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Difference in Efficacy of Antihypertensive Given in Morning vs Evening

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ABSTRACT

Background: The long-term antihypertensive drugs of 24-hour stable blood pressure can control the large fluctuation of morning blood pressure and reduce the rise of morning peak blood pressure caused by failure to take medicine on time or missing. **Objective:** To determine the difference in efficacy of antihypertensive given in morning vs evening, at a tertiary care hospital, Karachi. **Material and Methods:** A randomized controlled trial was conducted at Liaquat National Hospital & Medical College, Karachi from March 2024 to Sep 2024. 200 hypertensive patients were randomly assigned to Morning (Group-A) or Evening/Night (Group-B) medication groups. For diagnosing and evaluating hypertension, ABPM was performed using validated devices that recorded systolic and diastolic blood pressure at regular intervals over 24 hours. Data were analyzed using SPSS, applying appropriate statistical tests (parametric and non-parametric) to compare outcomes. A p-value ≤0.05 was considered statistically significant. **Results:** Group-A had 62% males and 38% females, while Group-B had 66% males and 34% females. Hypertension duration was significantly longer in Group-B (16.32±8.10 months vs. 10.64±5.82 months, p<0.001). Blood pressure reductions favored evening administration, with post-systolic and post-diastolic blood pressures decreasing significantly in Group-B (135.40±9.00 mmHg, 73.81±6.78 mmHg) compared to Group-A (142.41±12.93 mmHg, 82.39±6.19 mmHg, p<0.001). The main outcome revealed superior efficacy in the evening group, where 87% reported effectiveness compared to 53% in the morning group. **Conclusion:** Our study results demonstrate that evening administration of antihypertensive medications significantly improves efficacy compared to morning dosing, with greater reductions in systolic and diastolic blood pressures and higher effectiveness rate.

INTRODUCTION

Hypertension (HT) is the most common chronic disease which affects around one-third of the adult population worldwide.[1] Poor control of hypertension contributes to increased healthcare costs and resource utilization.[2] Hypertension is a significant risk factor for cardiovascular diseases such as arrhythmia, stroke, and valvular heart disease.[2,3] Both ESC/ESH and ACC/AHA guidelines for the management of arterial hypertension suggest that most patients require drug therapy to achieve optimal blood pressure control.[4,5] The latest study (PURE) showed 22.3% of cardiovascular disease (CAD) cases and deaths were attributed to hypertension.[6]

BP varies throughout the day, has a distinct and reproducible 24 h circadian rhythm in both normotensive and uncomplicated hypertensive patients.[7] In patients who are awake during the daytime and asleep during the nighttime, their BP and heart rate show a typical circadian variation, with lower BP levels during nighttime sleep and an abrupt rise upon arising in the morning.[8]

Though traditionally, daytime blood pressure (BP) has been the sole treatment target for HT, BP during sleep (i.e., nocturnal BP) consistently emerges as a stronger predictor of cardiovascular outcomes and mortality, even after controlling for daytime BP.[9] Moreover, successful treatment of nocturnal HT may reduce cardiovascular risk.[10] Based on this, researchers began to apply the timing of drug effect to the treatment of essential hypertension to improve BP control and cardiovascular outcome. The MAPEC study demonstrated that bedtime therapy relative to conventional morning therapy benefits more in reducing the asleep BP mean, with additional 61% reduction of cardiovascular disease events.[11]

One reason for morning dosing may be that adherence with the antihypertensive regime has been documented to diminish with evening dosing.[12,13] This morning tradition has been challenged; for almost 2 decades multiple data from a single center suggested improved blood pressure (BP) control and cardiovascular outcomes with evening dosing.[14] In contrast, a recently reported prospective randomized trial of 21,104 patients, randomized to morning Downloaded from stroke, and vascular death occurred to a similar proportion regardless of the time of administration.[13,15] This led to a consensus document

which concluded that evening dosing should not be preferred.[16]

A cohort study showed that a 1-mmHg increase in morning BP was associated with a 2.1% increased risk of cardiovascular death.[17] It is well known that morning blood pressure surge increases the risk of myocardial events in the first several hours post-awakening.[18] The mechanisms involved in the morning increase in cardiovascular events have been unclear, but recent clinical studies have shown that an exaggerated morning BP surge is a plausible factor involved in the triggering of cardiovascular events, particularly in the case of stroke.[19] More and more evidences show that the morning surge of blood pressure is closely related to cardiovascular events, stroke, and renal impairment. And for medication, guidelines suggest the long-term antihypertensive drugs of 24-hour stable blood pressure can control the large fluctuation of morning blood pressure and reduce the rise of morning peak blood pressure caused by failure to take medicine on time or missing. It could be suggested to non-dipper type or anti-dipper type hypertension patients to take long-term antihypertensive drugs before going to bed.[20,21]

In Hermida et al study the number of patients with a nondipper BP pattern at baseline was unaltered after ingestion of the 80 mg/d telmisartan dose on awakening, but nondipping was significantly reduced from 34% to 8% when the same dose was ingested at bedtime.[22]

As for as local data is concerned no study with large sample size is available from our region looking into this entity. Therefore our study will serve as the first study from our region to look into this disease. It will serve as basis for future research references as well as hypothesis generation regarding disease outcomes in such patients.

MATERIAL AND METHODS

To achieve the objective of the study, a randomized controlled trial was designed. Patients were recruited from the Department of Cardiology at Liaquat National Hospital & Medical College, Karachi from March 2024 to Sep 2024. Approval for the study was obtained from the CPSP and the ERC committee prior to induction of patients. The total duration of the study spanned six months from the date of approval. Informed written consent was obtained from all study participants before enrollment.

Patients between 30 and 70 years of age, of either gender, and with a confirmed diagnosis of hypertension for more than three months, as defined by office blood pressure measurements (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg), were included in the study. Individuals with severe hypertension (grade 3, BP ≥ 180/110 mm Hg), type 1 diabetes, secondary arterial hypertension, cardiovascular disorders such as unstable angina, heart failure, stroke, or life-threatening arrhythmias were excluded, along with shift workers, heavy drinkers, heavy smokers, and those engaging in intensive exercise.

The sample size was calculated based on a prior efficacy estimate of antihypertensive drugs administered in the morning versus the evening, at 34%[22] and 8%[22], respectively. Using a confidence level of 95% and power of 90%, the required sample size was determined to be 47 patients per group, totaling 94 patients. However, to enhance statistical validity, 100 patients were recruited per group, resulting in a total study population of 200 hypertensive patients. A non-probability consecutive sampling technique was employed for participant selection.

Patients were randomly assigned to two groups: The Group-A (Morning) received the antihypertensive medication between 6:00 AM and 12:00 noon. The Group-B (Evening / Night) received same antihypertensive medication between 5:00 PM and 12:00 midnight. Antihypertensive drugs utilized in the study included ACE inhibitors, calcium channel blockers, beta-blockers, diuretics, angiotensin receptor blockers, and alpha-blockers. The efficacy of antihypertensive treatment was assessed after three days of therapy, with successful control defined as SBP <140 mm Hg or DBP <90 mm Hg, as measured by ambulatory blood pressure monitoring (ABPM), which was considered the gold standard for hypertension diagnosis and evaluation.

Demographic details, duration of hypertension, number of antihypertensive drugs, and co-morbidities such as diabetes mellitus, smoking, dyslipidemia, and obesity were documented by the principal investigator using a predesigned proforma. Operational definitions ensured consistency in the categorization of diabetes mellitus, smoking status, dyslipidemia, and obesity. Efforts were made to minimize confounding variables by strictly adhering to exclusion criteria.

Data were analyzed using SPSS version 22. Frequencies and percentages were calculated for categorical variables such as gender, place of residence, and co-morbid conditions. Continuous variables, including age, duration of hypertension, number of antihypertensive drugs, pretreatment and post-treatment blood pressure measurements, were expressed as mean±standard. Normality of the data was assessed using the Shapiro-Wilk test, and in cases of non-normal distribution deviation, median (IQR) were presented. For analysis the Mann-Whitney U test was applied. The efficacy of antihypertensive drugs in the two groups was compared using the Chi-square test, and Fisher's exact test was applied when cell counts were below five. Effect modifiers, including age, gender, place of residence, duration of hypertension, number of antihypertensive drugs, and co-morbid conditions, were controlled through stratification. A p-value ≤0.05 was considered statistically significant in all analysis.

RESULTS

The study compared the efficacy of antihypertensive medications administered in the morning versus the evening. The Table 1 showed that Group A (morning administration) consisted of 62% males and 38% females, whereas Group B (evening administration) included 66% males and 34% females. Urban residency was notably more common in Group B (52%) compared to Group A (32%), while rural residency dominated in Group A (68%) relative to Group B (48%).

The number of antihypertensive drugs used by participants revealed that a higher proportion of individuals in Group A were on monotherapy (66%) compared to Group B (52%), whereas dual therapy was

more prevalent in Group B (46%) than in Group A (30%). A small percentage in both groups required triple therapy, constituting 4% in Group A and 2% in Group B.

In terms of comorbidities, Group A demonstrated a higher prevalence of diabetes mellitus (48%) compared to 32% in Group B. Smoking was also more common in Group A (32%) compared to 22% in Group B. Dyslipidemia exhibited a low prevalence in both groups, being slightly more frequent in Group A (12%) than in Group B (6%). Obesity was notably more prevalent in Group A (46%) compared to Group B (22%).

The mean age of participants in both groups was comparable, with Group A averaging 54.75±9.98 years and Group B averaging 54.82±8.02 years. However, the duration of hypertension differed, as Group B exhibited a longer mean duration of 16.18±7.64 months, compared to 11.18±5.37 months in Group A.

Regarding blood pressure parameters, Group A had a mean pre-systolic blood pressure of 146.84±12.56 mmHg and post-systolic blood pressure of 146.17±11.25 mmHg, indicating minimal reduction. In contrast, Group B showed a mean pre-systolic blood pressure of 153.07±10.36 mmHg, which decreased substantially to 136.55±8.96 mmHg post-treatment. Similarly, pre-diastolic blood pressure in Group A (85.95±8.30 mmHg) showed minimal change post-treatment (88.22±8.01 mmHg), whereas in Group B, pre-diastolic blood pressure (84.22±8.11 mmHg) significantly decreased to 76.60±9.67 mmHg post-treatment.

Among those receiving morning administration (Group A), 53% of individuals reported that the medication was effective. In contrast, evening administration (Group B) demonstrated superior outcomes, with 87% of participants reporting effective antihypertensive treatment. The cumulative percentage data emphasized a stark difference between the two groups. The findings highlighted that antihypertensive medications administered in the evening were associated with higher efficacy, as evidenced by the greater proportion of participants reporting favorable results. The findings also presented in Figure-1.

The Table 2 revealed distinct patterns in the efficacy of antihypertensive medications administered in the morning versus evening across various demographic and clinical variables. In terms of gender, males in both groups demonstrated higher efficacy rates, with Group B (69%) showing a greater proportion of effectiveness compared to Group A (58.5%). Among females, efficacy rates were lower in both groups, but Group B again exhibited higher effectiveness at 31%, compared to 41.5% in Group A. However, statistical significance was not achieved for gender comparisons in either group, as indicated by p-values greater than 0.05.

The influence of residential status showed contrasting trends between groups. Urban participants in Group B exhibited higher efficacy rates (49.4%) compared to Group A (26.4%), while rural participants demonstrated higher efficacy in Group A (73.6%) relative to Group B (50.6%). Despite these differences, the p-values did not indicate statistical significance for residential comparisons, suggesting that efficacy was not strongly associated with urban or rural residency.

The number of antihypertensive drugs used by participants showed a noteworthy difference. In Group A, monotherapy demonstrated a significantly higher efficacy rate (54.7%) compared to participants without efficacy (78.7%, p=0.028). However, no significant difference was observed in Group B for monotherapy or other combinations, with p-values exceeding 0.05. These findings may imply that drug regimen plays a role in determining efficacy, particularly for morning administration.

Smoking status influenced efficacy in Group B, with non-smokers exhibiting significantly higher efficacy rates (81.6%) compared to smokers (18.4%, p=0.024). No significant difference was observed for smoking status in Group A, suggesting that smoking may have a greater impact on efficacy for evening administration. Other factors, including diabetes mellitus, dyslipidemia, and obesity, did not demonstrate significant associations with efficacy in either group, as indicated by p-values greater than 0.05.

Age and hypertension duration were not significantly associated with efficacy in either group, although Group B participants reporting efficacy exhibited slightly older mean ages (58.42±6.6 years) compared to Group A (56.52±9.56 years). Blood pressure parameters revealed significant differences in post-treatment measures. Post-systolic blood pressure significantly decreased in Group B participants reporting efficacy (135.40±9.00 mmHg) compared to those without efficacy (144.23±2.84 mmHg, p<0.001). Similarly, post-diastolic blood pressure showed significant reductions in Group B participants with efficacy (73.81±6.78 mmHg) compared to those without efficacy (95.23±3.06 mmHg, p<0.001). Group A participants did not exhibit significant reductions in post-systolic or post-diastolic blood pressure relative to efficacy status.

Table 1

Demographic, Clinical Characteristics, and Blood Pressure Metrics of Study Participants According to Administration Timing

		Morning Time (Group A)	Evening / Night Time (Group B)
Gender	Male	62(62)	66(66)
	Female	38(38)	34(34)
Residence	Urban	32(32)	52(52)
	Rural	68(68)	48(48)
Number of anti-hypertensive drugs	1	66(66)	52(52)
	2	30(30)	46(46)
	3	4(4)	2(2)
Diabetes Mellitus	Yes	48(48)	32(32)
	No	52(52)	68(68)
Smoking	Yes	32(32)	22(22)
	No	68(68)	78(78)
Dyslipidemia	Yes	12(12)	6(6)
	No	88(88)	94(94)
Obesity	Yes	46(46)	22(22)
	No	54(54)	78(78)
(Mean±SD)			
Age (years)		54.75±9.98	54.82±8.02
Hypertension Duration (months)		11.18±5.37	16.18±7.64
Pre Systolic BP (mmHg)		146.84±12.56	153.07±10.36
Post Systolic BP (mmHg)		146.17±11.25	136.55±8.96
Pre Diastolic BP (mmHg)		85.95±8.30	84.22±8.11
Post Diastolic BP (mmHg)		88.22±8.01	76.60±9.67

Figure 1

Efficacy according to Antihypertensive Drugs Administration Timing Groups

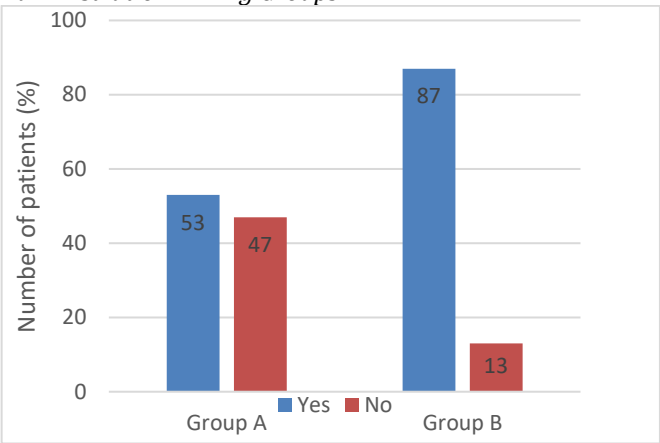

Table 2

Comparison of Efficacy of Antihypertensive Medications Administered in Morning versus Evening across Demographic and Clinical Variables

	Morning Time (Group A)			Evening / Night Time (Group B)		
	Efficacy		p-value	Efficacy		p-value
	Yes	No		Yes	No	
Gender						
Male	31(58.5)	31(66)	0.443	60(69)	6(46.2)	0.105
Female	22(41.5)	16(34)		27(31)	7(53.8)	
Residence						
Urban	14(26.4)	18(38.3)	0.204	43(49.4)	9(69.2)	0.182
Rural	39(73.6)	29(61.7)		44(50.6)	4(30.8)	
Number of anti-hypertensive drugs						
1	29(54.7)	37(78.7)	0.028**	47(54)	5(38.5)	0.447
2	22(41.5)	8(17)		38(43.7)	8(61.5)	
3	2(3.8)	2(4.3)		2(2.3)	0(0)	
Diabetes Mellitus						
Yes	28(52.8)	20(42.6)	0.305	28(32.2)	4(30.8)	0.919
No	25(47.2)	27(57.4)		59(67.8)	9(69.2)	
Smoking						
Yes	18(34)	14(29.8)	0.655	16(18.4)	6(46.2)	0.024**
No	35(66)	33(70.2)		71(81.6)	7(53.8)	
Dyslipidemia						
Yes	6(11.3)	6(12.8)	0.824	6(6.9)	0(0)	0.329
No	47(88.7)	41(87.2)		81(93.1)	13(100)	
Obesity						
Yes	22(41.5)	24(51.1)	0.339	20(23)	2(15.4)	0.537
No	31(58.5)	23(48.9)		67(77)	11(84.6)	
Age(years)*	56.52 ±9.56	52.75 ±10.18	0.059	54.28 ±8.11	58.42 ±6.6	0.082
Hypertension duration (months)*	10.64 ±5.82	11.79 ±4.80	0.290	16.32 ±8.10	15.23 ±3.06	0.377
Pre Systolic blood pressure (mmHg)*	148.27 ±15.10	145.23 ±8.75	0.216	153.28 ±10.34	151.62 ±10.80	0.611
Post Systolic blood pressure (mmHg)*	142.41 ±12.93	150.40 ±6.98	<0.001**	135.40 ±9.00	144.23 ±2.84	<0.001**
Pre DIA (unit)*	83.11 ±9.45	89.15 ±5.25	<0.001**	83.82 ±7.89	86.88 ±9.37	0.206
Post DIA (unit)*	82.39 ±6.19	94.79 ±3.39	<0.001**	73.81 ±6.78	95.23 ±3.06	<0.001**

Chi-square/fisher exact test was applied.
* Independent t-test was applied.
** Significant at 0.05 levels.

The Table 3 explored the positive efficacy of antihypertensive medications administered in the morning versus the evening across various demographic and clinical variables. Gender comparisons revealed that males exhibited higher efficacy rates in both groups, with Group B demonstrating 69% efficacy compared to 58.5% in Group A. Similarly, females reported lower efficacy rates in both groups, with 41.5% in Group A and 31% in Group B. However, gender differences were not statistically significant, as indicated by the p-value of 0.208. Residence data revealed a notable trend.

Urban participants in Group B exhibited significantly higher positive efficacy (49.4%) compared to 26.4% in Group A, with statistical significance achieved (p=0.007). Rural participants demonstrated higher positive efficacy in Group A (73.6%) relative to Group B (50.6%), though this finding lacked statistical significance. The number of antihypertensive drugs used showed minimal variation between the two groups. Monotherapy was associated with slightly higher efficacy rates in Group A (54.7%) compared to Group B (54%), with no statistically significant difference (p=0.851). Dual therapy efficacy rates were also comparable between Group A (41.5%) and Group B (43.7%), and neither group showed significant differences for triple therapy, which was rare among participants.

Diabetes mellitus had a significant association with efficacy. Participants with diabetes reported greater positive efficacy in Group A (52.8%) compared to Group B (32.2%), while those without diabetes demonstrated higher efficacy in Group B (67.8%) relative to Group A (47.2%), with statistical significance achieved for diabetes status (p=0.016). Smoking status showed significant differences in Group B, where non-smokers demonstrated higher positive efficacy (81.6%) compared to smokers (18.4%, p=0.037). However, smoking status did not exhibit significant associations with efficacy in Group A. Dyslipidemia showed no significant association with efficacy in either group, as indicated by p-values exceeding 0.05.

Obesity was significantly associated with efficacy. Obese participants in Group A exhibited greater efficacy (41.5%) compared to Group B (23%), while non-obese individuals reported higher efficacy in Group B (77%) relative to Group A (58.5%), with statistical significance observed (p=0.020).

Age and hypertension duration showed differing trends between groups. Although age did not significantly differ with efficacy in either group (p=0.158), hypertension duration was significantly longer among participants with positive efficacy in Group B (16.32±8.10 months) compared to Group A (10.64±5.82 months, p<0.001). Blood pressure parameters demonstrated significant associations with efficacy. Pre-systolic blood pressure was slightly higher in Group B participants with positive efficacy (153.28±10.34 mmHg) compared to Group A (148.27±15.10 mmHg, p=0.036). Post-systolic blood pressure showed substantial reductions in Group B participants with positive efficacy (135.40±9.00 mmHg) compared to Group A (142.41±12.93 mmHg, p<0.001). Pre-diastolic blood pressure exhibited no significant differences, but post-diastolic blood pressure demonstrated marked reductions in Group B participants with positive efficacy (73.81±6.78 mmHg) relative to

Group A (82.39±6.19 mmHg, p<0.001).

Table 3

Association of Positive Efficacy of Antihypertensive Medications with Demographic, Clinical, and Blood Pressure Variables Based on Administration Timings

	POSITIVE EFFICACY		p-value
	Morning Time (Group A)	Evening / Night Time (Group B)	
Gender			
Male	31(58.5)	60(69)	0.208
Female	22(41.5)	27(31)	
Residence			
Urban	14(26.4)	43(49.4)	0.007**
Rural	39(73.6)	44(50.6)	
Number of anti-hypertensive drugs			
1	29(54.7)	47(54)	0.851
2	22(41.5)	38(43.7)	
3	2(3.8)	2(2.3)	
Diabetes Mellitus			
Yes	28(52.8)	28(32.2)	0.016**
No	25(47.2)	59(67.8)	
Smoking			
Yes	18(34)	16(18.4)	0.037**
No	35(66)	71(81.6)	
Dyslipidemia			
Yes	6(11.3)	6(6.9)	0.370
No	47(88.7)	81(93.1)	
Obesity			
Yes	22(41.5)	20(23)	0.020**
No	31(58.5)	67(77)	
Age(years)*	56.52±9.56	54.28±8.11	0.158
Hypertension duration(months)*	10.64±5.82	16.32±8.10	<0.001**
Pre Systolic blood pressure(mmHg)*	148.27±15.10	153.28±10.34	0.036**
Post Systolic blood pressure(mmHg)*	142.41±12.93	135.40±9.00	<0.001**
Pre DIA (unit)*	83.11±9.45	83.82±7.89	0.649
Post DIA (unit)*	82.39±6.19	73.81±6.78	<0.001**

DISCUSSION

The incidence of cardiovascular events, such as myocardial infarction, sudden death, and stroke, is highest in the early hours after waking.[23,24] The mechanisms involved in the morning increase in cardiovascular events have been unclear, but recent clinical studies have shown that an exaggerated morning BP surge is a plausible factor involved in the triggering of cardiovascular events, particularly in the case of stroke.[24,25] 1 mmHg morning BP increase was associated with a 2.1% increased risk of cardiovascular death.[26] More and more evidences[27,28] show that the morning surge of blood pressure is closely related to cardiovascular events, stroke, and renal impairment. And for medication, guidelines suggest the long-term antihypertensive drugs of 24-hour stable blood pressure can control the large fluctuation of morning blood pressure and reduce the rise of morning peak blood pressure caused by failure to take medicine on time or missing. It is debatable whether the morning administration or evening administration provides the more effective cardiovascular benefit. The objective of this study is to compare effects of morning administration versus evening administration in the management of patients with hypertension.

Our study findings strongly support the notion that evening administration of antihypertensive medications yields superior blood pressure control and overall efficacy compared to morning dosing. The demographic differences between the two groups, including variations in gender distribution and urban-rural residency, suggest potential lifestyle and environmental influences on treatment response. While urban residency showed a significant association with better efficacy in the evening group (p=0.007), rural participants demonstrated higher efficacy in the morning group, highlighting the possible impact of daily activity patterns and medication metabolism. The overwhelmingly higher efficacy in evening administration (87% vs. 53%) presents strong evidence for timing optimization in antihypertensive therapy. These findings align with previous chronopharmacological studies that advocate for evening dosing to leverage nocturnal blood pressure dipping and optimize drug bioavailability. Given the statistical significance of multiple parameters, future research should explore individualized treatment strategies, considering metabolic, behavioral, and lifestyle factors to maximize therapeutic outcomes.

A critical factor influencing antihypertensive response was hypertension duration, where longer-standing hypertension in Group B (16.32±8.10 months vs. 10.64±5.82 months, p<0.001) corresponded with improved evening treatment efficacy. This may indicate that patients with chronic hypertension benefit from circadian-based drug optimization. Furthermore, blood pressure parameters provide compelling evidence for evening superiority, as post-systolic and post-diastolic reductions in Group B were significantly greater (135.40±9.00 mmHg, 73.81±6.78 mmHg) compared to Group A (142.41±12.93 mmHg, 82.39±6.19 mmHg, p<0.001). These differences reinforce the influence of circadian physiology on antihypertensive pharmacodynamics. Additional clinical variables demonstrate important associations. Diabetes mellitus favored morning administration efficacy (p=0.016), suggesting that metabolic factors may alter drug responsiveness. Conversely, smoking significantly impaired efficacy in Group B (p=0.037), underscoring its negative impact on evening drug absorption and cardiovascular benefit. Obesity also exhibited a noteworthy effect, with reduced efficacy in evening administration (p=0.020), potentially implicating metabolic dysregulation in medication absorption and therapeutic action.

A study[29] showed that the morning surge of BP, a risk factor for stroke, was significantly reduced only after bedtime administration of nifedipine. Bedtime in comparison to awakening-time ingestion of nifedipine was also associated with a reduction in the incidence of edema from 13% to 1%. Taking antihypertensive drugs before going to bed can improve the compliance of patients, and some commonly used drugs, such as statins, in the same way, are suggested to be taken before going to bed. Especially for many elderly people who live a lifestyle of get up early and doing morning exercises tend to be affected by morning blood pressure surge.

Some opposing views are that the sharp decrease in blood

pressure at night would bring adverse effects on organ blood supply. A study[30] showed that although no obvious difference was found in adverse drug reactions between the 2 groups (patients were provided with a single pill containing amlodipine / atorvastatin (5/20 mg) to be taken each night at 10 PM vs patients were taking amlodipine (5 mg) and atorvastatin (20 mg) each morning at 7 AM), compliance was much better in the single-pill group than in patients taking 2 medications separately.

Another research[31] showed that taking antihypertensives at bedtime nearly halved cardiovascular deaths when compared with morning dosing.

A meta-analysis showed that evening administration could significantly improve asleep BP control and 24 h/48 h BP control in patients with essential hypertension and the non-dipper hypertensive patients, except for the awake BP control.[4] These findings were consistent with some of the previous studies.[32] Similarly, the same meta-analysis compared with morning administration, evening administration noted a significant decrease of asleep BP and awake BP in patients with renal hypertension, except for the 24 h/48 h BP control. These findings were consistent with Wang's study.[33]

In brief, evening administration of antihypertensive medications indicated better BP-lowering effect on asleep BP when compared to conventional morning dosage.[4] An increased nocturnal decline has been shown to indicate a more variable pattern in daily BP which stabilizes BP and lowers cardiovascular risk.[34] This meta-analysis found that the evening administration showed advantages in reducing cardiovascular disease events and overall adverse effects. These therapeutic benefits of the ingestion-time differences may be caused by the circadian rhythm-dependent disparity in effects upon the pharmacokinetics and pharmacodynamics of BP-lowering medications that occur in association with the differential staging during the 24 h of neuroendocrine and other circadian rhythm-organized mechanisms of BP regulation.[35]

In another meta-analysis of 72 RCTs that also evaluated the effect of antihypertensive drugs morning versus evening dosing showed significant reduction of ambulatory BP, and numerically lower risk of cardiovascular events in patients randomized to evening dosing when compared with morning dosing. Traditionally antihypertensive drugs are administered in the morning.[36] For almost 2 decades, numerous concerns were voiced about these data, particularly also about the 2 randomized controlled trials by Hermida et al, MAPEC and HYGIA.[37-39] These considerations led to a letter of concern issued by European Heart Journal in 2020,[40] which could not document scientific misconduct but outlined concerns regarding some of the findings.[41]

The data of the same meta analysis documented that evening dosing compared to morning dosing lowers night-time SBP by about 4 mmHg (4.6 mm Hg in Hermida trials and 3.4 mmHg in the non-Hermida trials). This nocturnal BP fall is clinically meaningful and, depending on the situation, as Burnier et al[39] have outlined, may possibly confer benefits or harm. Clearly, it should be carefully taken into account when evening dosing is considered and these results are in line with a recent census document by Stergiou et al,[16].

Most recently, the TIME (Treatment in Morning versus Evening) study from the United Kingdom which randomized 21,104 patients (10,503 in evening dose group and 10,601 in morning dose group) with a median follow-up of 5.2 years reported no significant differences (unadjusted hazard ratio 0.95 [95% CI, 0.83–1.10]; P=0.53) in primary composite end point (hospitalization for nonfatal myocardial infarction or nonfatal stroke, or vascular death) between the 2 groups.[13,15,42] Similarly, the TIME study documented nonadherence at any time of 22.5% with morning dosing as opposed to 39% with evening dosing (P<0.001).[13]

This study has certain limitations. First, our analysis consisted mainly of small-scale in specific geographic areas so the extent of generalizability and trends in different populations is unknown. Second, adherence with antihypertensive drugs was not reported. Third, not all commercially available antihypertensive drugs were represented in this analysis.

CONCLUSION

Our study results demonstrate that evening administration of antihypertensive medications significantly improves efficacy compared to morning dosing, with greater reductions in systolic and diastolic blood pressures and a higher effectiveness rate (87% vs. 53%). Further, urban residency was associated with better treatment response in the evening group, while longer hypertension duration also favored evening administration efficacy. Additionally, metabolic and lifestyle factors influenced treatment outcomes, with diabetes favoring morning dosing, smoking reducing efficacy in the evening group, and obesity showing a significant association.

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