Original Article

The effects of nebivolol and irbesartan on postdialysis and ambulatory blood pressure in patients with intradialytic hypertension: a randomized cross-over study

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Objectives: Intradialytic hypertension is estimated at 5–15% of hemodialysis patients and is associated with poor prognosis. Studies on therapeutic interventions for this entity are extremely few. We aimed to evaluate the effects of nebivolol and irbesartan on peridialytic, intradialytic, and ambulatory BP in patients with intradialytic hypertension.

Methods: This is a pilot randomized-cross-over study in 38 hemodialysis patients (age: 60.4 ± 11.1 years, men: 65.8%) with intradialytic hypertension (intradialytic SBP rise ≥10 mmHg at ≥4 over six consecutive sessions]. After baseline evaluation, patients were randomly assigned to nebivolol 5 mg and subsequently irbesartan 150 mg, or vice versa. Nineteen patients received a single drug-dose 1 h before hemodialysis and 19 received the drug for a week before evaluation. A 2-week wash-out period took place before the initiation of the second drug. Patients had three respective 24-h ambulatory BP measurements starting before a midweek session.

Results: In total, 20 (52.6%) patients received nebivolol first and 18 (47.4%) received irbesartan. Patients receiving a single dose of either drug had lower postdialysis BP (baseline: 160.2 ± 17.8/93.2 ± 13.6 mmHg; nebivolol: 148.0 ± 20.8/84.5 ± 13.1 mmHg, $P = 0.013$/$P = 0.027$; irbesartan 142.9 ± 29.9/87.2 ± 18.1 mmHg, $P = 0.003$/$P = 0.104$ for SBP and DBP, respectively). The 24-h BP presented a trend towards reduction, but was significant only for 24-h DBP in the nebivolol arm. Patients on weekly administration of either drug had lower postdialysis BP (baseline: 162.5 ± 16.8/95.4 ± 12.7 mmHg; nebivolol: 146.7 ± 16.3/91.8 ± 12.2 mmHg, $P = 0.001$/$P = 0.235$; irbesartan: 146.0 ± 23.9/85.8 ± 12.9 mmHg, $P = 0.004$/$P = 0.007$, respectively), lower intradialytic BP and lower 24-h BP (baseline: 148.3 ± 12.6/90.2 ± 9.0 mmHg; nebivolol: 139.2 ± 10.6/85.0 ± 7.7 mmHg, $P < 0.001$/$P = 0.001$; irbesartan: 142.4 ± 16.4/85.1 ± 9.9 mmHg, $P = 0.156$/$P = 0.030$). No significant differences were observed in comparisons between the two drugs, with the exception of heart rate, being lower with nebivolol.

Conclusion: Both nebivolol and irbesartan reduced postdialysis and 24-h BP in patients with intradialytic hypertension. Weekly administration had greater effect and nebivolol was numerically slightly more potent than irbesartan.

Keywords: ambulatory blood pressure monitoring, hemodialysis, intradialytic hypertension, irbesartan, nebivolol

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEIs, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; CLIA, chemiluminescence immunoassay; ESRD, end-stage renal disease; NO, nitric oxide; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation; SNS, sympathetic nervous system

INTRODUCTION

Hypertension is highly prevalent in patients with end-stage-renal-disease (ESRD) undergoing hemodialysis, with prevalence being estimated at 72–88% based on different definitions [1]. Blood pressure (BP) levels are highly variable in hemodialysis, with the majority of patients presenting a particular pattern of BP changes during intradialytic and interdialytic periods; that is, progressive increase in BP during the interdialytic interval and rapid

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decrease during the dialysis session following sodium and water accumulation and removal, respectively [2,3]. However, about 5–15% of the hemodialysis patients present an abnormal hemodynamic response to ultrafiltration, with BP rising during or immediately after sessions, a phenomenon known as 'intradialytic hypertension' [4,5]. Importantly, large cohort studies suggest that the presence of intradialytic hypertension is strongly associated with increased risk of all-cause and cardiovascular mortality [6–8].

The pathophysiology of intradialytic hypertension is complex and not fully elucidated [5]. Within the frame of increased cardiac output and/or increased peripheral vascular resistance, several mechanisms have been proposed to cause BP rise during hemodialysis, including, sympathetic nervous system (SNS) overdrive, excess renin–angiotensin–aldosterone system (RAAS) activation stimulated by acute volume removal with the ultrafiltration, abnormal endothelial response leading to endothelin-1 production and nitric oxide (NO) decrease, intradialytic sodium gain, acute drop in dialyzable antihypertensive drug levels during sessions, or even inability to achieve optimal dry weight associated with chronic volume overload [5,9].

The management of hypertension in hemodialysis patients is a complicated process, and becomes even more difficult in those with intradialytic hypertension [5,10]. So far, only few studies have been specifically designed to evaluate therapeutic interventions for the management of intradialytic hypertension. An earlier uncontrolled trial in six patients with intradialytic hypertension suggest that single-dose administration of 60 mg captopril before dialysis attenuated the BP rise during session [11]. A randomized cross-over study of 16 patients with intradialytic hypertension, showed that prescription of low versus high dialysate sodium (5 mEq/l lower or higher than serum sodium, respectively) was associated with a significant reduction of 9.9 mmHg in the weekly average of intradialytic SBP [12]. In another nonrandomized study in 25 patients with intradialytic hypertension, 12-week treatment with carvedilol was associated with reduced occurrence of intradialytic hypertensive episodes and with a significant fall 7 mmHg in 44-h ambulatory SBP [13]. Thus, this study aimed to evaluate the effects of a single or weekly administration of nebivolol and irbesartan in peridialytic, intradialytic, and ambulatory BP.

MATERIALS AND METHODS

Study population

Patients receiving maintenance hemodialysis therapy in seven Hemodialysis Units of northern Greece were screened for intradialytic hypertension. Intradialytic hypertension was diagnosed on the basis of intradialytic rise at least 10 mmHg in SBP in at least four over six consecutive hemodialysis sessions. Adult (>18 years) patients with ESRD treated with thrice-weekly maintenance hemodialysis for more than 3 months with intradialytic hypertension were invited to participate in this study. Exclusion criteria consisted of: existing comorbidity requiring treatment with RAAS-blockers or β-blockers (i.e. congestive heart failure, previous acute myocardial infraction, angina pectoris, cardiac arrhythmia or secondary hypertension because of renal artery stenosis, etc.); existing contraindications to receive the aforementioned drug classes (i.e. history of hyperkalemia, angioedema, nondrug-related bradyarrhythmia, asthma, anaphylactic, or allergic reaction); antihypertensive treatment with RAAS-blockers or β-blockers during 1 month prior to study enrollment; prehemodialysis or posthemodialysis SBP levels less than 130 mmHg in four out of six sessions during the 2 weeks of the diagnosis of intradialytic hypertension; nonfunctional arteriovenous fistula in the contralateral arm of the one used as vascular access for the hemodialysis session that could interfere with ABPM; active malignant disease or other advanced noncardiac comorbidity resulting in poor prognosis. The study protocol was approved by the Ethics Committee of School of Medicine, Aristotle University of Thessaloniki, and all participants provided informed written consent prior to study enrollment. All evaluations were performed according to the declaration of Helsinki (2013 Amendment). The study is registered with the ISRCTN registry (http://www.isrctn.com, Nr 13587185).

Study protocol

The current study followed a single-blind randomized cross-over design. Baseline evaluation included recording of demographics, anthropometric characteristics, cause of ESRD, comorbidities, concomitant medications, dialysis-related parameters, and a detailed physical examination. After baseline evaluation, patients were randomly assigned to two different sequences of drug intake: sequence 'a' – nebivolol 5 mg, 2-week washout period, irbesartan 150 mg and sequence 'b' – irbesartan 150 mg, 2-week washout period, nebivolol 5 mg. In addition, two modes of drug administration were prespecified in order to study the ability of administered agents to reduce BP when dosed acutely or not. Patients were not randomized between modes of administration. The first 19 among consecutive patients entering the study in each unit received a single drug-dose 1 h prior to dialysis session. The remaining 19 patients received the drug for a whole week before evaluation. Patients were unaware of the sequence and the specific substance of the two drugs given. For the single-drug study, all tablets were administered by a single investigator, 1 h before the start of each hemodialysis session. For the weekly dosing, participants were supplied with seven tablets of each studied drug, which were to be taken at the same time of each day, matching the clock time of 1 h before the start of dialysis.

Each participant was evaluated on three different occasions, starting prior to a mid-week week hemodialysis session (e.g. the second weekly session, Wednesday or Thursday). The study design diagram presenting the chronologic order of the three evaluations is presented in Fig. 1. The first was the baseline evaluation. A period of 1 week took place between baseline and the second evaluation, that with the first drug. A 2-week wash-out period took place before the initiation of the second drug in both occasions. Thus, participants with the single drug intake were evaluated again 2 weeks after the second evaluation (total study time 3 weeks), whereas participants with the weekly drug intake, started the relevant drug after the 2-week wash-out period and evaluated after another week

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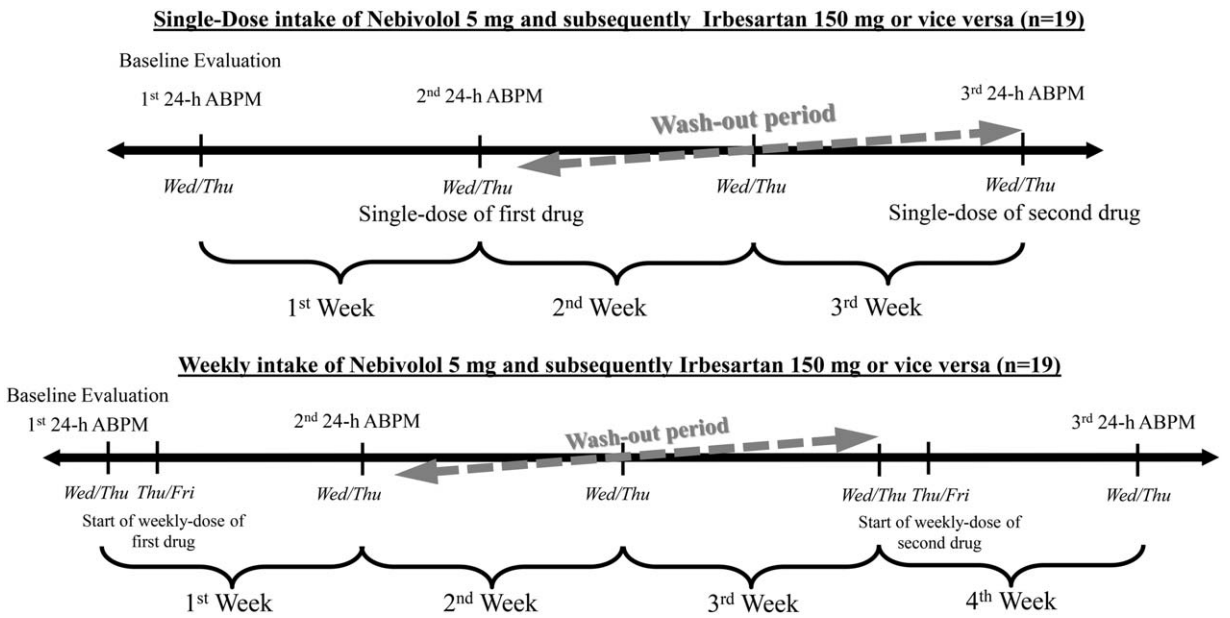

FIGURE 1 Study design diagram presenting the chronologic order of the evaluations in the (a) single-dose and in the (b) weekly dose study groups.

(total study time 4 weeks). During the study periods, dry weight probing or changes in other cardiovascular medications were not allowed.

At baseline, study participants were instructed to arrive at their Hemodialysis Unit 1 h before their session for their initial evaluation. At the end of this evaluation and the following occasions, predialysis and postdialysis BP measurements were obtained with the patient in the sitting position in their dialysis chair for at least 5 min directly before needling and dialysis start and directly after dialysis end. A validated oscillometric device was used to perform BP measurements, at the level of brachial artery in the nonfistula arm. On each occasion two measurements 2 min apart were taken, according to the current guidelines [14]. Predialysis blood specimens were acquired for routine hematological and biochemical laboratory testing. Predialysis and postdialysis blood specimens were obtained for the evaluation of plasma renin activity (PRA), serum aldosterone, adrenaline, and noradrenaline. After blood sampling, all patients started the 24-h ambulatory BP monitoring (ABPM). All participants underwent their regular hemodialysis session, during which volume withdrawal was programmed based on their prespecified dry weight, which was defined in detail up to the previous session by their treating physicians according to standard clinical criteria and, if necessary, the use of bioimpedance analysis [15]. Dialysate conductivity was also predefined by treating physicians based on patient characteristics. Dry weight, dialysate conductivity, and background antihypertensive medications were not altered during course of the study.

Ambulatory blood pressure monitoring

Ambulatory BP was performed with the Mobil-O-Graph NG (IEM, Stolberg, Germany), an oscillometric device, whose brachial BP-detection unit was validated according to standard protocols [16,17] and was shown to provide practically identical values with a widely used ABPM monitor [18]. ABPM started before the mid-week session with a cuff of appropriate size fitted in the nonfistula arm and lasted for 24 h. Patients were specifically instructed to follow their usual activities and maintain their usual interdialytic weight gain until the next session. The device was monitoring BP every 20 min during the day time (0700–2300 h) and every 30 min during the night-time (2300–0700 h). Measurements were used for the analysis if more than 80% of recordings were valid with two or less nonconsecutive day-hours with less than two valid measurements, and one or less night-hour without valid recording [19]. Patients with invalid measurements were invited to undertake the ABPM again in another week. In order to minimize the possible effect of manual BP measurements, only measurements recorded at the prespecified time intervals at which the device was set to take measurements were used in this analysis.

Laboratory analyses

Routine hematological and biochemical parameters were measured with standard laboratory methods. For the determination of circulatory markers of RAAS and SNS activity under study blood samples were drawn under a standard process and were delivered to the laboratory for immediate serum and plasma extraction using a standard and a refrigerated centrifuge device accordingly. The supernatants were stored at −70 °C until the quantitative determination of parameters under study. PRA and aldosterone levels were measured with the method of chemiluminescence immunoassay (CLIA) using commercially available kits (Shenzhen-New-Industries-Biomedical-Engineering, Shenzhen, China and DiaSorin Inc., Stillwater, Minnesota, USA, respectively). Adrenaline and noradrenaline levels were measured with the method of competitive enzyme-linked immunoassay using a commercially available ELISA kit (Labor-Diagnistika-Nord, Nordhorn, Germany).

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Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences 23 (SPSS Inc, Chicago, Illinois, USA). Continuous variables are expressed as mean values ± standstandard deviation (SD) or median [interquartile range] according to the normality of distribution with Shapiro–Wilk test. Categorical variables are presented as absolute frequencies and percentages (*n*, %). Comparisons for continuous variables were performed with the paired Student *t*-test or Wilcoxon's signed rank test, according to the normality of the distribution. Probability values of $P < 0.05$ (two-tailed) were considered statistically significant for all comparisons.

RESULTS

Baseline characteristics

The baseline demographic, clinical, and laboratory characteristics of the total study population and the subgroups studied (single dose and weekly dose) are presented in Table 1. A total of 38 hemodialysis patients (25 men and 13 women) with mean age 60.7 ± 11.1 years and mean dialysis vintage 37.3 ± 36.0 months were included in this study. After baseline evaluation, 20 (52.6%) patients were randomized to receive irbesartan first and 18 (47.4%) received nebivolol first. With regards to the existing cardiovascular risk factors and comorbidities, 26.3% had diabetes, 23.7% dyslipidemia, 5.3% peripheral vascular disease, 13.2% coronary heart disease, 7.9% heart failure, 5.3% history of stroke, and 23.7% were smokers. As expected by the exclusion criteria, none of the participants was receiving RAAS or β-blockers, whereas 97.4% were receiving calcium channel blockers (CCBs), 57.9% loop diuretics, and 50% centrally active antihypertensive drugs.

Blood pressure changes with a single dose of nebivolol or irbesartan

The BP changes achieved with nebivolol and irbesartan treatment are shown in Table 2 and Fig. 2. Patients receiving a single dose of nebivolol had lower posthemodialysis SBP and DBP (baseline: 160.2 ± 17.8/93.2 ± 13.6 mmHg; nebivolol: 148.0 ± 20.8/84.5 ± 13.1 mmHg, $P = 0.013$ for SBP and $P = 0.027$ for DBP) A single dose of nebivolol reduced nonsignificantly intradialytic BP and produced nonsignificantly lower 24-h SBP and significantly lower 24-h DBP (baseline: 147.7 ± 16.0/87.6 ± 11.9 mmHg; nebivolol: 144.3 ± 19.5/83.6 ± 11.7 mmHg, $P = 0.164$ and $P = 0.019$ for SBP and DBP). Patients receiving a single irbesartan dose had lower posthemodialysis SBP and insignificantly lower posthemodialysis DBP (142.9 ± 29.9/87.2 ± 18.1 mmHg, $P = 0.003$ and $P = 0.104$ for SBP and DBP, respectively. Intradialytic BP was nonsignificantly reduced with a single dose of irbesartan; 24-h SBP and DBP were also nonsignificantly reduced (143.2 ± 21.7/85.0 ± 12.7 mmHg, $P = 0.147$ and $P = 0.126$), as shown in Table 2 and Fig. 2a. BP changes during the 20-h out-of dialysis period were of similar significance with these for the total 24-h period. Importantly, no significant differences

TABLE 1. Baseline demographic, anthropometric, clinical and routine laboratory characteristics of the study participants

Characteristic	Whole population	Single intake	Weekly intake
N	38	19	19
Age (years)	60.7 ± 11.1	59.3 ± 10.6	62.1 ± 11.7
Female (*n*, %)	13 (34.2)	7 (36.8)	6 (31.6)
Weight (kg)	66.5 ± 14.1	66.5 ± 13.8	66.4 ± 14.8
Height (cm)	167.4 ± 8.8	166.7 ± 8.4	168.2 ± 9.3
BMI (kg/m^2)	23.6 ± 3.9	23.8 ± 4.2	23.3 ± 3.6
Dialysis vintage (months)	37.3 ± 36.0	47.7 ± 41.8	26.8 ± 26.0
Diabetes mellitus (*n*, %)	10 (26.3)	7 (36.8)	3 (15.8)
Dyslipidemia (*n*, %)	9 (23.7)	7 (36.8)	2 (10.5)
Peripheral vascular disease (*n*, %)	2 (5.3)	2 (10.5)	0 (0)
Coronary heart disease (*n*, %)	5 (13.2)	2 (10.5)	3 (15.8)
Heart failure (*n*, %)	3 (7.9)	2 (10.5)	1 (5.3)
History of stroke (*n*, %)	2 (5.3)	1 (5.3)	1 (5.3)
Smoking history, (*n*, %)	9 (23.7)	3 (15.8)	6 (31.6)
Hemoglobin (g/dl)	11.21 ± 1.05	10.86 ± 1.10	11.55 ± 0.91
Serum urea (mg/dl)	137.0 ± 40.1	138.3 ± 42.1	135.6 ± 39.2
Serum creatinine (mg/dl)	8.29 ± 2.27	8.95 ± 2.73	7.62 ± 1.50
Serum sodium	138.6 ± 2.7	138.4 ± 2.8	138.8 ± 2.7
Serum potassium	4.97 ± 0.66	5.28 ± 0.67	4.67 ± 0.51
Serum calcium (mg/dl)	8.9 ± 0.7	8.9 ± 0.7	8.9 ± 0.7
Serum phosphate (mg/dl)	5.2 ± 1.4	5.3 ± 1.5	5.0 ± 1.4
Parathormone (ng/l)	233.0 [204.0]	269.0 [230.0]	216.0 [157.0]
Albumin (g/dl)	4.1 ± 0.4	4.1 ± 0.4	4.2 ± 0.4
Dialysate conductivity (ms/cm)	14.0 [0.2]	13.9 [0.2]	13.9 [0.2]
CCBs (*n*, %)	37 (97.4%)	18 (94.7%)	19 (100%)
Loop diuretics (*n*, %)	22 (57.9%)	9 (47.4%)	13 (68.4%)
Centrally active drugs (*n*, %)	19 (50%)	10 (52.6%)	9 (47.4%)
Statins (*n*, %)	18 (47,4%)	11 (57.9%)	7 (36.8%)
EPO (*n*, %)	36 (94,7%)	18 (94.7%)	18 (94.7%)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; RAAS, renin–angiotensin–aldosterone system.

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TABLE 2. Comparisons for peridialytic and ambulatory blood pressure between baseline and nebivolol or irbesartan intake for patients receiving (a) single-dose or (b) weekly treatment

Parameter	Baseline	Nebivolol	P^a	Irbesartan	P^b	P^c
(a) Single-dose intake ($n=19$)						
Prehemodialysis SBP (mmHg)	145.4 ± 17.0	151.1 ± 23.5	0.073	151.5 ± 23.7	0.107	0.910
Posthemodialysis SBP (mmHg)	160.2 ± 17.8	148.0 ± 20.8	0.013	142.9 ± 29.9	0.003	0.235
Intradialytic SBP (mmHg)	147.0 ± 16.9	142.8 ± 17.9	0.165	142.7 ± 25.0	0.349	0.445
20-h SBP (mmHg)	147.6 ± 16.9	144.4 ± 21.0	0.202	143.2 ± 21.9	0.205	0.715
24-h SBP (mmHg)	147.7 ± 16.0	144.3 ± 19.5	0.164	143.2 ± 21.7	0.147	0.469
Prehemodialysis DBP (mmHg)	88.8 ± 13.4	92.6 ± 14.5	0.081	91.1 ± 11.0	0.461	0.620
Posthemodialysis DBP (mmHg)	93.2 ± 13.6	84.5 ± 13.1	0.027	87.2 ± 18.1	0.104	0.463
Intradialytic DBP (mmHg)	88.3 ± 13.0	85.2 ± 11.8	0.116	85.4 ± 12.4	0.274	0.908
20-h DBP (mmHg)	87.3 ± 11.9	83.1 ± 12.1	0.016	84.6 ± 13.4	0.106	0.397
24-h DBP (mmHg)	87.6 ± 11.9	83.6 ± 11.7	0.019	85.0 ± 12.7	0.126	0.378
Intradialytic HR (bpm)	71.6 ± 8.1	68.4 ± 4.8	0.110	70.1 ± 7.4	0.497	0.290
24-h HR (bpm)	73.1 ± 7.9	67.7 ± 5.4	0.005	72.2 ± 7.1	0.593	<0.001
Intradialytic weight loss (kg)	2.05 ± 0.90	2.30 ± 1.07	0.059	2.29 ± 0.99	0.122	0.930
Interdialytic weight gain (kg)	2.16 ± 0.85	2.29 ± 0.99	0.188	2.36 ± 1.06	0.204	0.574
(b) Weekly intake ($n=19$)						
Prehemodialysis SBP (mmHg)	148.7 ± 19.1	146.4 ± 20.3	0.372	146.5 ± 23.8	0.507	0.920
Posthemodialysis SBP (mmHg)	162.5 ± 16.8	146.7 ± 16.3	0.001	146.0 ± 23.9	0.004	0.912
Intradialytic SBP (mmHg)	149.2 ± 15.3	141.3 ± 13.4	0.011	145.1 ± 19.2	0.376	0.283
20-h SBP (mmHg)	146.9 ± 14.3	138.5 ± 11.4	0.004	141.5 ± 17.2	0.232	0.410
24-h SBP (mmHg)	148.3 ± 12.6	139.2 ± 10.6	<0.001	142.4 ± 16.4	0.156	0.351
Prehemodialysis DBP (mmHg)	90.6 ± 11.6	89.4 ± 12.5	0.649	91.1 ± 11.3	0.895	0.609
Posthemodialysis DBP (mmHg)	95.4 ± 12.7	91.8 ± 12.2	0.235	85.8 ± 12.9	0.007	0.107
Intradialytic DBP (mmHg)	93.8 ± 11.2	87.0 ± 10.1	0.005	87.8 ± 9.4	0.017	0.726
20-h DBP (mmHg)	89.2 ± 9.3	84.3 ± 7.6	0.006	84.2 ± 11.1	0.061	0.940
24-h DBP (mmHg)	90.2 ± 9.0	85.0 ± 7.7	0.001	85.1 ± 9.9	0.030	0.975
Intradialytic HR (bpm)	73.2 ± 12.6	65.7 ± 10.9	0.033	69.6 ± 11.7	0.155	0.038
24-h HR (bpm)	72.1 ± 8.9	66.3 ± 9.9	0.016	69.9 ± 11.3	0.204	0.005
Intradialytic weight loss (kg)	1.64 ± 0.78	1.72 ± 0.85	0.586	1.86 ± 0.92	0.113	0.351
Interdialytic weight gain (kg)	1.71 ± 0.90	1.89 ± 0.80	0.209	1.95 ± 0.99	0.051	0.685

[a]*P*-values for comparisons between baseline versus nebivolol intake.
[b]*P*-values for comparisons between baseline versus irbesartan intake.
[c]*P*-values for comparisons between nebivolol and irbesartan.

on the magnitude of BP reduction between the two drug groups were observed in any of the periods studied (Fig. 3a). In contrast, as expected 24-h heart rate was significantly lower with nebivolol. Finally, as shown in Table 2, intradialytic weight loss and interdialytic weight gain were similar between baseline, nebivolol, and irbesartan administration.

Blood pressure changes after weekly administration of nebivolol or irbesartan

Patients on a weekly administration of nebivolol had significantly lower posthemodialysis SBP and nonsignificantly lower posthemodialysis DBP compared with baseline (baseline: 162.5 ± 16.8/95.4 ± 12.7 mmHg; nebivolol: 146.7 ± 16.3/91.8 ± 12.2 mmHg, $P=0.001$ and $P=0.235$; Table 2). Intradialytic BP was significantly reduced with nebivolol, and this was the case with 24-h SBP and DBP (baseline: 148.3 ± 12.6/90.2 ± 9.0 mmHg; nebivolol: 139.2 ± 10.6/85.0 ± 7.7 mmHg, $P<0.001$ and $P=0.001$, respectively). Patients on a weekly administration of irbesartan had significantly lower posthemodialysis SBP and DBP (146.0 ± 23.9/85.8 ± 12.9 mmHg, $P=0.004$ and $P=0.007$), and significantly lower intradialytic DBP compared with baseline. The 24-h SBP was nonsignificantly reduced but 24-h DBP was significantly reduced with a week of irbesartan treatment (142.4 ± 16.4/85.1 ± 9.89 mmHg, $P=0.156$ and $P=0.030$, respectively; Table 2 and Fig. 2b). As above, BP changes during the 20-h period were of similar significance with these for the 24-h and no significant differences on the magnitude of BP reduction between the two drugs were noted (Fig. 3b). The 24-h heart rate was again significantly lower with nebivolol. Intradialytic weight loss and interdialytic weight gain were again similar in the three study occasions.

Daytime and night-time blood pressure changes

In Table 3, differences in ambulatory BP during daytime and night-time periods are presented. Daytime ambulatory SBP and DBP (including the hemodialysis period) were lower for patients receiving either a single dose or weekly administration of nebivolol compared with baseline. In contrast, night-time SBP and DBP were significantly lower only for patients receiving a weekly dose of nebivolol. For irbesartan, daytime and night-time SBP was nonsignificantly reduced after single or weekly administration; daytime and night-time DBP were significantly reduced only with weekly administration. Heart rate was significantly lower with nebivolol in all periods studied, with the exception of the intradialytic period in patients on a single dose of drugs.

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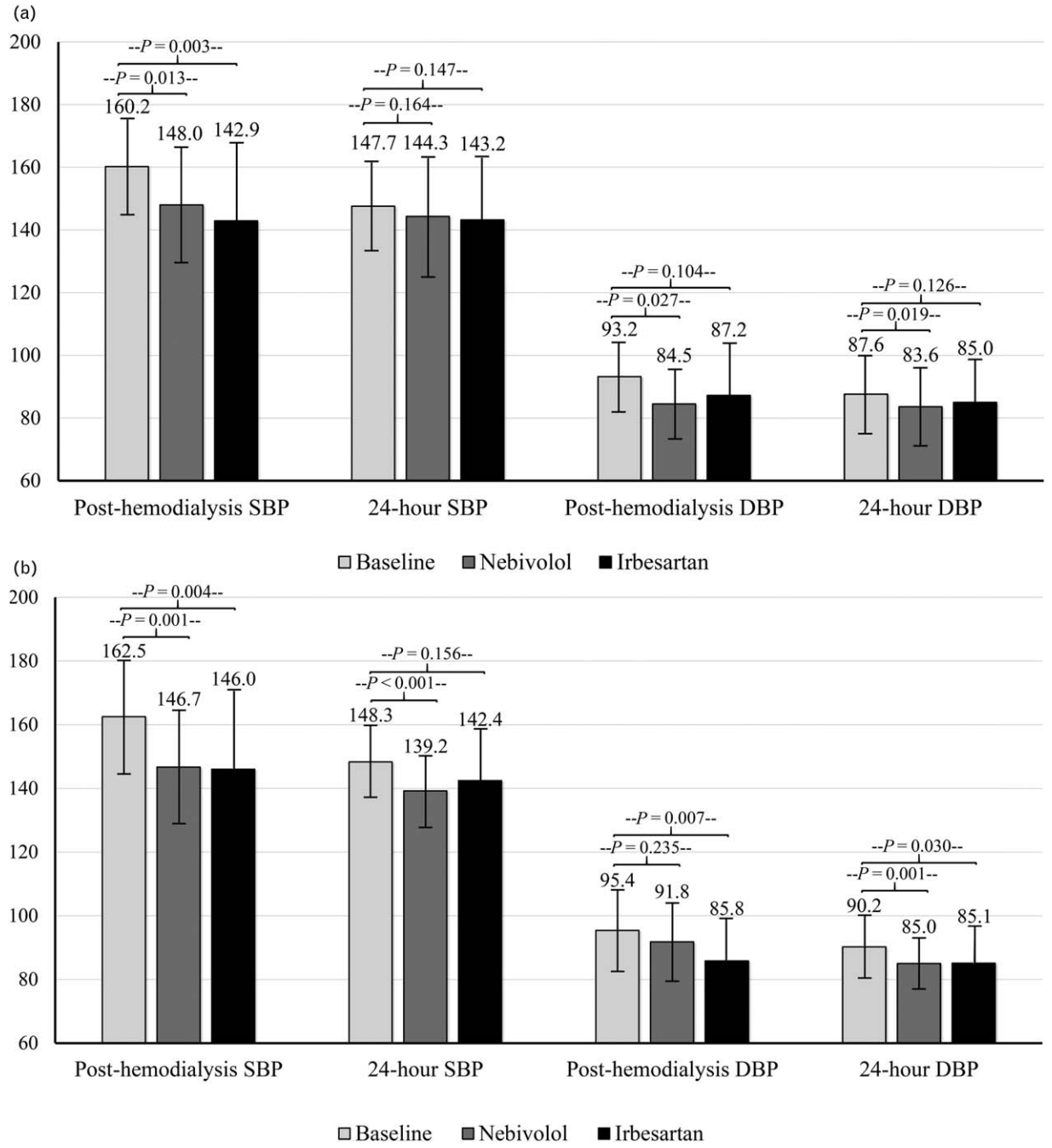

FIGURE 2 Comparisons for posthemodialysis and 24-h blood pressure in patients receiving (a) single-dose and (b) weekly dose of either nebivolol or irbesartan.

Changes in circulatory markers of renin–angiotensin–aldosterone system and sympathetic nervous system activity during a standard hemodialysis session and during nebivolol or irbesartan administration

Table 4 presents the changes in adrenaline, noradrenaline, PRA, and aldosterone levels during a standard hemodialysis session and during single or weekly nebivolol or irbesartan administration. Patients receiving a single-dose of drugs, during baseline hemodialysis had almost significantly decreased posthemodialysis adrenaline levels and similar levels of all other markers compared with prehemodialysis. During nebivolol administration, patients presented similar prehemodialysis and posthemodialysis adrenaline, noradrenaline and PRA levels, whereas aldosterone levels were significantly reduced (14.60 [18.80] vs 7.90 [15.15] ng/l, $P = 0.003$). A single-dose treatment with irbesartan significantly decreased posthemodialysis noradrenaline and increased PRA levels (124.50 [227.83] versus 74.00 [87.00] ng/l, $P = 0.010$ and 1.69 ± 1.39 versus 3.13 ± 4.02 ng/ml per h, $P = 0.012$).

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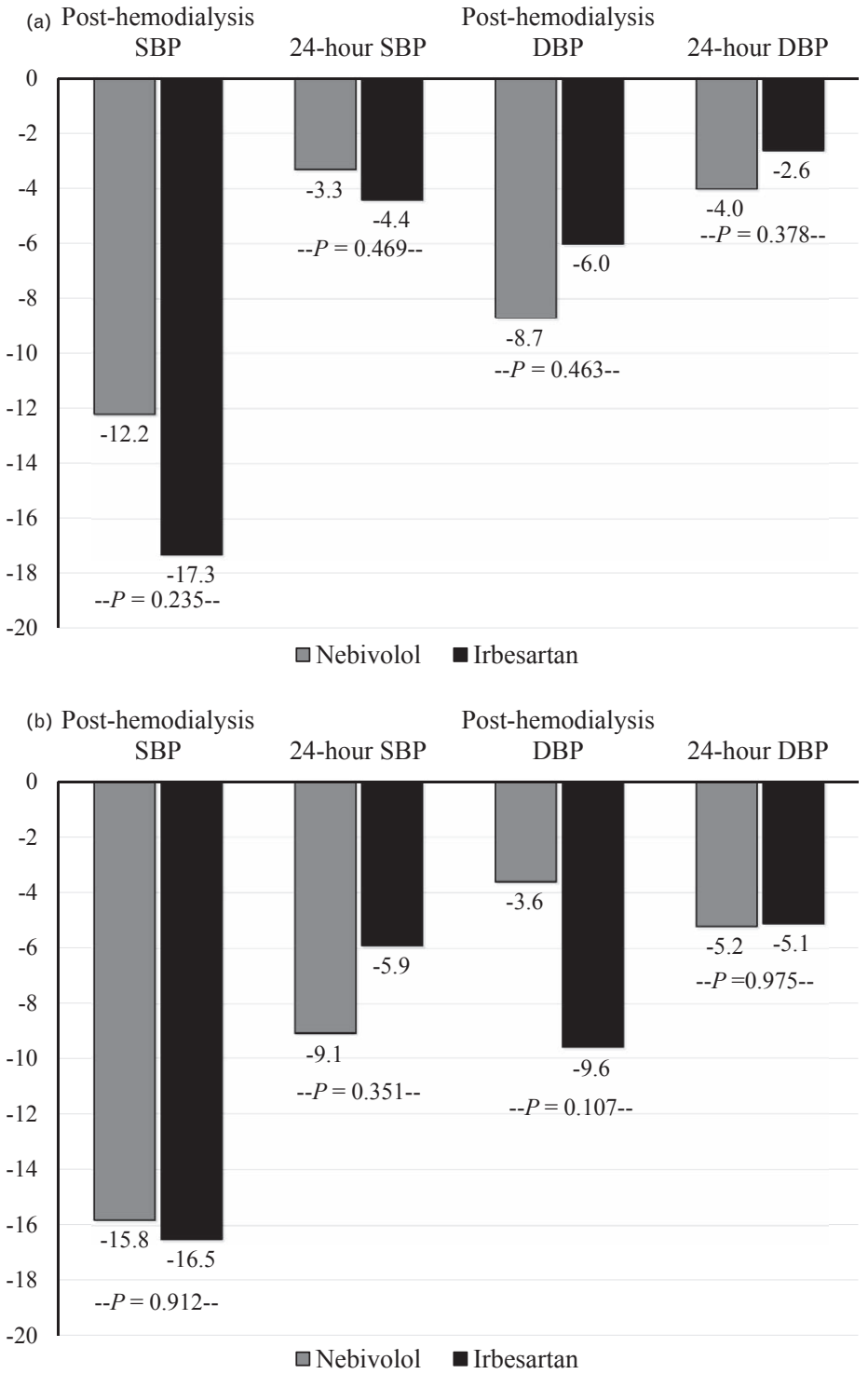

FIGURE 3 Between-drug comparisons of the changes in posthemodialysis and 24-h BP in patients receiving (a) single-dose and (b) weekly dose of either nebivolol or irbesartan.

For patients allocated in the weekly treatment study group, baseline hemodialysis yielded similar adrenaline and noradrenaline, and significantly lower posthemodialysis aldosterone levels compared with prehemodialysis. Weekly treatment with nebivolol resulted in significantly lower posthemodialysis noradrenaline levels (15.90 [53.30] versus 14.90 [66.30] ng/l, $P = 0.027$), and no other significant changes. Finally, weekly treatment with irbesartan was associated with significant reduction of aldosterone levels from prehemodialysis to posthemodialysis (15.60 [29.10] versus 8.00 [25.10] ng/l, $P = 0.042$).

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TABLE 3. Comparisons for hemodialysis, daytime and night-time blood pressure levels between baseline and nebivolol or irbesartan intake for patients receiving (a) single-dose or (b) weekly treatment

Parameter	Baseline	Nebivolol	P^a	Irbesartan	P^b	P^c
(a) Single-dose intake ($n = 19$)						
Day-time SBP without hemodialysis (mmHg)	148.2 ± 16.7	144.7 ± 21.4	0.158	143.6 ± 22.8	0.212	0.601
Day-time SBP with hemodialysis (mmHg)	148.0 ± 15.8	144.6 ± 19.7	0.036	143.7 ± 22.4	0.171	0.520
Night-time SBP (mmHg)	146.6 ± 19.5	142.9 ± 21.0	0.270	141.7 ± 21.7	0.183	0.675
Day-time DBP without hemodialysis (mmHg)	88.0 ± 11.7	83.6 ± 12.9	0.016	84.9 ± 14.1	0.113	0.601
Day-time DBP with hemodialysis (mmHg)	88.2 ± 11.9	84.2 ± 12.2	0.021	85.3 ± 13.1	0.113	0.520
Night-time DBP (mmHg)	85.9 ± 13.3	81.8 ± 11.3	0.059	84.4 ± 13.2	0.198	0.675
Day-time HR without hemodialysis (bpm)	75.6 ± 9.2	68.9 ± 6.4	0.001	73.0 ± 8.0	0.226	0.001
Night-time HR (bpm)	68.5 ± 7.7	64.7 ± 6.3	0.038	70.3 ± 6.5	0.367	<0.001
(b) Weekly intake ($n = 19$)						
Day-time SBP without hemodialysis (mmHg)	149.2 ± 14.6	139.5 ± 12.0	0.002	143.6 ± 17.5	0.236	0.316
Day-time SBP with hemodialysis (mmHg)	149.4 ± 13.0	140.1 ± 10.6	0.001	144.4 ± 16.3	0.241	0.261
Night-time SBP (mmHg)	144.0 ± 14.5	136.4 ± 12.9	0.004	137.1 ± 18.4	0.110	0.860
Day-time DBP without hemodialysis (mmHg)	91.00 ± 9.5	84.9 ± 8.7	0.001	85.2 ± 11.3	0.038	0.908
Day-time DBP with hemodialysis (mmHg)	91.5 ± 9.3	85.6 ± 8.5	0.001	86.2 ± 9.7	0.030	0.805
Night-time DBP (mmHg)	89.7 ± 15.6	83.3 ± 6.6	0.030	82.1 ± 11.9	0.040	0.637
Day-time HR without hemodialysis (bpm)	73.9 ± 9.4	68.1 ± 10.9	0.021	70.5 ± 11.7	0.083	0.093
Night-time HR (bpm)	68.2 ± 7.2	62.7 ± 8.2	0.004	68.2 ± 11.5	0.993	0.001

[a]*P* values for comparisons between baseline versus nebivolol intake.
[b]*P* values for comparisons between baseline versus irbesartan intake.
[c]*P* values for comparisons between nebivolol and irbesartan intake.

TABLE 4. Comparisons between prehemodialysis and posthemodialysis values of adrenaline, noradrenaline, plasma renin activity, and aldosterone at the three time-point evaluations for patients receiving (a) single-dose or (b) weekly treatment

(a) Single-dose treatment

Parameter	Prehemodialysis	Posthemodialysis	*P* value
Baseline			
Adrenaline (ng/l)	59.50 [33.72]	42.00 [43.65]	0.051
Noradrenaline (ng/l)	99.25 [290.53]	80.00 [135.85]	0.248
PRA (ng/ml per h)	1.84 ± 1.31	1.85 ± 2.03	0.275
Aldosterone (ng/l)	11.85 [18.95]	8.27 [21.47]	0.170
Nebivolol			
Adrenaline (ng/l)	49.90 [56.78]	50.00 [44.25]	0.266
Noradrenaline (ng/l)	85.00 [187.40]	71.60 [80.25]	0.170
PRA (ng/ml per h)	1.94 ± 1.47	2.06 ± 2.03	0.955
Aldosterone (ng/l)	14.60 [18.80]	7.90 [15.15]	0.003
Irbesartan			
Adrenaline (ng/l)	42.30 [67.03]	41.95 [41.53]	0.725
Noradrenaline (ng/l)	124.50 [227.83]	74.00 [87.00]	0.010
PRA (ng/ml per h)	1.69 ± 1.39	3.13 ± 4.02	0.012
Aldosterone (ng/l)	10.85 [16.78]	8.07 [15.20]	0.094

(b) Weekly treatment

Parameter	Prehemodialysis	Posthemodialysis	*P* value
Baseline			
Adrenaline (ng/l)	20.90 [30.70]	17.60 [28.30]	0.533
Noradrenaline (ng/l)	41.60 [108.70]	47.20 [99.40]	0.702
PRA (ng/ml per h)	1.19 ± 2.65	1.17 ± 2.86	0.999
Aldosterone (ng/l)	17.80 [24.60]	13.90 [27.30]	0.028
Nebivolol			
Adrenaline (ng/l)	15.90 [53.30]	14.90 [66.30]	0.227
Noradrenaline (ng/l)	64.20 [82.40]	29.30 [35.30]	0.027
PRA (ng/ml per h)	0.67 ± 0.74	0.94 ± 1.91	0.529
Aldosterone (ng/l)	19.10 [26.50]	20.90 [26.40]	0.147
Irbesartan			
Adrenaline (ng/l)	18.90 [50.30]	14.60 [45.50]	0.809
Noradrenaline (ng/l)	35.90 [82.20]	42.30 [61.20]	0.904
PRA (ng/ml per h)	1.30 ± 2.19	1.56 ± 2.55	0.362
Aldosterone (ng/l)	15.60 [29.10]	8.00 [25.10]	0.042

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DISCUSSION

The current pilot study aimed to evaluate the effects of a single or weekly administration of nebivolol and irbesartan in peri-dialytic and ambulatory BP, as well as in levels of circulatory markers of RAAS and SNS in patients with intradialytic hypertension. Both agents in both single and weekly administration were able to reduce BP, with different levels of significance for different study periods. Of importance, both drugs in both modes of administration significantly reduced posthemodialysis SBP, whereas single-dose nebivolol and weekly irbesartan significantly lowered posthemodialysis DBPs compared with baseline. Administration of either drug was associated with lower ambulatory SBP and DBP levels, an effect that was more prominent for nebivolol and weekly administration. Weekly administration of either drug significantly reduced intradialytic and 24-h DBP. No difference was observed in between-group comparisons between the two drugs, with the exception of heart rate, which was always lower with nebivolol.

The definition of intradialytic hypertension is not uniform; studies defined it as rise in mean arterial pressure (MAP) more than 15 mmHg within or immediately post-dialysis [9] or more than 10 mmHg increase in SBP in the same period [6,7] or as a BP elevation of any degree during the second or third intradialytic hour [20]. However, it was suggested that 5–15% of hemodialysis patients may present this phenomenon [4,5], whereas large cohort studies suggest that intradialytic hypertension is strongly associated with increased risk of all-cause and cardiovascular mortality [6–8]. Of note, previous studies evaluating BP changes in patients with intradialytic hypertension using ABPM have found that hemodialysis-stimulated hypertensive response in these patients persists also during interdialytic intervals [21].

The pathophysiology of intradialytic hypertension is complex and not fully elucidated [5,9]. Volume overload is considered a major mechanistic pathway in development of intradialytic hypertension. Earlier studies suggest that inability to achieve optimal dry weight is associated to intradialytic BP rise, while decrease in dry weight can achieve remarkable intradialytic BP reductions and disappearance of the phenomenon of intradialytic hypertension [22–24]. Abnormal endothelial response during hemodialysis, may promote BP rise through increased endothelin-1 and decreased endothelial-derived NO release [25,26]. Rapid intravascular volume reduction with ultrafiltration may act as a stimulus for excess activation of the RAAS during dialysis, inducing sudden elevation in peripheral vascular resistance and consequently, 'paradoxical' rise in BP [5]. However, in some studies plasma renin concentrations remained unchanged during dialysis among patients prone to intradialytic hypertension, despite vasoconstriction suggesting that RAAS activation maybe not be directly implicated [25]. Activation of SNS during dialysis leading to stroke volume and/or peripheral vascular tone increase maybe an additional mechanistic pathway of intradialytic hypertension [27]. In baseline tests in our study, we observed nonsignificant reductions from prehemodialysis to posthemodialysis in adrenaline, noradrenaline, and aldosterone, whereas PRA remained unchanged. Weekly nebivolol further significantly reduced noradrenaline levels, whereas single-dose irbesartan increased, as expected, PRA but also significantly reduced noradrenaline levels. These findings may reflect an inter-relation of RAAS and SNS activation in intradialytic hypertension and probably beneficial effects of RAAS blockers or β-blockers in both systems. Additional factors proposed to contribute to BP increase during hemodialysis include positive sodium balance [28], increased serum ionized calcium levels [29], acute drop in dialyzable antihypertensive drug concentrations, treatment with erythropoietin stimulating agents, and increased arterial stiffness [5,9].

Data on management of increased BP levels during hemodialysis are scarce; even fewer are the studies specifically designed to evaluate drug treatments for intradialytic hypertension. An older uncontrolled trial in six patients with intradialytic hypertension suggests that single-dose administration of 60 mg captopril before dialysis attenuated the BP rise during session [11]. Of note, five of six patients studied had increased posthemodialysis PRA levels, as we observed with acute dose irbesartan. In a nonrandomized clinical study, Inrig *et al.* evaluated the effect of carvedilol on BP and brachial artery flow-mediated dilatation in 25 patients with intradialytic hypertension. Carvedilol was administered on an initial dose of 6.25 mg twice daily and was titrated every week up to 50 mg twice daily. After 12 weeks of treatment, carvedilol associated with improvement in flow-mediated vasodilatation of brachial artery, which was the primary study endpoint, as well as reduced occurrence of intradialytic hypertensive episodes during follow-up and a significant fall of 7 mmHg in 44-h SBP [13]. Our findings are in general agreement with this result, as we found a 9 mmHg drop in 24-h SBP with nebivolol after a week of treatment. The same group also performed a randomized cross-over study including 16 patients with intradialytic hypertension, to compare the effect of low-sodium versus high-sodium concentration in the dialysate (5 mEq/l lower or higher than serum sodium, respectively) on intradialytic BP. Prescription of low dialysate sodium for a 3-week period was associated with a significant reduction of 9.9 mmHg in the weekly average of intradialytic SBP [12]. A post hoc analysis of the Dry-weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, in which 100 hypertensive hemodialysis patients (not specifically having intradialytic hypertension) were randomly assigned to receive intensive ultrafiltration during dialysis over 8 weeks whereas another 50 controls did not follow dry-weight probing, showed that patients allocated in the intensive ultrafiltration group had a steepening of the slopes of intradialytic SBP during the course of the trial and each percentage per hour steepening of the intradialytic SBP slope was associated with 0.71 mmHg lower 44-h interdialytic SBP [23].

With regards to intermittent (i.e. per dialysis session) administration of antihypertensive agents, there are currently no studies examining this mode in patients with intradialytic hypertension, although this strategy is occasionally used in these patients. The seminal HDPAL study [30], randomized 200 hemodialysis patients with hypertension and left ventricular hypertrophy to lisinopril or atenolol, each administered three times per week after

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hemodialysis. Atenolol was superior to lisinopril in reducing cardiovascular outcomes (incidence of yocardial infarction, stroke, heart failure, and cardiovascular death) but both drugs significantly reduced 44-h ambulatory BP and left ventricular mass in comparison with baseline. Although comparisons between modes of administration was not made in our study, we observed that postdialysis BP was reduced in both modes but the effect of the continuous administration on 24-h BP was more prominent, something expected according to standard pharmacokinetics [10,31].

Although, treatment with a RAAS blocker or a β-blocker is suggested as a reasonable, pathophysiology-based approach to treat intradialytic hypertension, to our knowledge, this is the first randomized study to examine these approaches in comparison. In order to avoid confounding we used a rigorous definition of intradialytic hypertension as an inclusion criterion. Additional strengths of this study is the use of ABPM (three different measurements in every patient according to the protocol) to evaluate persistent BP elevation in the intradialytic interval, as well as the examination of two different modalities (single-drug use and weekly administration). We specifically used agents that are nondialyzable and their pharmacokinetics are unchanged in patients with ESRD, as β-blockers are characterized by variability in dialyzability, and almost all angiotensin-converting enzyme inhibitors [ACEIs; but not angiotensin II receptor blockers (ARBs)] are removed during standard hemodialysis [10,31]. We also captured intradialytic changes of RAAS and SNS markers. Our limitations include the sample size, especially as we evaluated two different modes of drug administration. A larger sample would probably lead several of our comparisons to be statistically significant. We must note, however, that this is a common limitation of studies in the field and ours is clearly the largest on this issue. Another limitation is the short-study duration of continuous administration. Finally, this is a pilot study on the effects of nebivolol and irbesartan in intradialytic hypertension, and our results may not be generalizable to other types of hemodialysis patients.

In conclusion, this study showed that in patients with intradialytic hypertension, nebivolol and irbesartan dosed acutely significantly reduce posthemodialysis SBP and have a beneficial trend in interdialytic and ambulatory BP. Continuous administration of each of these agents has a more prominent effect, providing reasonable reductions, apart from posthemodialysis in ambulatory BP. Although, there were no significant changes between the drugs compared, nebivolol provided numerically slightly larger BP drops. These results suggest that β-blockers and RAAS blockers are viable treatment options for intradialytic hypertension. Further studies should better delineate the true burden, prognostic associations and optimal management of this understudied, but not rare phenomenon.

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Conflicts of interest

There are no conflicts of interest.

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