REVIEW

Korean J Intern Med 2024;39:205-214
https://doi.org/10.3904/kjim.2023.304

Nighttime administration of antihypertensive medication: a review of chronotherapy in hypertension

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Hypertension remains a global health concern because of suboptimal blood pressure control despite advancements in antihypertensive treatments. Chronotherapy, defined as evening or bedtime administration of medication based on biological rhythms, is emerging as a potential strategy to improve blood pressure control and treatment outcomes. Clinical trials have investigated the potential effects of nighttime administration of antihypertensive medication in the improvement of 24 hours blood pressure control and reduction of cardiovascular risk. Implementing chronotherapy in clinical practice could have significant implications in enhancing blood pressure control and improving clinical outcomes in patients with hypertension, particularly those with resistant hypertension. However, recent trials have reported contradictory results, causing confusion in real-world practice. Herein we review, analyze, and critique the current evidence and propose suggestions regarding the clinical application and future directions of chronotherapy.

Keywords: Hypertension; Chronotherapy; Blood pressure

INTRODUCTION

Hypertension is a significant global health concern and the primary cause of numerous cardiovascular diseases (CVDs) [1]. Despite advancements in antihypertensive treatments, optimal blood pressure control has not been achieved [2]. A recent study from South Korea highlighted this issue, showing that in 2020, the rates of hypertension awareness, treatment, and management were 69.5, 64.8, and 47.4%, respectively [3]. The lack of adequate control is a major contributor to the unchanged trend in cardiovascular incidents and deaths over recent decades, both nationally and globally [2,4]. Therefore, the lower-than-expected rates of awareness, treatment, and control of hypertension underscore the need for fundamental reassessment and innovative solutions in this field. This study focuses on one potential solution: the emerging concept of chronotherapy in hypertension. Chronotherapy involves the timing of medication administration in line with biological rhythms, an approach that can significantly enhance treatment efficacy and patient outcomes [5].

CHRONOBIOLOGY IN HUMANS AND ANIMALS

Diurnal variation in cardiovascular parameters, such as blood pressure, heart rate, and contractility, plays an essential role in maintaining cardiac homeostasis [6]. Such variation is regulated by the molecular clock, a fundamental mechanism that governs circadian rhythms and ensures optimal cardiovascular function and responses to injury [7]. Disruptions in circadian rhythms can profoundly impact cell death signaling processes, including apoptosis, autophagy, and necrosis, contributing to the pathogenesis and progression of CVDs such as myocardial infarction, heart failure, and arrhythmia

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

[8]. The intricate molecular mechanisms underlying the circadian control of these signaling processes involve specific clock genes, reactive oxygen species, and stress-response metabolic pathways [9].

Chronobiology, the study of biological rhythms and their synchronization with external cues, has shed light on the circadian regulation of physiological processes in humans and other animals [10]. In human studies, diurnal variation has been observed in various cardiovascular parameters [11]. For instance, blood pressure tends to be higher during the day and lower at night, reflecting the influence of circadian rhythms [12,13]. Heart rate follows a similar pattern, with higher rates during wakefulness and lower rates during sleep [14]. This diurnal variation plays a critical role in maintaining cardiac homeostasis and optimizing cardiovascular function. Animal studies have provided further insight into chronobiology. In experiments conducted on rodents, disruptions in circadian rhythms have been shown to adversely affect cardiovascular health [15]. Altering the light–dark cycle or manipulating clock genes can lead to abnormal cardiovascular function, increasing the risk for morbidity and mortality [15-18]. Furthermore, cardiac contractility demonstrates diurnal fluctuations, with higher values during the day and lower values at night [19]. These findings highlight the importance of the circadian system in cardiovascular physiology and pathology and emphasize the need to consider chronobiological factors to understand and treat CVDs. Therefore, gaining a comprehensive understanding of the molecular intricacies of chronobiology and harnessing the potential of targeting the clock or aligning drug administration with circadian rhythms hold great promise for enhancing treatment efficacy and improving outcomes in individuals with CVD. By incorporating these insights into clinical practice, we can unlock new paths for precision medicine and optimize therapeutic interventions to improve cardiovascular health.

BIOLOGICAL RHYTHM AND BLOOD PRESSURE

Blood pressure exhibits a natural circadian rhythm characterized by diurnal variation, including morning surges and nighttime dips. In people with essential hypertension, the observed increase in daytime blood pressure predominantly originates from an elevated sympathetic tone [20,21]. This elevation has been substantiated by increased plasma levels of norepinephrine and epinephrine along with higher urine concentrations of catecholamine, which are particularly noticeable in the hours after awakening in the morning [22,23]. Furthermore, the circadian rhythm in the renin-angiotensin-aldosterone system, which shows its highest activity levels in renin, angiotensin-converting enzyme (ACE), angiotensin I and II, and aldosterone immediately before the typical morning wake-up time, also significantly contribute to 24 hours blood pressure regulation [24,25]. Blood pressure variability, specifically the morning surge, is closely associated with a higher risk for cardiovascular events such as stroke and myocardial infarction [26,27]. The morning surge is a rapid increase in blood pressure after waking up and commencing activities. Importantly, many patients with hypertension do not experience the typical nighttime blood pressure dip of approximately 10–20%, amounting to approximately 30–45% of the hypertensive population [28,29]. This non-dipping pattern is associated with a higher risk for cardiovascular events (particularly left ventricular hypertrophy), increased arterial stiffness, and chronic kidney disease [30,31]. These findings underline the importance of considering circadian rhythm in hypertension management, specifically the potential benefits of nighttime drug administration to reduce blood pressure variability and increase nighttime blood pressure dip.

CONCEPT OF CHRONOTHERAPY

Chronotherapy is a therapeutic approach that aligns treatment with the patient's biological clock to optimize efficacy and minimize side effects. The concept has been applied in many fields such as oncology, psychiatry, and cardiology [30,32,33]. Circadian rhythms significantly modulate the outcomes of cancer therapies, and emerging evidence supports the use of chronomodulated chemotherapy [32]. This therapeutic strategy, which is synchronized with the patient's biological clock, aims to optimize treatment efficacy while reducing side effects by aligning drug delivery with the periods of greatest sensitivity in cancer cells and least vulnerability in normal cells. Circadian rhythms fundamentally influence various psychiatric conditions, including mood and sleep disorders [33]. Chronotherapeutic strategies such as light therapy, sleep regulation, and the use of melatonin agonists highlight the essential role of circadian rhythms in managing depressive disorders. Moreover, for

https://doi.org/10.3904/kjim.2023.304

the treatment of CVD, understanding the circadian rhythms of cardiovascular parameters such as blood pressure, heart rate, and endothelial function has led to tailored therapeutic strategies. For instance, the timing of antihypertensive medication and statin administration is often adjusted based on these rhythms. Ambulatory blood pressure monitoring over 24 hours is utilized to identify non-dipping patterns, thus guiding individualized treatment plans. Furthermore, the scheduling of certain cardiac procedures is influenced by circadian variation to optimize outcomes [30].

NIGHTTIME ADMINISTRATION OF ANTIHYPERTENSIVE MEDICATIONS

The practice of administering antihypertensive medications at night is rooted in the principles of chronotherapy. Nighttime administration of certain antihypertensive drugs can better control early morning blood pressure surges, which are associated with an increased risk for cardiovascular events [34]. Among antihypertensive drugs, the literature on ACE inhibitors predominantly emphasizes the effects of their evening or nighttime dosing on blood pressure control [35-46]. When administered in the evening, ACE inhibitors seem to notably modulate the circadian blood pressure rhythm toward a more physiological dipping pattern compared to morning administration [47,48]. This effect is attributed to the 24 hours fluctuations in the renin-angiotensin-aldosterone system and its enhanced activation during nighttime sleep. Such dynamics are postulated to be key reasons for the more pronounced blood pressure reduction when ACE inhibitors and angiotensin II receptor blockers are administered at bedtime than in the morning. Importantly, these findings were predominantly derived from studies with small numbers of participants, potentially limiting the generalizability of the results. However, this approach may be particularly beneficial for patients exhibiting non-dipping blood pressure patterns because nighttime treatment is associated with improved cardiovascular outcomes, including a reduced risk for myocardial infarction and stroke [49].

The effect of nighttime administration of antihypertensive medication may be applicable to shift workers. Shift workers, particularly those working night or rotating shifts, can experience a range of health issues caused by disrupted circadian rhythms. This can result in poor sleep quality, reduced cognitive function, and a greater risk for various health problems, including CVDs, increased 24 hours blood pressure and blood pressure during sleep, and reduced blood pressure dipping during sleep [50-52]. However, limited research has been conducted on the effects of chronotherapy on hypertension, specifically among shift workers. Implementing effective chronotherapy for shift workers can be challenging because their schedules may not align well with typical daily patterns.

CLINICAL TRIALS AND STUDIES

Zhao et al. [53] conducted a systematic review and meta-analysis that explored the comparative efficacy of morning and evening administration of antihypertensive medications. Based on 21 randomized controlled trials involving 1,993 patients, evening administration led to superior 24 hours blood pressure control compared to morning administration, with a decrease in the 24 hours systolic blood pressure (by an average of 1.61 mmHg) and a decrease in the 24 hours diastolic blood pressure (by an average of 1.23 mmHg). Notably, applying the doxazosin gastrointestinal therapeutic system (4 mg/d) led to a reduction in the 24 hours systolic blood pressure (by 5.10 mmHg) and a decrease in the 24 hours diastolic blood pressure (by 2.70 mmHg). Similarly, for diuretic torsemide (5 mg/d), the evening dosing regimen showed a reduction in the 24 hours systolic blood pressure by 6.24 mmHg and in the 24 hours diastolic blood pressure by 5.95 mmHg compared to the morning regimen. However, the rates of overall adverse effects and withdrawals due to such effects were statistically indistinguishable between the morning and evening regimens. Despite these promising results, the clinical implications of these encouraging findings remain uncertain because of the lack of clear benefits on mortality and morbidity. Therefore, more long-term randomized controlled trials are necessary to gain a more comprehensive understanding of the time-dependent effects of antihypertensive drug administration on cardiovascular outcomes. Several clinical trials have shed light on the potential benefits of chronotherapy for the management of hypertension (Table 1). The Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares study (MAPEC) [30] was a key study on the impact of the timing of antihypertensive medication. It found that taking at least one antihypertensive medication at night could significantly reduce the risk for cardiovascular events compared to taking all

Table 1. Current and ongoing clinical trials of chronotherapy in hypertension management

Trial name	Study design	Study population	Sample size	Intervention	BP control	Primary outcome (CVD outcome)	Result
MAPEC [30]	Prospective, randomized, open-label, blinded endpoint	Hypertensive adults	2,156 adults	Administration of all hypertension medications upon awakening vs. ingesting ≥ 1 of them at bedtime	Sleep-time systolic BP was significantly lower in the bedtime treatment group (110.9 mmHg vs. 116.1 mmHg; $p < 0.001$)	Incidence of total events (death from all causes, CVD events, cerebrovascular events, heart failure, acute arterial occlusion of the lower extremities, rupture of aortic aneurysms, and thrombotic occlusion of the retinal artery)	Reduced incidence of total events. Bedtime treatment group: Lower risk of total events: RR 0.39, 95% CI 0.29–0.51 Lower risk of major CVD events[a]: RR, 0.33; 95% CI, 0.19–0.55
Hygia Chronotherapy [49]	Prospective randomized open-label, blinded endpoint trial	Hypertensive adults	19,084 adults	Bedtime vs. Upon-waking administration	Lower sleep-time blood pressure: Nighttime BP: 123.0 mmHg (bedtime) vs. 126.2 mmHg (upon-waking)	Incidence of cardiovascular events (myocardial infarction, coronary revascularization, heart failure, stroke, and CVD death)	Reduced incidence of cardiovascular events. Bedtime treatment group: Lower risk of CVD outcome: HR 0.55, 95% CI, 0.50–0.61
TIME [55]	Randomized controlled trial	Hypertensive patients	21,104 patients	Morning vs. Evening administration	-	Incidence of primary outcome event (vascular death or hospitalization for non-fatal myocardial infarction or stroke)	Evening group: 3.4% (0.69 events/100 patient-years) Morning group: 3.7% (0.72 events/100 patient-years)
BedMed [56]	Prospective randomized open-label	Ongoing study	Ongoing	Bedtime vs. Morning administration	-	All-cause mortality or hospitalization for myocardial infarction, stroke, heart failure	-
BedMed-Frail [57]	Prospective randomized open-label	Frail, older population residing in long-term care facilities	Ongoing	Bedtime vs. Morning administration	-	All-cause mortality or hospital admissions or emergency department visits due to cardiovascular events	-

BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MAPEC, Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares; RR, relative risk; TIME, Treatment in Morning versus Evening.

[a]Included CVD deaths, myocardial infarction, ischemic stroke, and hemorrhagic stroke.

https://doi.org/10.3904/kjim.2023.304

medications in the morning. This prospective, randomized, open-label, blinded endpoint trial involved 2,156 patients with hypertension who were randomized to ingest either all of their prescribed hypertension medications upon awakening or one or more of the medications at bedtime. Patients who took at least one of their antihypertensive medications at bedtime had significantly lower mean sleep-time blood pressure (110.9 mmHg in the bedtime treatment group vs. 116.1 mmHg in the upon-waking treatment group; $p < 0.001$) and a reduced prevalence of non-dipping during an average 5.6-year follow-up. Most importantly, the bedtime treatment group showed a significantly lower risk for total events including all-cause death, CVD events, cerebrovascular events, heart failure, acute arterial occlusion of the lower extremities, rupture of aortic aneurysms, and thrombotic occlusion of the retinal artery. This significantly reduced risk was consistent across the major CVD events including CVD death, myocardial infarction, ischemic stroke, and hemorrhagic stroke.

Building on this evidence, the Hygia Chronotherapy Trial [49] conducted a more in-depth investigation of the influence of the timing of antihypertensive medication administration on cardiovascular outcomes. It included a large cohort of 19,084 hypertensive adults, and participants were assigned to receive their entire daily dose of one or more hypertension medications at bedtime or upon awakening. Patients who took their medications at bedtime exhibited significantly lower sleep-time blood pressure during an average 6.3-year follow-up (nighttime blood pressure: 123.0 mmHg in the bedtime treatment group vs. 126.2 mmHg in the upon-waking treatment group; $p < 0.001$) and better blood pressure control ($p < 0.001$). The bedtime treatment group had a lower incidence of primary CVD outcomes, including myocardial infarction, coronary revascularization, heart failure, stroke, and CVD death. This significantly reduced risk was consistent across various CVD events, including cardiovascular death, myocardial infarction, and stroke. Thus, that trial provided robust evidence that bedtime administration of antihypertensive medication significantly reduces the risk for CVD compared to upon-waking treatment. However, it also raised several ethical concerns that merit rigorous scrutiny [54]. Notably, the trial's participant numbers increased without a clear explanation, and the absence of well-established interim analysis protocols also undermines the study's ethical framework. Furthermore, inconsistencies in the reporting of the trial designs bring the validity of the data into question. Statistically significant initial group differences and an unusually large effect size raised concerns about potential imbalances and biases impacting the outcomes. Finally, there was no independent verification of the source data. Hence, despite the promising findings of the trial, these methodological and ethical discrepancies need to be addressed before the results can be considered applicable to clinical practice.

In contrast, the Treatment in Morning versus Evening (TIME) study [55] conducted in the UK presented a different perspective regarding the influence of timing on antihypertensive medication administration. This randomized controlled trial included 21,104 patients who were randomly assigned to take antihypertensive medications in the morning or evening. The study was conducted from December 2011 to June 2018 with a median follow-up of 5.2 years. No significant differences were observed in the primary endpoint events, which included vascular death or hospitalization for nonfatal myocardial infarction or stroke, with 362 (3.4%) patients in the evening group (0.69 events per 100 patient-years; 95% confidence interval [CI], 0.62–0.76) and 390 (3.7%) patients in the morning group (0.72 events per 100 patient-years; 95% CI, 0.65–0.79), yielding an unadjusted hazard ratio of 0.95 (95% CI, 0.83–1.10; $p = 0.53$). However, the timing of medication intake influenced side effects, adherence, and blood pressure patterns, with a slightly lower occurrence of falls and higher nonadherence reported in the evening group.

Building on the findings of both trials, two major ongoing studies are investigating the impact of dosing times on antihypertensive agents: the BedMed [56] and BedMed-Frail [57] trials. Both studies have adopted a prospective, open-label, blinded endpoint design to further elucidate the nuances and potential implications of the timing of antihypertensive medication administration. The BedMed [56] trial is a prospective, randomized, open-label trial designed to explore the impact of the timing of antihypertensive medication intake to identify the most effective timing for antihypertensive medication and thus improve patient health outcomes. Including participants from five Canadian provinces, this study is comparing bedtime administration with traditional morning intake and investigating their potential effects on adverse cardiovascular events. The participants are being monitored at precise intervals of 1 week, 6 weeks, 6 months, and every 6 months thereafter. The primary outcome measure is a composite of all-cause death

or hospitalization for myocardial infarction, acute coronary syndrome, stroke, or congestive heart failure. The secondary outcomes include individual primary outcome components, new glaucoma diagnoses, and cognitive decline. Extending the inquiry from the general population to a more specific demographic, the BedMed-Frail trial [57] has turned its focus toward the frail, older populations residing in long-term care facilities. Following the same investigative team as that of BedMed, this prospective, randomized, open-label clinical trial is investigating the effects of the timing of antihypertensive medication in a vulnerable cohort. Participants were chosen based on the following criteria: they live in a care facility where caregivers control medication timing, have had at least two recorded hypertension diagnoses since 2002, and are taking once-daily antihypertensive medication. Individuals with a history of glaucoma are excluded to avoid nocturnal hypotension. The central hypothesis of the study is that administering antihypertensive medications at bedtime, compared to traditional morning intake, can significantly reduce the incidence of major adverse cardiovascular events. The primary outcome is a composite measure of all-cause mortality and hospital admissions or emergency department visits for acute coronary syndrome, myocardial infarction, heart failure, or stroke.

CURRENT GUIDELINES FOR CHRONOTHERAPY

The nocturnal administration of at least one antihypertensive agent, as opposed to the conventional morning dosing, is associated with potential benefits including improved blood pressure control and a reduced risk for cardiovascular events. Recent studies have the potential to influence forthcoming revisions of hypertension treatment guidelines, incorporating recommendations regarding the strategic timing of antihypertensive medication. Nevertheless, specific directives regarding chronotherapy using antihypertensive medications have not yet been established by either the American Heart Association [58] or the European Society of Hypertension [59] (Table 2). The Korean Society of Hypertension guidelines [60] also do not provide specific recommendations regarding chronotherapy. Furthermore, the 2023 American Diabetes Association (ADA) guidelines [61] have taken a cautious approach. Although the potential benefits of evening dosing of antihypertensive medications were acknowledged in early clinical trials, these results were not consistently reproduced in subsequent trials. As a result, the ADA does not currently recommend the preferential use of antihypertensives at bedtime. By contrast, the Japanese Society of Hypertension guidelines [62] recommend nighttime or evening administration of antihypertensive drugs for patients with resistant or poorly controlled hypertension, particularly those who exhibit morning or nighttime hypertension, because of the insufficient duration of drug efficacy.

Chronotherapy offers potential benefits but also raises concerns. A significant concern is the phenomenon of "over-dipping," defined as an excessive decline in nighttime blood pressure [54]. Such over-dipping has been linked to increased risks for myocardial ischemia and silent cerebral infarction, particularly among elderly patients [63,64]. Given these potential risks and the varying results from different studies, a balanced perspective is essential. For hypertension management using chronotherapy, clinicians should consider nighttime administration of antihypertensive agents for

Table 2. Guidelines for chronotherapy in hypertension management

Organization	Recommendations
American Heart Association guideline, 2017 [58]	No specific recommendations for chronotherapy of antihypertensive medication
European Society of Hypertension guideline, 2018 [59]	No specific recommendations for chronotherapy of antihypertensive medication
Korean Society of Hypertension guideline, 2022 [60]	No specific recommendations for chronotherapy of antihypertensive medication
American Diabetes Association guideline, 2023 [61]	Cautious approach to chronotherapy of antihypertensive medications - Acknowledges potential benefits of evening dosing based on early trials - Results not consistently reproduced in subsequent trials - Does not recommend preferential use of antihypertensives at bedtime
Japanese Society of Hypertension guideline, 2019 [62]	Nighttime or evening administration of antihypertensive drugs for patients with resistant or poorly controlled hypertension due to insufficient duration of drug efficacy

https://doi.org/10.3904/kjim.2023.304

potentially improved blood pressure control, while closely monitoring for over-dipping and associated risks, particularly in elderly patients.

The discrepancy between the results of clinical trials and the current guidelines highlights the complexity of this issue. Therefore, further research is essential to confirm these findings and identify the potential risks and challenges inherent in implementing chronotherapy in the management of patients with hypertension.

CONCLUSION

Chronotherapy in hypertension management shows promise for improving blood pressure control and reducing cardiovascular risk. Clinical trials have demonstrated the potential benefits of nocturnal antihypertensive medications. However, current guidelines do not provide specific recommendations regarding chronotherapy. Further research is needed to establish the optimal timing and guide the development of comprehensive guidelines. Understanding the time-dependent effects of medication administration could have significant clinical implications, leading to improved treatment strategies for hypertension and patient outcomes.

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Received : July 19, 2023
Revsied : August 14, 2023
Accepted : September 1, 2023

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Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by grant from Ministry of Trade, Industry and Energy of Korea (no. 20016181).

https://doi.org/10.3904/kjim.2023.304