Open Access

Original Article

Comparison of Effects of Morning versus Evening dosing of Anti-hypertensive Medications on Blood Pressure Control and Complications

Maryam Saleem, Amer Fakhr, Ahsan Amer*, Ahmed Amer**

Department of Medicine, Pak-Emirates Military Hospital Rawalpindi/National University of Medical Sciences (NUMS) Pakistan, *Department of Medicine, Fauji Foundation Hospital, Rawalpindi Pakistan, **Department of Medicine, Combined Military Hospital, Kharian/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare blood pressure control in morning versus evening dosing of anti-hypertensive medications in hypertensive patients.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Medicine, Pak-Emirates Military Hospital Rawalpindi, Pakistan from Jan to Aug 2023.

Methodology: Total 450 hypertensive patients were enrolled and segregated into two groups of 225 each. Group-A was given anti-hypertensive in the morning while Group-B was given in the evening. Blood pressure was noted at the start of the study and on every 2 monthly follow-ups with medication titration. Variables including hypertension duration, medications and complications were assessed and compared.

Results: A total 268 patients were included in the final analysis with a mean age of 48.03±9.70 years in Group-A and 48.38±10.02 years in Group-B participants. Non-fatal myocardial infarction was in 51(36.2%) of Group-A and 43(33.9%) of Group-B individuals. Baseline systolic and diastolic BP were 154.24±12.03 & 91.96±5.56 mmHg respectively in morning dosing group and 156.58±12.36 & 92.77±6.13 mmHg in evening dosing group. There was slightly better control in the evening dosing group with SBP and DBP at the 6-month follow-up 141.40±4.22 and 85.28±3.05 mmHg respectively versus 142.23±5.26 and 86.60±3.58 mmHg in morning dosing group.

Conclusion: Slightly well but statistically insignificant control of SBP and DBP was observed in the evening dosing group with no significant difference in overall BP control and complications.

Keywords: Anti-hypertensive, Cardiovascular, Diastolic BP, Primary Hypertension, Systolic BP.

How to Cite This Article: *Saleem M, Fakhr A, Amer A, Amer A. Comparison of Effects of Morning versus Evening dosing of Anti-hypertensive Medications on Blood Pressure Control and Complications. Pak Armed Forces Med J 2025; 76(Suppl-2): S363-S367.*
DOI: https://doi.org/10.51253/pafmj.v76iSUPPL-2.11150

INTRODUCTION

Hypertension (HTN) is a major modifiable risk factor for cardiovascular complications including coronary artery disease (CAD), cerebrovascular disease (CVA), and chronic kidney disease (CKD).[1] It is invariably considered as non-communicable disease and infamously regarded as silent killer owing to high incidence of complications and deaths.[2] The documented overall global prevalence of HTN is 46.7% with around 31.1% of adult (aged 25-60) population (1.39 billion) which is increasing with subsequent years.[3] The prevalence of HTN is on the rise in developed as well as in developing countries making it substantial risk factor for high incidence of morbidity and mortality.[4] According to National Health Survey of Pakistan (NHSP), around 18.9% of Pakistan population 15-44 years and 33% in adults above 45 years are suffering from HTN contributing to overall disease burden and leading to adverse events even in earlier stages of life.[5] Pakistan has high rate of urbanization which strongly effects dietary habits, sedentary lifestyle, lack of physical activities which all contributes towards increasing prevalence of HTN in urban (21.6%) than (16.2%) rural populations.[6]

Studies have demonstrated that Blood pressure (BP) exhibits a circadian rhythm with diurnal variations in morning and night time reason of which is not well known.[7] It is shown that there is physiological decrease in BP during night-time with a surge in early morning or wake-up BP.[7] Nocturnal BP and its dipping pattern during night has significantly prognostic importance towards cardiovascular events during night time in most individuals.[8] In some patients with HTN, lack of fall in BP in night-time (non-dipping pattern) or marked surge in BP during early morning is linked with higher incidence of cardiovascular and cerebrovascular complication.[9]

Correspondence: Dr Maryam Saleem, Department of Medicine, Pak-Emirates Military Hospital Rawalpindi Pakistan
Received: 07 Nov 2023; revision received: 01 Apr 2024; accepted: 24 Apr 2024

Therefore, the main goal for managing HTN is to ascertain that anti-hypertensive to be used which give good control of BP around the clock and preserve normal circadian rhythm of BP in order to minimize the risk for complication and fatal events including myocardial infarction, stroke and renal failure.[10]

Being a developing country, Pakistan has higher incidence of HTN with concerning rate of increasing hypertension and related complication, it needs to improve strategy to prevent and tackle drastic rise in HTN cases. There were multiple small as well as intermediate scale studies around the globe on effects on morning and evening dose of anti-hypertensive medication on diurnal control of BP but there were very limited studies nationwide.

The rationale for conducting this was to compare the effect of morning versus evening dose of anti-hypertensive agents in patients with primary hypertension and to assess BP control among local population.

METHODOLOGY

This Quasi-experimental study was conducted in the department of medicine, Pak-Emirate Military Hospital (PEMH) Rawalpindi from Jan 2023 to Aug 2023 over a period of 8 months following approval from Institutional Ethical Committee (IEC 593/23). Sample size was 236 calculated by online WHO sample size calculator taking confidence level of 95%, margin of error 5% and prevalence of primary hypertension in Pakistan population 18.9%.[11] Total 450 patients with diagnosed primary hypertension presenting to PEMH Rawalpindi fulfilling inclusion criteria were enrolled in the study after informed consent.

Inclusion Criteria: Patients of either gender with age 25-65 years with diagnosed primary hypertension and on at least 1 or more anti-hypertensive medication were included in the study.

Exclusion Criteria: All patients of age more 65 years, underlying diabetes mellitus, thyroid disease, renal disease, cardiac disease, previous stroke, endocrine disease, pheochromocytoma, malignancy, pregnancy and patients working in shifts were all excluded from the study.

All consented hypertensive patients (n=450) included in study were explained the study and then segregated in two groups of 225 in each by lottery method. All patients taking either one or more combination anti-hypertensive medications were included. Group-A participants were advised to take their anti-hypertensive medications in morning (0700 hours) and Group-B were to take their medication in evening (1900 hours). Baseline blood pressure of each individual at the start of study were noted and all patients were advised for twice BP charting daily for two months. All participants were instructed to follow-up for dose adjustment after two months or earlier if experienced any symptoms or developed any complication. BP on every review and mean of their BP record were noted on follow-up review with dose adjustment if needed. Dose titration and medication adjustment if required was done in every follow-up in accordance with sign and symptoms and BP charting. All patients were followed up for at least 6 months till completion of study. The end point of study was considered to be 6 months or any adverse event including cardiovascular, cerebrovascular event or renal failure whichever was earlier. Total 450 patients with primary hypertension were screened and included in study out of which 127 patients lost to follow-up till completion of study and 55 patients died during study period due to cardiovascular and cerebrovascular complications. Total 141 participants in Group-A and 127 in Group-B completed study and were included in final analysis Figure.

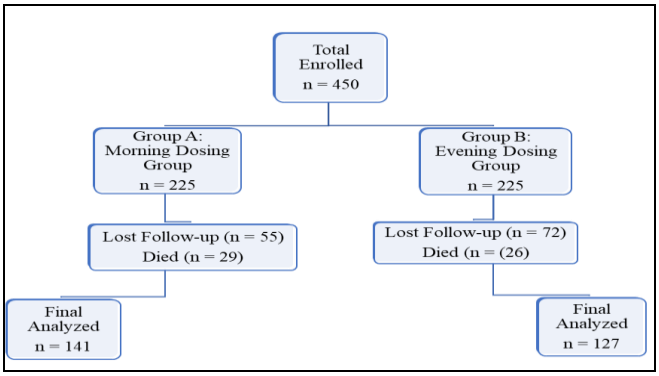

Figure: Summary of Enrolled and Analyzed Participants

Patient`s age, gender, smoking, BMI, family history, mean blood pressure, complications were noted in all patients for analysis. Data were analyzed using Statistical Package for Social Sciences version 25 (SPSS v25). Quantitative data was represented using mean ± standard deviation and qualitative data was represented by using percentage and frequency. Chi square test and paired Samples t test was applied and p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

A total of 268 patients with primary hypertension were included in the final analysis with mean age of 48.03±9.70 years in Group-A versus 48.38±10.02 years in Group-B participants (p=0.227). There were 83 (58.9%) males and 58(41.1%) females in morning dosing Group-A whereas, there were 67(52.8%) males and 60(47.2%) female patients in evening dosing Group-B (p=0.312). There was no statistically significant difference was noted in terms of smoking history, BMI, or duration of HTN among both groups. The majority of the participants of both groups, 62(44.0%) in Group-A and 51(40.2%) in Group-B were noted to have HTN for 3-5 years (p=0.001). Angiotensin-converting enzyme inhibitors (ACEi) or Angiotensin receptor blockers (ARBs) were used by 61 (43.3%) of Group-A patients and 36 (28.3%) of Group-B patients. Calcium channel blockers (CCB) as a single agent were used by 17(12.1%) of Group-A patients and 12(9.4%) of Group-B patients. Dual agents ACEi/ARBs with CCB were given in 31(22.0%) of Group-A patients and 50(39.4%) of Group-B patients whereas ACEi/ARBs with Diuretics were needed in 22(15.6%) of Group-A patients and 8(6.3%) of Group-B patients. A combination of three drugs (ACEi/ARBs + CCB + Diuretics) was noted to be used by 10(7.1%) of Group-A patients and 21(16.5%) of Group-B patients (p<0.05) Table-I.

Table-I: Comparison of Baseline Characteristics Among Groups (n=268)

Parameter(s)		Group-A (Morning Dose Group) n=141	Group-B (Evening Dose Group) n=127	p-value
Age (Mean years±SD)		48.03±9.70	48.38±10.02	0.227
Gender	Male	83(58.9%)	67(52.8%)	0.312
	Female	58(41.1%)	60(47.2%)	
Smoking	Yes	74(52.5%)	80(63.0%)	0.107
	No	67(47.5%)	47(37.0%)	
BMI	20-24	65(46.1%)	76(59.8%)	0.091
	25-30	76(54.9%)	51(40.2%)	
HTN*	1-3 years	21(14.9%)	35(27.6%)	0.001
	4-5 years	62(44.0%)	51(40.2%)	
	>5 years	58(41.1%)	41(32.3%)	
Drugs	ACEi/ARBs*	61(43.3%)	36(28.3%)	< 0.05
	CCB*	17(12.1%)	12(9.4%)	
	ACEi/ARBs + CCB	31(22.0%)	50(39.4%)	
	ACEi/ARBs + Diuretics	22(15.6%)	8(6.3%)	
	Combination (3 drugs)	10(7.1%)	21(16.5%)	
Complications	None	44(31.2%)	43(33.9%)	0.435
	Non-fatal MI	51(36.2%)	43(33.9%)	
	Non-fatal stroke	28(19.9%)	31(24.4%)	
	Vascular Complication	18(12.8%)	10(7.9%)	

HTN: Hypertension, BMI: Body Mass Index, ACEi: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCB: Calcium Channel Blocker

In Group-A 51(36.2%) individuals had non-fatal myocardial infarction (MI) requiring thrombolysis or percutaneous coronary intervention (PCI) vs 43 (33.9%) of Group-B individuals. Also, cerebrovascular accident (CVA)/Stroke was noted in 28(19.9%) of Group-A patients vs 31(24.4%) of Group-B patients. Vascular complications were also observed in a few participants 18(12.8%) of Group-A and 10(7.9%) of Group-B (p=0.387).

Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were noted at the start of the study and then the mean of SBP and DBP on every follow-up visit were also noted for final analysis. In the final analysis no statistically significant difference was observed in mean SBP and DBP among studied groups of morning dosing of anti-hypertensive vs evening dosing of prescribed medications groups Table-II.

Table-II: Comparison of Mean Systolic and Diastolic Blood Pressure among Groups (n=268)

Follow-up		Group-A (Morning Dose Group) n=141 Mean±SD	Group-B (Evening Dose Group) n=127 Mean±SD	p-value
Baseline (0 month	SBP	154.24±12.03	156.58±12.36	0.001
	DBP	91.96±5.56	92.77±6.13	0.031
At 2 months	SBP	150.77±8.46	150.57±8.74	0.634
	DBP	89.76±4.02	90.09±4.28	0.227
At 4 months	SBP	145.89±6.49	145.46±7.08	0.820
	DBP	87.99±4.79	88.06±4.89	0.820
At 6 months	SBP	142.23±5.26	141.40±4.22	0.132
	DBP	86.60±3.58	85.28±3.05	< 0.05

**SBP: Systolic Blood Pressure, DBP: Diastolic blood pressure*

DISCUSSION

In our study there was a slightly better but statistically insignificant control of SBP and DBP observed in the evening dosing group as compared to the morning dosing group. Hypertension (HTN) is a global health concern causing cardiovascular complications leading to increased morbidity and mortality. There is considerable variation in BP during the day and it exhibits circadian rhythm with a fall in BP during sleep with an early morning surge in BP. If once-daily dosing of the anti-hypertensive agent is being used in the morning, it is critical that BP control be maintained 24-hour cycle especially at the end of the dose interval to cover the early morning surge in BP.[12] The latest PURE (Prospective Urban and Rural Epidemiology) study done by Zhou *et al.*, showed that 22.3% of coronary artery disease (CAD) was attributed to HTN.[13] In a study by Saito *et al.*, it was concluded

that patients with higher morning blood pressure (SBP >145mmHg) have greater risk of cardiovascular complications than patients with morning SBP<130 mmHg (Hazard ratio [HR] 2.47, 95% confidence Interval [CI], 1.23-5.08).[14] In the TIME (Treatment in Morning versus Evening) study by Mackenzie *et al*., it was explained that there were 0.69 endpoint event per 100 patient-years (95% CI: 0.65-0.79) observed in 362(3.4%) of evening dose treatment group and 0.72 endpoint event per 100 patient-years (95% CI: 0.83-1.10) were observed in 390(3.7%) participants of morning dosing group (p=0.53).[15]

In our study it was noted that there was a slightly better but statistically insignificant control of SBP and DBP was observed in Group-B (Evening dosing) as compared to Group-A (morning dosing group) which was consistent with many other studies. Olde Engberink *et al*., concluded in a randomized open trial in 19084 hypertensive patients that there was a 3.3 mmHg reduction in systolic nighttime BP in evening dosing individuals and 1.3 mmHg reduction in 48-hour SBP when compared with morning dose group.[16] In this study baseline, SBP and DBP were noted at the start of the study, in the morning dosing group SBP and DBP were 154.24±12.03 & 91.96±5.56 respectively as compared to the evening dosing group 156.58±12.36 & 92.77±6.13. When all participants of both groups followed up and analyzed at the end of the study it was noted there was slightly better control in the evening dosing group with SBP and DBP of 141.40±4.22 and 85.28±3.05 respectively when compared with SBP and DBP morning dosing group 142.23±5.26 and 86.60±3.58 respectively.

It has been explained in studies that risk of cardiovascular incidence like MI, sudden cardiac death and stroke is highest in early hours after waking up whose pathophysiology is not clearly known but morning surge of BP is considered a plausible triggering factor of adverse events. It was observed in studies that 1 mmHg rise in morning BP was linked with 2.1% increased risk of myocardial infarction (MI) and CAD.[17] Similar to other studies, in this study there was slight decreased but statistically insignificant incidence of non-fatal MI events in patients taking anti-hypertensive medications at evening time as compared to morning dosing group 43(33.9%) versus 51(36.2%) respectively. In a study by Hoshide *et al*., it was showed that bedtime administration of nifedipine (Calcium channel blocker) significantly reduced morning surge of BP but there was no statically significant difference in cardiovascular events in morning versus evening dosing of anti-hypertensive agents.[18] Similar study by Salah *et al*., described that evening dosing of anti-hypertensive drugs give slight better control but overall incidence of complications of HTN remained equal in either morning or evening dosing of medicines.[19] Aung *et al*., concluded in a study that there is no significant difference in 5 year major cardiovascular complication of HTN in morning vs evening dosing of anti-hypertensive medicines.[20]

Elahi et al., concluded in his study that Pakistan being a developing country needs to improve strategic plan for prevention of HTN and improvement in policies regarding HTN prevention. Nationwide studies for HTN prevalence and morning versus evening dosing effect on BP control in local population needed to be carried out on a larger scale.[21]

LIMITATIONS OF STUDY

The authors are well aware of the limitation of the study most important being the single-center study and limited sample size. There is the possibility of non-adherence to medication and a large number of participants who lost to follow-up affecting the final analysis and results. The effect of a sedentary lifestyle, high salt diet, and work-related stress on BP variations were also not studied which could have affected BP control. Further studies including control trials are needed with larger sample sets covering multiple centers for more authentic results. Also, studies on the local population with the effect of different groups of anti-hypertensive medication are needed for authentic results before making any conclusion and widespread implementation on the general population.

CONCLUSION

There was a slightly better but statistically insignificant control of SBP and DBP observed in the evening dosing group as compared to the morning dosing group as concluded in some other studies as well. But overall, no significant difference and advantage was noted in morning versus evening dosing of anti-hypertensive drugs regarding BP control and major cardiovascular as well as cerebrovascular adverse events and mortality.

ACKNOWLEDGEMENT

Authors are thankful to all colleagues for assistance in data collection and analysis. Also, we extend our gratitude to patient's attendants, doctors, OPD staff and nursing staff for assistance in patient follow-up charting, BP monitoring and data collection.

Conflict of Interest: None.

Funding Source: None.

Author`s Contribution

Following authors have made substantial contributions to the manuscript as under:

MS & AF: Conception, study design, drafting the manuscript, approval of the final version to be published.
AA & AA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.
Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Shah N, Shah Q, Shah AJ. The burden and high prevalence of hypertension in Pakistani adolescents: a meta-analysis of the published studies. Arch Public Health 2018; 76(1): 20. https://doi.org/10.1186/s13690-018-0265-5
2. Touyz RM. Hypertension 2022 Update: Focusing on the Future. Hypertension 2022; 79(8): 1559–1562. https://doi.org/10.1161/hypertensionaha.122.19564
3. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol 2020; 16(4): 223–237. https://doi.org/ 10.1038/s41581-019-0244-2
4. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 398(10304): 957–980. https://doi.org/10.1016/s0140-6736(21)01330-1
5. Basit A, Fawwad A, Qureshi H, Shera AS. Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016–2017. BMJ Open 2018; 8(8): e020961. https://doi.org/10.1136/bmjopen-2017-020961
6. Riaz M, Shah G, Asif M, Shah A, Adhikari K, Abu-Shaheen A. Factors associated with hypertension in Pakistan: A systematic review and meta-analysis. Wright JM, editor. PLOS ONE 2021; 16(1): e0246085. https://doi.org/10.1371/journal.pone.0246085
7. Burnier M, Kreutz R, Narkiewicz K, Kjeldsen S, Oparil S, Mancia G et al. Circadian variations in blood pressure and their implications for the administration of antihypertensive drugs: is dosing in the evening better than in the morning? J Hypertens 2020; 38(8): 1396–1406. https://doi.org/10.1097/hjh.0000000000002532
8. Douma LG, Gumz ML. Circadian clock-mediated regulation of blood pressure. Free Radic Biol Med 2018; 119: 108–114. https://doi.org/10.1016/j.freeradbiomed.2017.11.024
9. Zhang J, Sun R, Jiang T, Yang G, Chen L. Circadian Blood Pressure Rhythm in Cardiovascular and Renal Health and Disease. Biomolecules 2021; 11(6): 868. https://doi.org/10.3390/biom11060868
10. Gumz ML, Shimbo D, Abdalla M, Balijepalli RC, Benedict C, Chen Y, et al. Toward Precision Medicine: Circadian Rhythm of Blood Pressure and Chronotherapy for Hypertension - 2021 NHLBI Workshop Report. Hypertension 2023; 80(3): 503–522. https://doi.org/10.1161/hypertensionaha.122.19372
11. Iqbal M, Akram M, Rashid A, Zainab R, Laila U, Talha Khalil M, et al. Prevalence of Hypertension and Associated Co-Morbidities in Pakistan. Nurs Health Care 2023; 5(1): 11. https://doi.org/10.30654/MJNH.100011
12. Cortés-Ríos J, Rodriguez-Fernandez M. Circadian Rhythm of Blood Pressure of Dipper and Non-dipper Patients With Essential Hypertension: A Mathematical Modeling Approach. Front Physiol 2021; 11: 536146. https://doi.org/10.3389/fphys.2020.536146
13. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol 2021; 18(11): 785–802. https://doi.org/10.1038/s41569-021-00559-8
14. Saito I, Kario K, Kushiro T, Teramukai S, Yaginuma M, Mori Y, et al. Home blood pressure and cardiovascular risk in treated hypertensive patients: the prognostic value of the first and second measurements and the difference between them in the HONEST study. Hypertens Res 2016; 39(12): 857–862. https://doi.org/10.1038/hr.2016.99
15. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet 2022; 400(10361): 1417–1425. https://doi.org/10.1016/s0140-6736(22)01786-x
16. Olde Engberink RHG, van den Born BJH. [Morning or evening; What is the best time to take antihypertensive drugs?]. Ned Tijdschr Geneeskd 2020; 164: D4637.
17. Zhang P, Jin MY, Song XY, Wang Z, Jiang YH, Yang CH. Comparison of the antihypertensive efficacy of morning and bedtime dosing on reducing morning blood pressure surge: A protocol for systemic review and meta-analysis. Medicine 2021; 100(5): e24127. https://doi.org/10.1097/md.0000000000024127
18. Hoshide S, Yano Y, Haimoto H, Yamagiwa K, Uchiba K, Nagasaka S, et al. Morning and Evening Home Blood Pressure and Risks of Incident Stroke and Coronary Artery Disease in the Japanese General Practice Population: The Japan Morning Surge-Home Blood Pressure Study. Hypertension 2016; 68(1): 54–61. https://doi.org/10.1161/HYPERTENSIONAHA.116.07201
19. Salah HM, Mehta JL. Best time for administration of antihypertensive medications: morning or evening? Lancet 2022; 400(10361): 1383–1385. https://doi.org/10.1016/s0140-6736(22)01900-6
20. Aung K, Htay T. In hypertension, evening vs. morning dosing of antihypertensive drugs did not differ for major CV outcomes at 5.2 y. Ann Intern Med 2023; 176(2): JC16. https://doi.org/10.7326/j22-0116
21. Elahi A, Ali AA, Khan AH, Samad Z, Shahab H, Aziz N, et al. Challenges of managing hypertension in Pakistan - a review. Clin Hypertens 2023; 29(1): 17. https://doi.org/10.1186/s40885-023-00245-6