Received: 27 September 2022 | Revised: 18 December 2022 | Accepted: 20 December 2022

DOI: 10.1111/jch.14630

ORIGINAL ARTICLE

WILEY

Effect of administration of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times on the circadian rhythm of blood pressure and the levels of MMPs and TIMPs in non-dipper patients with grade 1 and 2 hypertension

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Funding information
ZHENHAI Medical & Health Leading Academic Discipline Project

Abstract

This study aimed to probe the effects of low-dose irbesartan and hydrochlorothiazide in combination with levamlodipine at different times on the circadian rhythm of blood pressure, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) levels in patients with non-dipper hypertension (NDH). In this prospective randomized controlled trial, 124 patients with NDH who visited our hospital between August 2018 and July 2021 were enrolled and divided into morning (62 patients) and night (62 patients) medication groups according to the random number table method. All patients received low-dose irbesartan and hydrochlorothiazide combined with levamlodipine, with the morning medication group taking the medication between 7:00 and 10:00 and the night medication group taking the medication between 19:00 and 22:00 for 24 weeks. The effect of antihypertensive medication in both groups was measured, and changes in ambulatory blood pressure, blood pressure circadian rhythm, left ventricular structure, vascular endothelial function, MMPs, and TIMPs levels were observed before treatment initiation and after 24 weeks of treatment in both groups. The percentage of the dipper type was higher in the night medication group than in the morning medication group, while the percentage of the non-dipper type was lower in the morning medication group ($p < .05$). Low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times can effectively treat NDH, but bedtime dosing is more beneficial in reducing nocturnal blood pressure, reversing NDH, improving the circadian rhythm of blood pressure,

left ventricular structure, regulating vascular endothelial function, increasing MMPs levels, and reducing TIMP levels.

KEYWORDS
chronotherapeutics, circadian rhythm of blood pressure, hydrochlorothiazide, irbesartan, levamlodipine, MMPs, non-dipper hypertension

1 | INTRODUCTION

Hypertension is a common chronic disease of the cardiovascular system, characterized by increased blood pressure in the arteries and elevated peripheral vascular resistance, which can increase the heart's systolic afterload, leading to structural and functional damage to relevant organs.[1,2] The 24-h blood pressure variability curve was mostly presented in a dipper type, that is, "two peaks and one valley."[3] In contrast, non-dipper blood pressure is a circadian rhythm abnormality in hypertensive patients, defined as a decrease in blood pressure of <10% at night or >20% of the daytime blood pressure.[4] Patients with non-dipper hypertension (NDH) have higher risks of target organ damage such as left ventricular hypertrophy, carotid atherosclerosis, and stroke.[5] Therefore, the circadian pattern and temporal pharmacological properties of blood pressure should be considered to stabilize nocturnal blood pressure, reverse non-aspirate hypertension, and protect target organ function.

Currently, most clinical studies on hypertension treatment are focused on developing new drugs and related receptor analyses, and few reports have been published on the timing of administration.[6] Irbesartan is a long-acting angiotensin II receptor antagonist that can specifically and highly selectively inhibit exogenous and endogenous angiotensin II binding to its receptors and affect the renin-angiotensin-aldosterone system (RAAS), thus exerting the effects of protecting the target organs, lowering blood pressure, and smoothing the blood pressure curve.[7] Hydrochlorothiazide is a thiazide diuretic that reduces total circulating water and sodium in the body and lowers total peripheral resistance and blood pressure by increasing sodium chloride excretion and inhibiting the reabsorption of chloride and sodium ions from the distal tubules.[8] Levamlodipine is a calcium channel blocker that effectively corrects the circadian rhythm of blood pressure and improves vascular endothelial function.[9,10] Angiotensin II receptor antagonists + diuretics and angiotensin II receptor antagonists + calcium antagonists are recommended treatment regimens in the guidelines for the diagnosis and treatment of hypertension, and their feasibility and safety have been confirmed. However, there is still some controversy about when to administer the medication. This prospective randomized controlled trial was conducted to evaluate the effects of low-dose irbesartan and hydrochlorothiazide in combination with levamlodipine at different times on the circadian rhythm of blood pressure and the levels of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in patients with NDH.

2 | MATERIALS AND METHODS

2.1 | Clinical data

One hundred and twenty-four patients with NDH who visited our hospital between August 2018 and July 2021 were grouped into morning and night medication groups according to the random number table method, with 62 patients in each group.

2.2 | Inclusion criteria

(1) Inclusion criteria: Patients who met the diagnostic criteria in the Chinese Guidelines for Prevention and Treatment of Hypertension,[11] and the 24 h blood pressure results showed a percentage of systolic blood pressure (SBP) diurnal difference <10%; patients with grade 1 [SBP of 140–159 mmHg and/or diastolic blood pressure (DBP) of 90–99 mmHg] or grade 2 (SBP of 160–179 mmHg and/or DBP of 100–109 mmHg) hypertension; patients who were treated with one or two drugs for more than 2 months, and the treatment regimen was adjusted repeatedly for those who did not respond well to treatment; and patients who voluntarily signed the informed consent form. This study was approved by the Ethics Committee of the Zhenhai District People's Hospital.

(2) Exclusion criteria: Patients who received antihypertensive medication before enrollment and discontinued for less than 4 weeks; secondary hypertension; night workers or abnormal sleep patterns and poor sleep within the last month; peripheral artery disease and cardiac diseases such as congenital heart disease, rheumatic heart disease, heart failure, cardiomyopathy, coagulation dysfunction, combined autoimmune diseases and acute and chronic inflammatory diseases, sleep apnea, malignant tumor, mental diseases, combined hyperuricemia, gout, or hypokalemia.

2.3 | Randomized treatment

(1) Treatment regimen: Irbesartan (75 mg, Zhejiang Nordic Pharmaceutical Co., Ltd., H20217083), orally, q.d.75 mg; hydrochlorothiazide (6.25 mg, North China Pharmaceutical Qinhuangdao Co.,

Ltd., H20033412), q.d.12.5 mg; and levamlodipine (2.5 mg, Huabei Pharmaceutical Co., Ltd., H20143054), q.d. 2.5 mg/time.

(2) Treatment timing: The morning medication group took their medication in the morning (7:00–10:00), and the night medication group took theirs at bedtime (19:00–22:00). The total efficacy was measured for 24 weeks.

2.4 | Outcome measurement

(1) Treatment efficacy: The efficacy criteria were formulated with reference to the Chinese Guidelines for the Prevention and Treatment of Hypertension; if the reduction in DBP exceeded 10 mmHg or SBP exceeded 20 mmHg after treatment, and the clinical symptoms disappeared, it was considered to be markedly effective. Likewise, if the reduction in DBP was <10 mmHg or SBP was about 10–19 mmHg after treatment, and the clinical symptoms improved, it was considered effective. However, if the blood pressure did not reach the above criteria after treatment and the clinical symptoms did not improve, or the condition worsened, it was regarded as ineffective. Markedly effective + effective rate = total effective rate.

(2) Ambulatory blood pressure: The blood pressure of patients was measured by an automatic ambulatory blood pressure monitor (KC-2820, Nanjing Bedeng Medical Co., Ltd.) before and 24 weeks after therapy, with fasting, prohibition of alcohol, coffee, smoking, etc., for 12 h before the measurement. A cuff was tied on the left upper arm of the patient, and measurements were performed every 30 min during the day (6:00–22:00) and every 1 h during the night (22:00–6:00). Measurements were taken once, and the mean DBP (nDBP), mean SBP (nSBP) at night, mean DBP (24 h DBP), mean SBP (24 h SBP), mean DBP (dDBP), and mean SBP (dSBP) during the day were automatically analyzed.

(3) Circadian rhythms of blood pressure: The formula was (mean daytime SBP—mean nighttime SBP)/mean daytime SBP × 100%; dipper hypertension: the percentage of diurnal difference of SBP ≥ 10%–18%; NDH: the percentage of diurnal difference of SBP < 10%. The percentage of dipper and non-dipper blood pressure before and after 24 weeks of treatment was assessed in both groups.

(4) Left ventricular structure: Left ventricular mass (LVM), left ventricular end-diastolic internal diameter (LVEDD), LVM index (LVMI), posterior wall thickness (PWT), and ventricular septal thickness (VST) of the left ventricle were measured using a color Doppler ultrasound diagnostic system (model: GE VIVID E9, Shanghai Hanfei Medical Equipment Co. PWT).

(5) Serum samples (3 ml) were collected from the mid-elbow vein before and after 24 weeks of drug administration, anticoagulated, centrifuged at 3000 rpm for 5 min, and the supernatant was collected and refrigerated at −80°C for measurement.

(6) Vascular endothelial function: The levels of endothelial nitric oxide synthase (eNOS), nitric oxide (NO), and endothelin-1 (ET-1) were measured using enzyme-linked adsorption assay kits (Shanghai Xuanya Biotechnology Co., Ltd.). The anterior and posterior wall sonograms before and after measurements were displayed using a color Doppler ultrasound diagnostic system. Brachial artery flow-mediated dilation (FMD) = (inner diameter of the brachial artery after filling − basal inner diameter of brachial artery)/basic inner diameter of brachial artery × 100%.

(7) MMPs and TIMPs levels: The levels of matrix metalloproteinase-2 (MMP-2), MMP-3, MMP-9, tissue inhibitor of matrix metalloproteinases-1 (TIMP-1), and TIMP-2 were measured by MMPs and tissue inhibitors.

2.5 | Statistical analysis

Data were analyzed using SPSS 23.0 statistical software, and data conforming to normal distribution were expressed as mean ± standard deviation by ($\bar{\chi} \pm S$). The *t*-test was used for comparison between the two groups. The count data were expressed as rates (%), and the χ^2 test was used to compare the two groups; statistical significance was set at $p < .05$.

3 | RESULTS

3.1 | General data

There were no significant differences in the general data of the two groups, including sex, course of disease, body mass index, smoking history, drinking history, family history of cardiovascular and cerebrovascular diseases, and grade of hypertension ($p > .05$), which were comparable (Table 1).

3.2 | Antihypertensive effect

In the study, there was no case of drug withdrawal due to excessive lowering of blood pressure during the medication. This was considered to be related to the fact that the included patients were all treated with one or two drugs for more than 2 months, and the treatment regimen was adjusted repeatedly for those who did not respond well to treatment. There was no statistically significant difference ($p > .05$) in the total effective rate between the night (91.24%) and morning (87.10%) medication groups (Table 2).

3.3 | Ambulatory blood pressure

Before drug administration, there was no statistically significant difference in ambulatory blood pressure between the two groups ($p > .05$); The 24 h DBP, 24 h SBP, dDBP, dSBP, nDBP, and nSBP were lower in both groups after drug administration ($p < .05$), and nDBP and nSBP were lower in the night medication group than in morning medication group ($p < .05$) (Figure 1).

TABLE 1 Comparison of general data (n (%), $\bar{x} \pm s$)

Baseline data	Morning medication group ($n = 62$)	Night medication group ($n = 62$)	χ^2	p
Gender (M/F)	34/28	37/25	.297	.586
Age (years old)	68.96 ± 5.52	69.79 ± 6.02	.8	.425
Course of disease (years)	9.86 ± 2.24	10.19 ± 3.34	.646	.519
Body mass index (kg/m2)	24.86 ± 2.96	24.76 ± 2.75	.773	.379
Smoking history	18	21	.337	.562
Drinking history	29	25	.525	.469
Family history of cardiovascular and cerebrovascular diseases	29	32	.29	.59
Grade of hypertension (grade 1/grade 2)	28/34	31/31	.291	.59

TABLE 2 Comparison of antihypertensive effect between two groups n (%)

Group	Markedly effective	Effective	Ineffective	Total effective rate
Morning medication group ($n = 62$)	12 (19.35)	42 (67.74)	8 (12.90)	54 (87.10)
Night medication group ($n = 62$)	21 (33.87)	36 (58.06)	5 (8.06)	57 (91.24)
χ^2				.773
P				.379

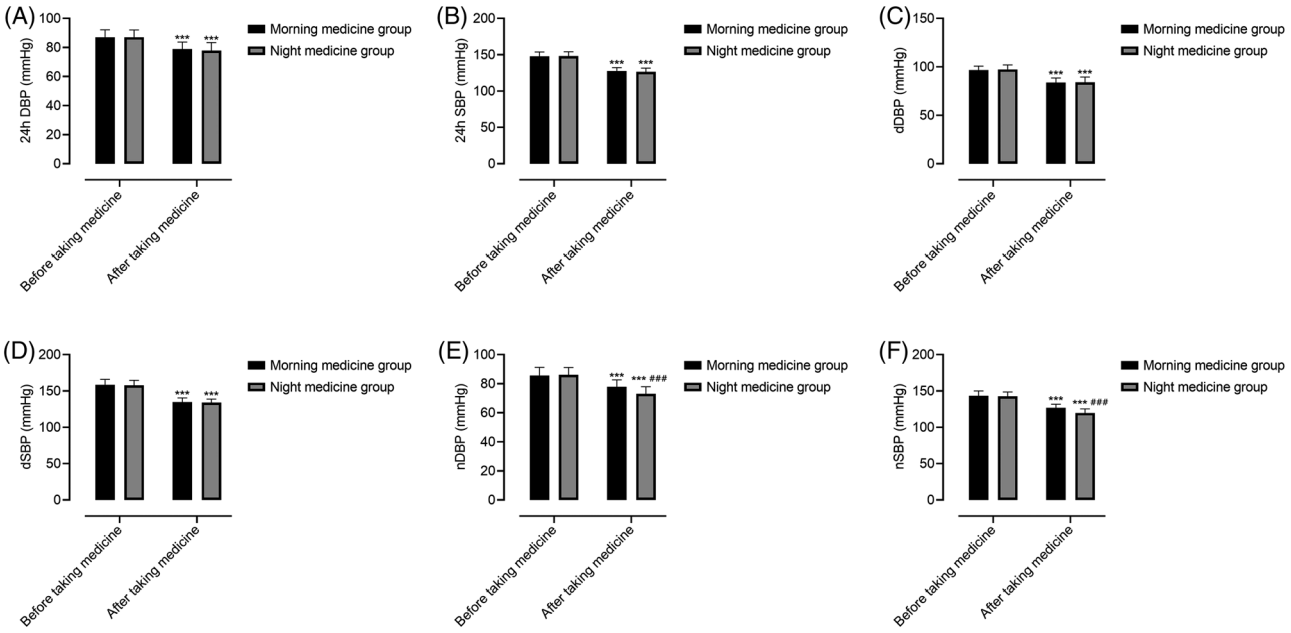

FIGURE 1 Effect of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different timing. Figure 1A: 24 h DBP; Figure 1B: 24 h SBP; Figure 1C: dDBP; Figure 1D: dSBP; Figure 1E: nDBP; Figure 1F. nSBP. Note: ***$p < .001$ compared with before drug administration; ###$p < .001$ compared with the morning medication group.

TABLE 3 Comparison of circadian rhythm of blood pressure between two groups (n (%), $\bar{x} \pm s$)

Timing	Group	Dipper	Non-dipper	SBP diurnal difference (%)
Before administration	Morning medication group ($n = 62$)	0	62 (100.00)	4.56 ± 1.24
	Night medication group ($n = 62$)	0	62 (100.00)	4.63 ± 1.34
	χ^2/t	.000		.302
	p	1.000		.763
After administration	Morning medication group ($n = 62$)	10 (16.13)	52 (83.87)	$6.53 \pm 2.02^{***}$
	Night medication group ($n = 62$)	30 (48.39)	32 (51.61)	$6.39 \pm 1.97^{***}$
	χ^2/t	14.762		.391
	p	<.001		.696

Note: $p < .001$ compared with this group before dosing.

3.4 | Circadian rhythm of blood pressure

Before drug administration, the proportion of dipper type, non-dipper type, and the percentage of day-night difference in SBP showed no significant difference between the two groups ($p > .05$). After drug administration, the proportion of dipper type in the night medication group was higher than that in the morning medication group, while the proportion of non-dipper type was lower in the night-medication group than in the morning medication group ($p < .05$). After drug administration, there was no significant difference in the percentage of day-night difference in SBP between the night and morning medication groups ($p > .05$) (Table 3).

3.5 | Left ventricular structure

Before drug administration, there were no significant differences in left ventricular structure indices between the two groups ($p > .05$). After drug administration, the VST, LVEDD, LVM, PWT, and LVMI were all lower in both groups ($p < .05$), and these indices were lower in the night medication group than in the morning medication group ($p < .05$) (Figure 2).

3.6 | Vascular endothelial function

Before drug administration, there was no significant difference in vascular endothelial function indices between the two groups ($p > .05$); after drug administration, ET-1 was lower, while NO, eNOS, and FMD were higher than those before drug administration in both groups ($p < .05$). After drug administration, ET-1 was lower, and NO, eNOS, and FMD were higher in the night medication group than in the morning medication group ($p < .05$) (Figure 3).

3.7 | Levels of MMPs

Before drug administration, there were no significant differences in MMPs levels between the two groups ($p > .05$). After drug administration, the levels of MMP-2, MMP-3, and MMP-9 increased in both groups ($p < .05$) and were higher in the night medication group than in the morning medication group ($p < .05$) (Table 4).

3.8 | Levels of TIMPs

Before drug administration, there were no statistically significant differences in the levels of TIMP-1 and TIMP-2 between the two groups ($p > .05$). After drug administration, the levels of TIMP-1 and TIMP-2 decreased in both groups ($p < .05$) and were lower in the night medication group than in the morning medication group ($p < .05$) (Table 5).

4 | DISCUSSION

During sleep at night, the human body's sympathetic nerve tone decreases, parasympathetic nerve excitability increases, and blood pressure reaches its lowest point between 3.00 and 5.00 in the morning, which is presented as a "dipper" curve. In some hypertensive patients, nighttime blood pressure is reduced by <10%, and the circadian rhythm of blood pressure is non-dipper; this may easily cause the cardiovascular system to be overloaded for a long time.[12,13] Blood pressure variability can increase the risk of cardiac and cerebral complications and impair target organ function by activating the RAAS, downregulating vagal function, and damaging the vascular endothelial function.[14,15] Therefore, clinical treatment focuses on reverse NDH, maintaining a normal circadian rhythm of blood pressure, and synchronizing drug action with blood pressure rhythm as much as possible.

Ventricular remodeling is the main pathological basis of impaired cardiac function caused by hypertension. Increased ventricular remodeling amplifies transmural dispersion of repolarization and delays cardiac electrical conduction, thus causing dyssynchronization of left ventricular contraction. MMPs and TIMPs were found to play an important role in ventricular remodeling by affecting extracellular matrix degradation and regulating matrix metabolism in myocardial tissue.[16] In this study, we found that the levels of VST, LVEDD, LVM, PWT, LVMI, TIMP-1, and TIMP-2 were lower, and those of MMP-2, MMP-3, and MMP-9 were higher in both groups than before drug

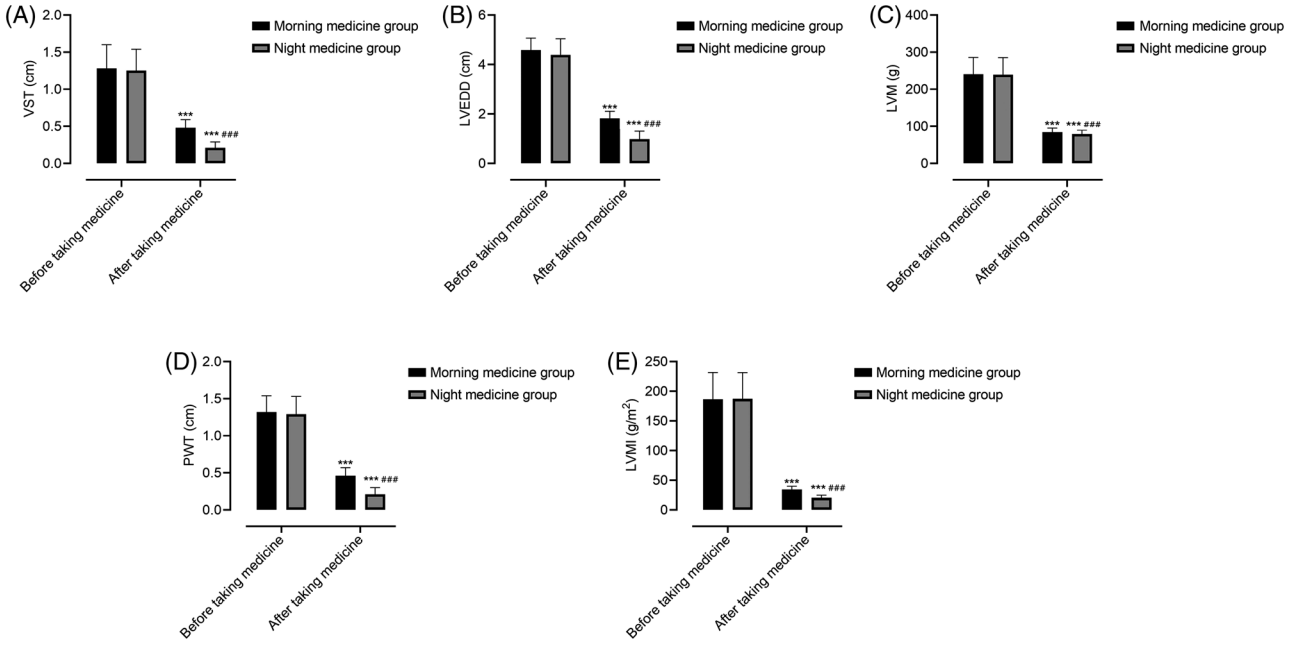

FIGURE 2 Effect of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine administered at different timing on structural indices of the left ventricle in patients with non-dipper hypertension. Figure 2A: VST; Figure 2B: LVEDD; Figure 2C: LVM; Figure 2D: PWT; Figure 2E: LVMI. Note: $^{***}p < .001$ compared with before drug administration; $###p < .001$ compared with the morning medication group.

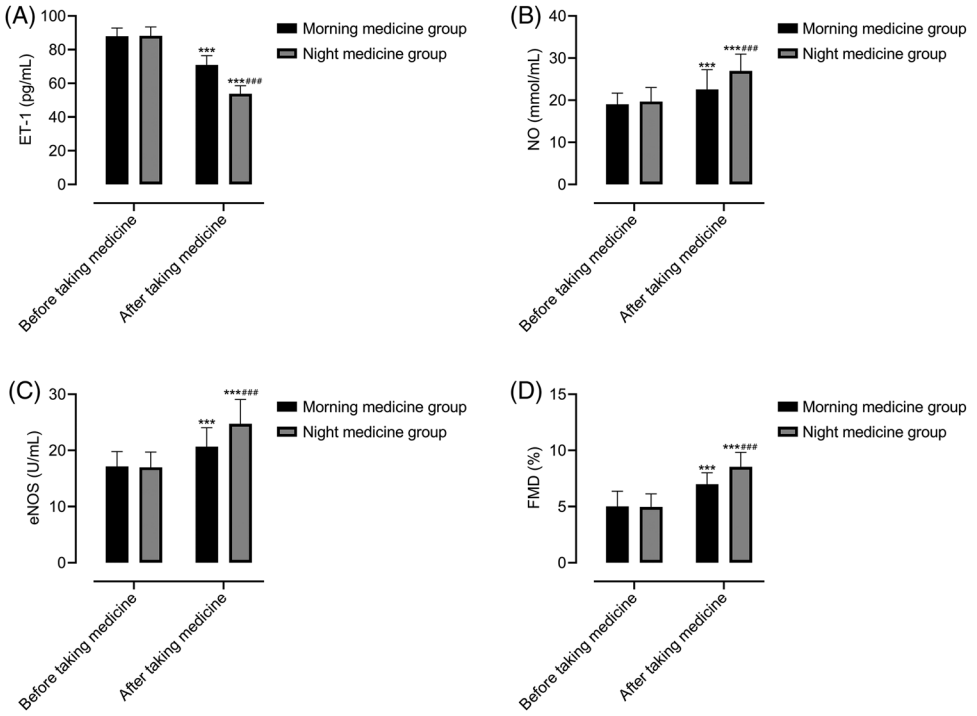

FIGURE 3 Effect of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different timing on the indexes of vascular endothelial function in patients with non-dipper hypertension. Figure 3A: ET-1; Figure 3B: NO; Figure 3C: eNOS; Figure 3D: FMD. Note: $^{***}p < .001$ compared with before drug administration; $###p < .001$ compared with the morning medication group.

TABLE 4 Comparison of MMPs levels between two groups ($\bar{x}\pm s$, pg/ml)

Timing	Group	MMP-2	MMP-3	MMP-9
Before administration	Morning medication group ($n = 62$)	38.96 ± 5.28	21.63 ± 4.98	53.95 ± 6.38
	Night medication group ($n = 62$)	37.49 ± 4.97	22.75 ± 4.13	54.18 ± 5.58
	t	.654	.598	.436
	p	.384	.476	.711
After administration	Morning medication group ($n = 62$)	47.53 ± 6.02***	37.06 ± 6.39***	72.16 ± 9.62***
	Night medication group ($n = 62$)	65.37 ± 8.12***	46.95 ± 7.12***	89.37 ± 11.08***
	t	19.653	15.021	21.356
	p	<.001	<.001	<.001

Note: $p < .001$ compared with this group before dosing.

TABLE 5 Comparison of TIMPs levels between the two groups ($\bar{x}\pm s$, pg/ml)

Timing	Group	TIMP1	TIMP2
Before administration	Morning medication group ($n = 62$)	12.15 ± 2.36	8.35 ± 1.27
	Night medication group ($n = 62$)	11.98 ± 3.34	8.03 ± 1.74
	t	.327	1.170
	p	.744	.244
After administration	Morning medication group ($n = 62$)	9.02 ± 1.34***	6.35 ± .87**
	Night medication group ($n = 62$)	7.12 ± .88***	4.11 ± .73***
	t	9.332	15.530
	p	<.001	<.001

Note: Compared within same group, **$p < .01$, ***$p < .001$.

administration, indicating that low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times can effectively improve ventricular remodeling in patients with NDH. This mechanism of action may be related to the regulation of MMPs and TIMPs levels. It is speculated that the reason may be as follows: (1) Angiotensin II receptors can up-regulate plasminogen activation inhibitor (PAI), thereby inhibiting plasminogen activation and controlling the activation amplification mechanism of MMPs. Irbesartan can block the binding of angiotensin II receptor to angiotensin receptor, thus blocking its downstream biological effects and regulating MMPs activity. (2) Hydrochlorothiazide can specifically block angiotensin II type I receptor, increase aldosterone secretion, improve plasma renin activity, improve ventricular remodeling caused by cardiac neuroendocrine disorders, and thus regulate MMPs and TIMPs levels. (3) Levamlodipine can effectively prevent atherosclerosis, protect the intima of blood vessels, improve myocardial oxygen supply, and effectively control left ventricular remodeling.

Moreover, this study also found that the total antihypertensive efficiency of the three-drug combination regimen at different times was 91.24% and 87.10% for morning and night medication groups, respectively, and they all contributed to blood pressure reduction and improvement of vascular endothelial function and circadian rhythm of blood pressure, which are related to the mechanism of action of the three drugs: (1) Irbesartan can relax blood vessels, reduce the burden on the heart, and restore the circadian rhythm of normal blood pressure, thus correcting the "non-dipper" curve of blood pressure; it can promote the dilatation of precapillary arteries, resistance arteries and veins, reduce anterior and posterior loads on the heart, thus improving ventricular remodeling and avoiding myocardial hypertrophy and vessel wall thickening caused by long-term hypertension[17,18]; (2) Hydrochlorothiazide can reduce intracellular calcium ion and sodium-calcium exchange in vascular smooth muscle, decrease intracellular calcium ion and vascular smooth muscle responsiveness to angiotensin and catecholamines, weaken vasoconstriction, and thus reduce blood pressure; its sustained hypotensive effect may be related to the local release of prostaglandins or other vasodilating substances that reduce small artery dilation and total peripheral resistance[19,20]; (3) Levamlodipine can block L-type calcium channels and inhibit the transfer of calcium ions into the cells, thus exerting a direct diastolic effect on vascular smooth muscle, improving hemodynamics and regulating blood pressure[21]; Levamlodipine promotes the release of NO and other potent vasodilatory substances, indirectly diastaging vascular smooth muscle and thus improving vascular endothelial function. Long-term use of hydrochlorothiazide can produce dose-related side effects such as elevated uric acid levels, abnormal glucose tolerance, hypokalemia, and reduced insulin sensitivity, while the irbesartan and levamlodipine combination can reduce or counteract the RAAS and sympathetic nerves activation caused by long-term use

of hydrochlorothiazide, which increases the antihypertensive effect and reduces adverse effects.[22] Meanwhile, hydrochlorothiazide can prolong the duration of action of irbesartan and levamlodipine and enhance the effect of irbesartan to inhibit angiotensin II and the effect of levamlodipine to relax vascular smooth muscle; therefore, the three-drug combination is in line with the principle of World Health Organization and the International Society of Hypertension guidelines for the management of hypertension. However, it is worth noting that drug indications and dosage should be strictly controlled in clinical drug combination to avoid the occurrence of adverse reactions such as hypotension caused by aggressive medication regimens.

At present, there is still some controversy regarding the chronotherapy of NDH. In 2019, the American Diabetes Association guidelines on the treatment of hypertension noted the increasing incidence of cardiovascular disease in patients with NDH and also suggested the importance of taking antihypertensive medications at bedtime.[23] The 2020 Chinese hypertension league guidelines on ambulatory blood pressure monitoring recommended that antihypertensive treatment should be optimized according to the circadian rhythm of blood pressure in hypertensive patients; for non-dipper and reverse dipper blood pressure, blood pressure control should be strengthened at night, and for extreme dipper blood pressure, attention should be paid to avoid excessive blood pressure drop at night.[24]

Hermida[25] et al. adopted a chronotherapeutic protocol to treat NDH, which reduced blood pressure and effectively corrected the "non-dipper" curve of blood pressure, with significant patient benefit. In a meta-analysis, Jiang[26] et al. reported that bedtime administration of antihypertensive drugs reduced dSBP by 1.17 mmHg and cardiovascular-related mortality by 2.1%. The present study found that nDBP, nSBP, and the percentage of non-dippers were lower in the night medication group than in the morning medication group. Similarly, the improvement of the left ventricular structure, vascular endothelial function, MMPs, and TIMPs levels were better in the night medication group than in the morning medication group, which is consistent with the findings of the above studies, confirming that compared with the morning medication group, bedtime drug administration is more beneficial in reducing nocturnal blood pressure in patients with NDH, reversing NDH, improving the circadian rhythm of blood pressure as well as left ventricular structure, and regulating vascular endothelial function. The reasons may be as follows: (1) According to pharmacokinetic characteristics, drug metabolism in the morning can cause low plasma drug concentrations at night, while drug administration at bedtime can increase plasma drug concentration at night, which can effectively correct the circadian rhythm of blood pressure and reduce the level of nDBP and nSBP; (2) patients with NDH have an obvious "morning peak phenomenon," in which the autonomic nerves and related fluid factors (epinephrine, etc.) that dominate the cardiovascular system enter a state of stress and excitement in the early morning, which can lead to increased cardiac blood displacement, increased blood pressure, accelerated heart rate, and increased blood coagulation.[27] Therefore, drug administration before bedtime can result in effective drug concentrations before the blood pressure peaks in the morning, thereby reducing the incidence of the "morning peak phenomenon"; (3) The RAAS regulates the pathological and physiological functions of the cardiovascular system, thus playing a key role in the humoral regulation of circadian rhythms and blood pressure. In contrast, bedtime dosing is more conducive to suppressing the nocturnal RAAS and alleviating the vascular inflammatory response, thus improving the left ventricular structure. However, some scholars held different opinions. They did not support the concept of nighttime medication neither in terms of prognosis nor in terms of blood pressure control, which may be due to the fact that NDH and reverse dipper hypertension patients have higher blood pressure at night than during the day, so the efficacy should cover the entire nighttime; meanwhile, secondary causes of nighttime hypertension, such as obstructive sleep apnea, should also be considered, and early morning medication may be more effective.[28] Patients with extreme dipper hypertension can take antihypertensive drugs in the morning to avoid taking them at bedtime, so as to avoid the occurrence of cardiovascular and cerebrovascular ischemic events; for patients with early morning hypertension, the drug effect can be covered to the stage of early morning hypertension as far as possible.[29]

In conclusion, low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times are effective in the treatment of NDH, and bedtime dosing is more beneficial in reducing nocturnal blood pressure, reversing NDH, improving the circadian rhythm of blood pressure and left ventricular structure, regulating vascular endothelial function, elevating MMPs levels, and reducing TIMP levels. The shortcomings of this study included the short follow-up period, single-center and small sample size, non-inclusion of patients with severe NDH, and the safety of different regimens was not evaluated; therefore, the above limitations need to be the focus of further research.

AUTHOR CONTRIBUTIONS

Peiling Yan and Yongjian Luo conceived the study and designed the experiments. Yongjian Luo, Jiancheng Zhang, Haifeng Liu, and Jiashi Chen contributed to the data collection. Jing Wang, Guofeng Dong, and Minghao Ge performed the data analysis and interpreted the results. Peiling Yan wrote the manuscript. Peiling Yan and Yongjian Luo contributed to the critical revision of article. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

This study was funded by ZHENHAI Medical & Health Leading Academic Discipline Project, Project Number: 2022-03.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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How to cite this article: Yan P, Luo Y, Zhang J, et al. Effect of administration of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times on the circadian rhythm of blood pressure and the levels of MMPs and TIMPs in non-dipper patients with grade 1 and 2 hypertension. *J Clin Hypertens*. 2023;25:137–145.
https://doi.org/10.1111/jch.14630