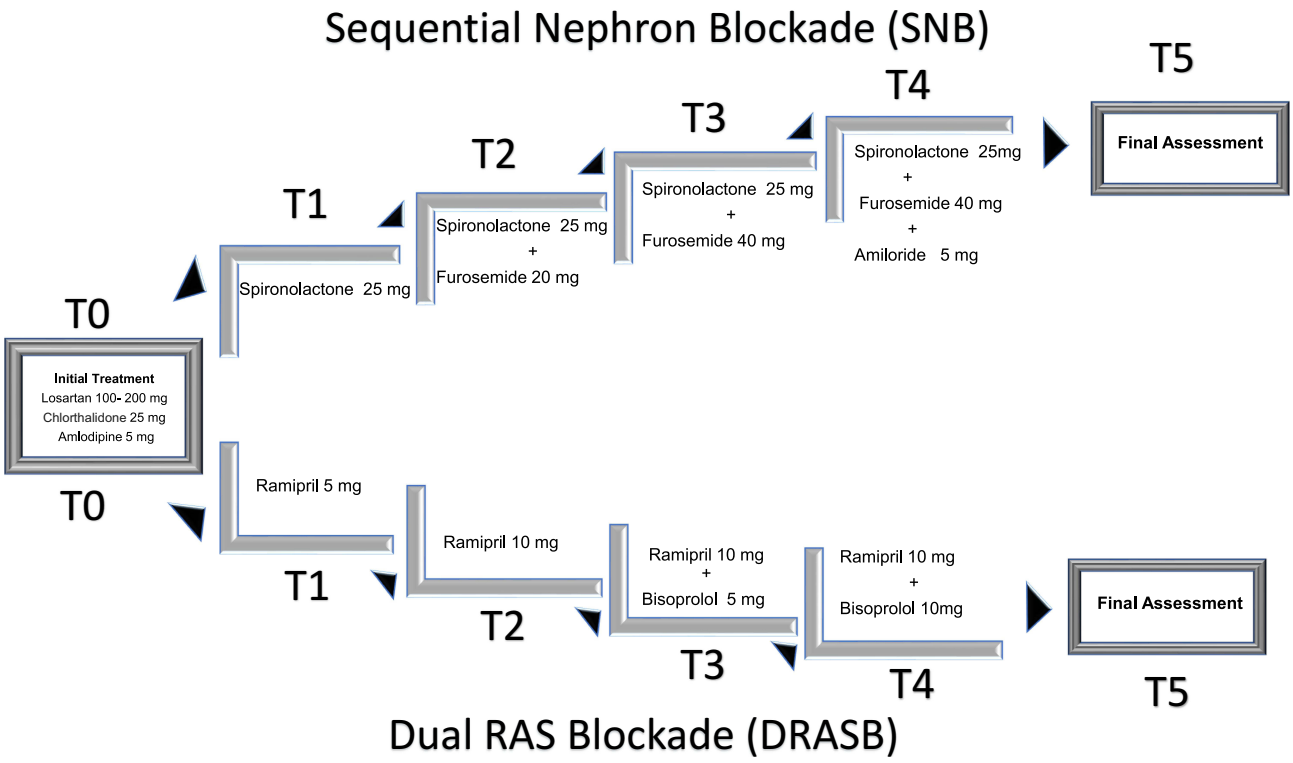

Figure 1 Study design. Process of randomization and follow-up of the patients. t0, Weeks −4 to 0. All patients maintained treatment with losartan (100–200 mg), chlorthalidone (25 mg), and amlodipine (5 mg). t1, Weeks 0–4. Individuals with BP levels ≥ 140/90 mmHg on office measurements and ≥ 130/80 mmHg on 24-hour ABPM were randomized to one of the study groups. Participants received spironolactone 25 mg (SNB group) or ramipril 5 mg (DRASB group). t2, Weeks 4–8. Participants with office BP <140/90 mmHg continued the same regimen, while those with office BP ≥140/90 mmHg received, in addition to the existing regimen, furosemide 20 mg (SNB group) or ramipril 10 mg (DRASB group). t3, Weeks 8–12. Participants with office BP <140/90 mmHg continued on the same regimen, while those with office BP ≥140/90 mmHg received furosemide 40 mg (SNB group) or bisoprolol 5 mg (DRASB group). t4, Weeks 12–16. Participants with office BP <140/90 mmHg continued on the same regimen, while those with office BP ≥ 140/90 mmHg received additional amiloride 5 mg (SNB group) or bisoprolol 10 mg (DRASB group). t5, Weeks 16–20. Blood samples were drawn from all patients, and office BP and ABPM were performed.

Abbreviations: ABPM, ambulatory blood pressure monitoring; DRASB, dual renin-angiotensin system blockade + bisoprolol; SNB, sequential nephron blockade.

Measurement of Office Blood Pressure and 24-Hour Ambulatory Blood Pressure Monitoring

Office BP was measured by the indirect method using an automatic electronic device (Omron HEM-711DLX, Omron Healthcare Inc., Bannockburn, Illinois, USA) in the office during follow-up visits, according to the VI Brazilian Guidelines on Hypertension.[21] The mean level of three measurements was considered. ABPM and was additionally carried out to investigate true RHTN, white-coat effect, and masked hypertension. ABPM was performed using the Mobil-O-Graph NG (IEM, Stolberg, Germany) according to technical norms by the V Guidelines for Ambulatory Blood Pressure Monitoring.[22]

Anthropometric Measurements

Weight and height, measured by anthropometric scales, were used to calculate body mass index (BMI) according to the formula weight (kg)/height squared (m^2). Abdominal circumference (waist) was measured and values ≤80 cm and ≤94 cm were considered appropriate for women and men, respectively. We also measured hip circumference and calculated the participants' waist/hip ratio.

Biochemical and Imaging Tests

Blood samples were drawn from all patients at the first and last visits after 12-hour fasting for measurement of serum total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), triglycerides (TG), glucose, insulin, creatinine, sodium, and potassium. Sodium and potassium were evaluated monthly. A diagnosis of diabetes was confirmed by the presence of two blood glucose measurements ≥126 mg/dL after at least 8-hour fasting. The low-density lipoprotein cholesterol (LDLc) fraction was calculated using the formula LDLc = TC - HDLc - TG/5 (for TG <400 mg/dL). Electrocardiography, echocardiography, Doppler ultrasonography of the carotids and renal arteries, and treadmill stress test were performed in all patients.

Compliance

Compliance was assessed by pill counting. The drugs were delivered at each appointment, and the patients were asked to return empty bottles at the following appointment. Patients were considered adherent when consuming above 80% of the prescribed medication. Adherence was calculated after the last visit using the Litt & Cuskey criterion, which defines adherence as the difference between pills consumed versus those that should have been consumed according to the prescription.[22]

Primary Outcome Measures

The primary outcome was the average of three office-measured systolic BP (SBP) and diastolic BP (DBP) levels at week 20, measured using an oscillometric device (time point, week 20).

Secondary Outcome Measures

The secondary efficacy outcome measures included the average of three office-measured mean BP (MBP) and pulse pressure (PP) levels at week 20, determined with an oscillometric device (time point, week 20), and the mean 24-hour SBP and DBP at week 20, measured with an ABPM device (time point, week 20). Safety and tolerability were also secondary outcome measures (time frame, throughout the study). During the study, BP levels were evaluated every 4 weeks by office-measured BP measurement to detect hypotension (time frame, every 4 weeks).

Sample Size Calculation

Sample size was calculated using Stata version 13.0 (StataCorp, College Station, TX, USA). The calculation was based on the detection of a difference ≥12 mmHg in SBP considering an alpha error of 5%, statistical power of 80%, and standard deviation (SD) of 8 mmHg, resulting in 36 patients per group (SNB versus DRASB + bisoprolol).

Statistical Analysis

Descriptive statistics were used for data analyses. Continuous variables are expressed as means ± 1 SD. Categorical variables are described as absolute and relative frequencies. The differences in the effects of the intensifying diuretic therapy with SNB and the DRASB intervention between baseline and 20 weeks were evaluated using paired Student's *t*-test. This same test was used to compare the means of normally distributed continuous variables for related and independent samples. Nonparametric tests were used to compare data without normal distribution. The analyses were performed using the software GraphPad Prism, version 6 (GraphPad Software, Inc., San Diego, CA, USA) and Stata SE, version 13.0 (Stata Corp LLC, Texas, USA). P values <0.05 were considered statistically significant.

Results

A total of 135 participants were invited and 80 were screened for the study. Of these, 72 met the criteria for inclusion in the trial and were randomly assigned to treatment with SNB (n=35) versus DRASB + bisoprolol (n=37). All the patients completed the study in both groups (Figure 2).

The baseline demographic and clinical characteristics of all subjects divided in each treatment group are shown in Table 1. No significant differences in baseline clinical characteristics were observed between subjects randomized to SNB or DRASB + bisoprolol. Distribution of risk factors (diabetes, dyslipidemia, sedentary lifestyle) between groups was also similar, although the SNB group had a higher prevalence of smoking (p<0.05). Significant reductions in weight (p=0.008), BMI (p=0.007), and waist (p=0.04) and hip circumference (p=0.03) were observed at week 20 compared with baseline in the SNB group, while the only significant difference in the DRASB group at week 20 compared with baseline was a reduction in waist circumference (p=0.04) (date no showed). In addition, no significant difference was observed in biochemical parameters into each group before, and after the treatment and between the groups at the end of treatment (Table 2).

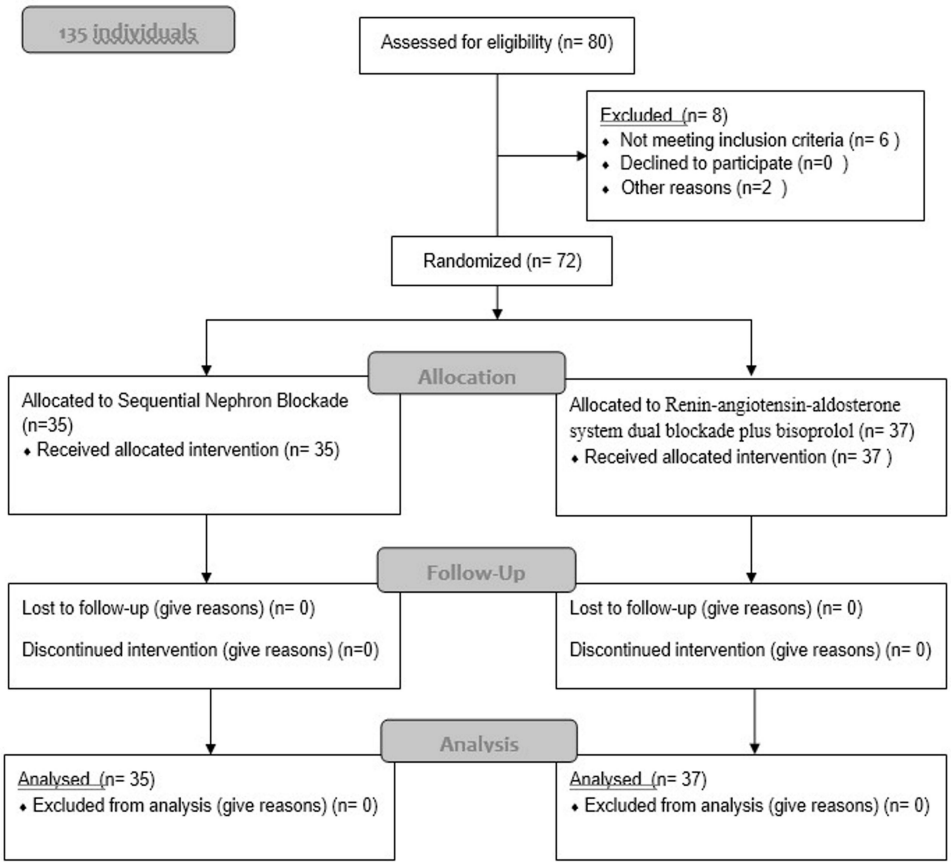

Figure 2 Flowchart of study.

Table 1 Baseline Demographic and Clinical Characteristics in Two Groups of the Study

	SNB (n=35)	DRASB (n=37)	*P*
Age	55.54±11.98	58.44±9.32	NS
Sex M/F	13/22	14/22	NS
Height (m)	1.63±008	1.62±0.074	NS
Weight (kg)	83.28±14.05	85.36±15.5	NS
BMI	31.56±4.84	32.40±4.93	NS
Waist (cm)	104.2±11.48	106.2±11.52	NS
Hip (cm)	107.2±10.10	111.3±13.86	NS
W/H ratio	0.97±0.09	0.96±0.10	NS
Diabetes	16	14	NS
Dyslipidemia	14	19	NS
Smoking	4	1	< 0.05
Alcoholism	4	4	NS
Sedentary lifestyle	14	10	NS

Abbreviations: SBN, Sequential Blockade Nephron; DRASB, Dual Renin-angiotensin System Blockade + Bisoprolol; BMI, body mass index; W/H, waist/hip.

Table 2 Comparison of the Biochemical Data Within of Each Group and Between Groups (SNB and DRASB + Bisoprolol) at Baseline and After Treatment

	SNB (n=35)		P	DRASB + Bisoprolol (n=37)		P	P - SNB x DRASB
	Before	After		Before	After		
Fasting glycose (mg/dL)	135.9±50.5	132.1±60.0	0.7	128.4±43.1	133.7±109.0	0.7	0.5
Glycated hemoglobin %	7.1±1.85	7.2±1.9	0.3	7.4±2.44	7.5±6.4	0.6	0.5
Creatinine (mg/dL)	1.0±0.33	1.1±0.4	0.3	1.1±0.33	1.1±1.0	0.2	0.4
eGFR (CKD-EPI)	77.89±23.1	71.8±25.9	0.1	70.56±20.3	68.5±69.2	0.4	0.2
Microalbuminuria 24h	77.74±195.6	30.78±49.73	0.3	100.4±235.7	95.38±287.7	0.6	0.3
Uric acid (mg/dL)	5.5±1.71	5.8±1.6	0.3	6.3±2.63	5.9±6.0	0.2	0.6
Potassium (mEq/L)	4.22±0.54	4.5±0.7	0.5	4.32±0.56	4.4±4.5	0.3	0.6
Sodium (mEq/L)	139.9±2.95	140.4±3.0	0.4	140.2±2.96	140.8±141.0	0.3	0.7
Urinary sodium 24 h	185.5±85.3	177.9±91.7	0.6	180.3±87.4	176.6±159.0	0.5	0.8
Total cholesterol (mg/dL)	181.3±43.4	183.0±42.1	0.8	182.0±34.7	181.6±178.5	1.0	0.9
HDLc cholesterol (mg/dL)	46.94±13.6	45.1±12.8	0.2	45.16±11.8	46.0±45.0	0.7	0.6
LDLc cholesterol mg/dL	99.08±43.5	103.4±39.4	0.4	1020.4±30.6	99.3±95.0	0.6	0.7
Triglycerides (mg/dL)	161.5±115	163.2±108	0.3	178.7±101	166.9±134.5	0.7	0.5
TSH (mIU/L)	2.6±2.03	2.3±1.4	0.1	8.08±31.69	6.4±2.5	0.3	0.3
FT4 µg/dL	1.23±0.24	1.2±0.2	0.8	1.24±0.26	1.3±1.3	0.4	0.9

(*Continued*)

Table 2 (Continued).

	SNB (n=35)		P	DRASB + Bisoprolol (n=37)		P	P - SNB x DRASB
	Before	After		Before	After		
ALT mg/mL	24.30±11.3	21.7±8.3	0.4	25.55±23.2	24.6± 19.5	0.4	0.8
AST mg/mL	22.34±6.43	25.8±15.3	0.6	30.08±36.0	22.4±16.5	0.6	0.2
CPK mg/mL	153.8±108	137.1±73.4	0.1	134.0±59.2	135.7±101.1	0.5	0.3
Hemoglobin g/dL	15.08±6.00	14.6±13.8	0.7	14.03±1.32	13.7±13.8	0.01	0.6
Hematocrit %	41.46±6.56	40.8±41.0	0.2	40.88±3.23	41.1±41.3	0.8	0.6

Abbreviations: SNB, Sequential Nephron Blockade; DRASB, Dual Renin-angiotensin System Blockade + Bisoprolol; eGFR, estimated glomerular filtration rate; HDLc, high density lipoprotein; LDLc, low density lipoprotein cholesterol; TSH, thyroid-stimulating hormone; FT4, free T4; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, Creatine phosphokinase; P, P-value.

Primary Outcome Measures

Office Blood Pressure

Patients in the SNB group had mean decreases from baseline to 20 weeks of 47.5 mmHg (174.5±21.08 to 127.0±14.74 mmHg, respectively, p<0.0001) in SBP and 24.6 mmHg (105.3±15.5 to 78.11±9.28 mmHg, respectively, p<0.0001) in DBP. In the DRASB + bisoprolol group, the corresponding mean reductions were 43.9 mmHg (178.4±21.08 to 134.4±23.25 mmHg, p<0.0001) in SBP and 28.0 mmHg (102.7±11.07 to 77.33±13.75 mmHg, p<0.0001) in DBP from baseline to final visit. No significant difference was found between the two groups for mean SBP (p=0.113) and mean DBP (p=0.779) at the final visit (Table 3).

Both groups presented significant reductions in pulse pressure (ΔPP) from baseline to 20 weeks, 22.29 mmHg (71.48 to 49.01 mmHg, respectively, p<0.0001 in the SNB group and 15.92 mmHg (73.05 to 57.13 mmHg, respectively, p<0.0001) in the DRASB + bisoprolol group. The ΔPP was greater in the SNB compared with the DRASB + bisoprolol group (p=0.019).

Table 3 Office Blood Pressure Results at Baseline (Pre-Intervention), Twelve Weeks and After Treatment (Post-Intervention) in SNB Group and DRASB Group

	SNB (n=35)	DRASB (N =37)	P
Pre-intervention			
SBP mm Hg	174.5±21.08	178.4±21.08	NS
DBP mm Hg	105.3±15.5	102.7±11.07	NS
MBP mm Hg	129.7±17.24	126.8±13.07	NS
PP mm Hg	73.05±15.63	71.88±16.63	NS
HR bpm	79.10±13.40	78.59±11.25	NS
Twelve weeks			
SBP mm Hg	140.1±16.20	151.1±21.45	0.015
DBP mm Hg	84.62±10.22	86.50±12.99	NS
MBP mm Hg	103.1±10.84	108.0±14.83	NS
PP mm Hg	56.30±13.58	64.63±14.36	0.013
HR bpm	76.36±14.99	68.04±11.31	0.010

(*Continued*)

Table 3 (Continued).

	SNB (n=35)	DRASB (N =37)	P
Post-intervention			
SBP mm Hg	127.0±14.74	134.4±23.25	NS
DBP mm Hg	78.11±9.28	77.33±13.75	NS
MBP mm Hg	94.42±10.19	96.51±15.73	NS
PP mm Hg	48.89±10.77	57.13±15.56	0.017
HR bpm	79.37±10.77	66.18±10.27	<0.0001

Abbreviations: SNB, Sequential Nephron Blockade; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; CI, confidence interval; SD, standard deviation; P, P-value. DRASB, Dual Renin-angiotensin System Blockade.

Treatment discontinuation due to drug-related adverse events was not observed in any of the groups.

Secondary Outcome

Results of Ambulatory Blood Pressure Monitoring

The Tables 4 and 5 show the SBP and DBP values during 24-hour ABPM in both groups. The BP values in SNB group were 151.9±18.4 / 93.9 ± 12 mmHg in pre-intervention phase versus 127.3±17.8 / 77.5±10.6 mmHg in post-intervention phase (p<0.0001) (Table 4). The BP values in DRASB + bisoprolol group were 153.3±16.2 / 92.9±13.8 mmHg in pre-intervention phase versus 134.1±26.5 / 74.9±16.3 mmHg in post-intervention phase (p<0.0001) (Table 5).

In the DRASB + bisoprolol group, the office values of SBP <140 mmHg and DBP <90 mmHg were achieved in 85.7% and 88.6% of the participants, respectively. The 24-hour ABPM values of SBP <130 mm Hg and DBP <80 mm Hg were achieved in 64.9% and 67.6% in the DRASB + bisoprolol group, respectively. In the SNB group, office SBP and DBP was achieved in 75.0% and 83.6%, respectively, and the ABPM values in 71.4% and 77.1% of the individuals, respectively (Figure 3).

Discussion

The present results of the ResHypOT trial show that patients with RHTN who fail to control BP levels with standard triple antihypertensive therapy present significant reductions in SBP and DBP 20 weeks after randomization to SNB or DRASB + bisoprolol group.

Table 4 Ambulatory Blood Pressure Monitoring Results at Baseline (Pre-Intervention) and After Treatment (Post-Intervention) in SNB Group

	N	Pre-Intervention				Post-Intervention				P
		Mean	CI 95%	Median	SD	Mean	CI 95%	Median	SD	Pre vs Post
SBP	35	151.9	145.6–158.2	142.0	18.4	127.3	121.2–133.4	123.0	17.8	<0.0001
DBP	35	93.9	88.9–97.1	94.0	12.0	77.5	73.9–81.2	75.0	10.6	<0.0001
MAP	35	114.2	109.7–118.7	112.0	13.1	96.7	92.4–100.9	95.0	12.3	<0.0001
PP	35	58.7	53.7–63.7	56.0	14.5	49.8	45.8–53.8	50.0	11.6	<0.0001
HR	35	80.2	77.4–83.1	80.0	8.3	82.3	78.5–86.1	81.0	11.1	0.29

Abbreviations: SNB, Sequential Nephron Blockade; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; CI, confidence interval; SD, standard deviation; P, P-value.

Table 5 Ambulatory Blood Pressure Monitoring Results at Baseline (Pre-Intervention) and After Treatment (Post-Intervention) in DRASB + Bisoprolol Group

	N	Pre-Intervention				Post-Intervention				P
		Mean	CI 95%	Median	SD	Mean	CI 95%	Median	SD	Pre vs Post
SBP	37	153.3	147.9 −158.7	149.0	16.2	134.1	126.3–141.9	129.0	26.5	<0.0001
DBP	37	92.9	88.2–97.4	92.0	13.8	80.3	74.9–85.7	80.0	16.3	<0.0001
MAP	37	114.8	110.1–119.5	112.0	14.1	101.8	95.8–107.7	103.0	17.9	<0.0001
PP	37	61.5	56.2–66.8	56.0	15.9	54.0	49.1–58.8	50.0	14.4	0.0049
HR	37	78.0	73.8–82.1	85.0	12.4	70.3	67.0–74.0	75.0	9.8	0.0007

Abbreviations: DRASB, Dual Renin-angiotensin System Blockade; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; CI, confidence interval; SD, standard deviation; P, P-value.

Despite standard triple antihypertensive therapy, many patients with RHTN fail to have adequate BP control, and new associations of antihypertensive drugs – some with relative contraindications – are necessary to treat these patients with high cardiovascular risk.[24] The challenge set by the present study was to analyze strategies to increase natriuresis by combining different diuretics that act at various nephron sites, rather than using the usual approach of increasing the dose of a single diuretic that acts only at one site or changing the diuretic class.[25]

Both TZDs and furosemide are effective in reducing BP levels, but high doses of these drugs are poorly tolerated. Other strategies include mineralocorticoid receptor blockade, especially in patients with RHTN, to produce substantial BP reduction when added to other antihypertensive drugs.[26,27] Some studies have shown that diuretics comprise the basis for RHTN treatment, especially mineralocorticoid receptor antagonists, which added to TZDs, have a summative effect in reducing blood pressure.[28–30]

The rationale for SNB using low/moderate doses of diuretics acting at different nephron sites is to neutralize the effects of intrarenal counterregulatory mechanisms that are triggered by the use of diuretics acting at a single site when administrated in high doses for a long time. The expression, transfer, and number of apical sodium transporters located in upstream or downstream segments of the nephron are modified towards stimulation of tubular sodium reabsorption, reducing the long-term efficacy of the diuretic.[31] The doses of each diuretic used in the SNB arm of this trial were low/moderate to avoid risks due to natriuresis, orthostatic hypotension, fatigue, cramps, sexual dysfunction, electrolytic disturbances, and functional renal insufficiency. We selected a low dose of spironolactone (25 mg/day), as used in other RHTN studies.[26]

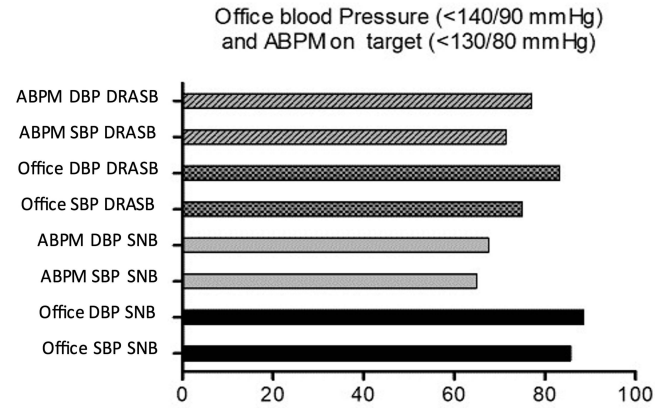

Figure 3 Percentage of patients with resistant hypertension controlled by dual renin-angiotensin blockade + bisoprolol and sequential nephron blockade as determined by ambulatory blood pressure monitoring and office measurements after 20 weeks of treatment.
Abbreviations: ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; DRASB, dual renin-angiotensin system blockade + bisoprolol; SNB - sequential nephron blockade.

Several studies addressing DRASB in patients with non-resistant HTN and diabetes have shown a significant reduction in BP levels and microalbuminuria. However, no additional benefit of DRASB compared to the use of ACEI or ARBs alone was observed in studies including patients with high cardiovascular risk but no RHTN and, in some cases, a significant increase in adverse events was observed.[32–38]

Bobrie et al have shown that the sequential addition of low doses of diuretics acting at different nephron segments increased BP control in 30–58% of the patients in the SNB arm at 12 weeks. In contrast to SNB, DRASB allowed BP control in only 20% of the patients with RHTN. The rationale for using DRASB was to neutralize another counter-regulatory mechanism – renin release – which is triggered by the use of combined ARBs plus TZDs and may limit the antihypertensive efficacy of these agents. A systematic review has shown an additional BP-lowering effect (3–5 mmHg) with dual RAS blockade using ACEIs and ARBs.[39]

Different from their study, our RepHypOT trial extended to 20 weeks. During the initial 1–3 visits, we observed no significant differences in SBP and DBP decrease in the SNB and DRASB + bisoprolol groups. Nonetheless, we found similar results at 12 weeks compared with those reported by Bobrie et al. Significant SBP reduction was observed in the SNB group compared with the DRASB + bisoprolol group at 12 weeks (140.1±16.20 versus 151.1±21.45, p=0.015), but the final measurements at 20 weeks showed no significant difference in SBP and DBP levels between both study groups.

Our results show that a progressive reinforcement of sodium depletion by the SNB strategy offers the possibility of early SBP control, reducing cardiovascular risk. In contrast, DRASB + bisoprolol group achieved the goal after 20 weeks of treatment, suggesting that patients with RHTN are more sensitive to the reinforcement of sodium depletion compared with reinforcement of RAS blockade.

Study Limitations

Even though the ResHypOT trial was not a multicenter study and our data with a small number of patients we showed the impact of SNB on early control of SBP and adds to current knowledge of this new strategy for BP control. Future multicentric studies are necessary to determine the potential positive effects of both strategies in relation to cardiovascular events, mortality, target-organ damage, and biomarkers like pulse wave velocity, arterial stiffness, carotid intima-media thickness, and renal dysfunction.

Conclusion

In patients with RHTN adherent to treatment, both SNB and DRASB plus bisoprolol showed excellent therapeutic efficacy, although SNB showed earlier and greater SBP reduction.

Abbreviations

ABPM, ambulatory blood pressure monitoring; ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, Blood Pressure; CCB, Calcium-channel blocker; C_RHTN, controlled RHTN; DBP, diastolic blood pressure; DRASB, dual renin-angiotensin system blockade; SBP, systolic blood pressure; MAP, Mean arterial pressure; HDLc, high density lipoprotein cholesterol; HR, Heart Rate; HTN, Hypertension; LDLc, low density lipoprotein cholesterol; PP, Pulse Pressure; RAS, Renin-angiotensin system; Resistant Arterial Hypertension; ReHOT, The ReHOT Randomized Study (Resistant Hypertension Optimal Treatment).; ResHypOT, Sequential Blockade vs Dual Blockade Renin-angiotensin System + Bisoprolol in; RHTN, Resistant Hypertension; SNB, sequential nephron blockade; TC, Total Cholesterol; TZD, thiazide diuretic.

Academic Link

This study is part of the Doctoral's thesis by Cestario EES.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on a reasonable request.

Consent Statement

Approval was obtained from the Research Ethics Committee of the State Medical School at Sao Jose do Rio Preto (FAMERP) according to national and international guidelines. The authors declare that this research complies with the privacy of the participants, with the data maintained anonymous and confidential. The current study was performed according to the ethical standards of the Helsinki Declaration.

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Disclosure

The authors declare no conflict of interest.

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