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Effect of bedtime administration of blood-pressure lowering agents on ambulatory blood pressure monitoring results: A meta-analysis

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Abstract

Background: *Bedtime administration of antihypertensive drugs currently receives more attention, but no clear consensus has been reached on the blood pressure (BP)-lowering effect of this strategy.*

Methods: *We systematically searched literature for clinical trials of ingestion time of antihypertensive drugs evaluated by ambulatory blood pressure monitoring (ABPM) to perform a meta-analysis which aimed at determining the difference in diurnal, nocturnal, and 24-h mean of systolic BP (SBP) and diastolic BP (DBP), absolute BP reduction from baseline between bedtime administration group (experimental group) and morning (awaking) administration group (control group).*

Results: *The synthesis analysis showed that the level of BP in bedtime administration group was lower than the morning administration group, which reduced diurnal SBP/DBP by 1.67/1.13 mm Hg ($p = 0.36/0.48$), 24-h SBP/DBP by 2.78/0.36 mm Hg ($p = 0.09/0.62$), nocturnal SBP/DBP by 6.32/3.17 mm Hg ($p = 0.03/0.007$). Furthermore, there was lack of statistically significant differences in the diurnal mean of SBP/DBP reduction from baseline between the two groups ($p = 0.94/0.85$), but bedtime administration resulted in significant reduction from baseline in the nocturnal mean of SBP/DBP, by –4.72/–3.57 mm Hg ($p = 0.01/0.05$). Funnel plot demonstrated that there was no evidence of publication bias.*

Conclusions: *Administration of ≥ 1 antihypertensive drugs at bedtime or evening results in a greater reduction of nocturnal hypertension than dosing in the morning without loss of efficacy of diurnal and 24 h mean BP reduction.* (Cardiol J 2016; 23, 4: 473–481)

Key words: hypertension, ABPM, antihypertensive drugs, bedtime, meta-analysis

Introduction

Hypertension is a global public health issue. As the World Heart Association data shows, globally cardiovascular (CV) disease accounts for approximately 17 million deaths a year, nearly one third of the total CV disease population. Of these, complications of hypertension account for 9.4 million deaths worldwide every year. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% due to stroke [1].

In recent hypertension guidelines [2–7], the criteria for hypertension in different measurement

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methods and the drugs recommended for treating hypertension with different clinical conditions are clear, but uncontrolled hypertension which may lead to serious CV events, increase dosage, and have lifethreatening consequences is present in most patients treated with only a single morning dose or fixed dose drug combination [8], therefore monitoring and management of high blood pressure (BP) is crucial. The mean nocturnal BP value has been suggested as the most sensitive predictor of cardio- and cerebrovascular morbidity and mortality, in other words, insufficient BP fall at night compared to daytime level or a non-dipping pattern is associated with elevated risk of end-organ injury, particularly to heart (left ventricular hypertrophy, congestive heart failure and myocardial infarction), brain (stroke), and kidneys (albuminuria and progression to end-stage renal failure), as well as poor prognosis [9–11]. Decreasing nighttime BP and bedtime administration of antihypertensive drugs have already been taken into account for the treatment strategy aiming to improve BP management, but no clear consensus has been reached on the BP-lowering effect of this strategy. Recent researches have documented that ingesting at least one antihypertensive medication at bedtime, compared with treatment with all medications upon awakening, showed a significant reduction in the 24-h mean systolic BP (SBP)/diastolic BP (DBP) and the reduction was much more prominent during nighttime, decreasing the prevalence of non-dipping [8, 11, 12], however, the similar 24-h mean SBP/DBP reduction for both treatment times was also reported [13–15]. Therefore, we conducted this meta-analysis to investigate the effects of bedtime administration of BP-lowering agents on ambulatory BP monitoring (ABPM) results.

Methods

Literature search

This meta-analysis was conducted in accordance with PRISMA guidelines [16]. ISI Web of Science, Embase, Cochrane, and Pubmed were searched in October 2015 using combinations of the following search terms: bedtime administration, night, evening, antihypertensive drugs, antihypertensive effect. No restrictions were imposed. The reference lists of all retrieved articles were also reviewed to identify additional articles missed by using these search terms. All searches were performed independently by two investigators and disagreements were resolved by consensus.

Inclusion criteria

Studies were included if they met the following criteria: 1) Adult patients who satisfied the diagnosis criteria of hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg), including essential hypertension and secondary hypertension; 2) Randomized or non-randomized experimental trials with at least 8 weeks' treatment duration of antihypertensive drugs (angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers, diuretics, angiotensin receptor blockers, and alpha-blockers); 3) Intervention was defined as one or more antihypertensive drugs administered at bedtime (from 5:00 p.m. to 12:00 midnight), the control group was matched to the experimental group by drug and dose but with a morning regimen or in awaking time (from 6:00 a.m. to 12:00 noon); 4) The pre- and post-treatment SBP and DBP of each patient were measured by ABPM. ABPM is now the gold standard method and the most cost-effective strategy for diagnosing hypertension, evaluating true BP level [17]. It has been shown to be a better predictor of CV morbidity and mortality as compared to office BP measurements [18].

Data extraction

We extracted the following data from each of the studies included: the first author, year of publication, study country, sample size, patient characteristics (age, gender, hypertension type), interventions (grouping, types of drugs, intervention duration), and study design. Any discrepancies were resolved by discussion. All of the obtained data were examined carefully for accuracy. Corresponding authors were contacted by email for additional information needed in this meta-analysis.

Statistical analysis

All included studies were grouped according to the intervention regimen. The data from each included trial were analyzed using Review Manager (RevMan, Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The meta-analysis was performed using the generic inverse variance. Statistical heterogeneity among studies was assessed using I^2 statistic. Mild, moderate, and severe heterogeneity were defined by I^2 values of 25%, 50%, and 75%, respectively. The random-effect model was applied throughout this meta-analysis, regardless of I^2 value, in order to get a consistent conclusion. The funnel plot was used to assess the presence of publication bias. $P \leq 0.05$ was considered statistically significant.

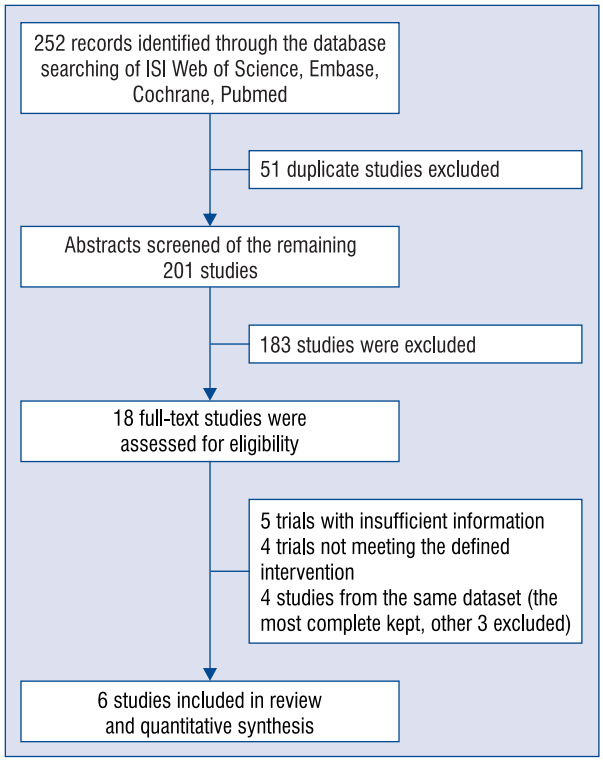

Figure 1. Flowchart for eligible studies.

Results

Flow of included studies

A total of 252 studies were identified by searching ISI Web of Science, Embase, Cochrane, and Pubmed. Fifty-one studies were duplicates, 183 were irrelevant, 18 relevant full-text studies were assessed for eligibility, and finally 6 trials fulfilled the inclusion criteria (Fig. 1).

Study characteristics

A total of 1,566 hypertensive individuals from 6 clinical trials were included in this meta-analysis. The 6 studies were randomized controlled trials (RCTs), one had a crossover design and the others were of a parallel design. Three studies were conducted in Spain but on independent groups of participants, 1 in Japan, 1 in Israel, 1 in Denmark. The numbers of participants were ranged from 41 to 661. The treatment duration of antihypertensive drugs ranged from 8 weeks to 5.4 years. The population of hypertension (primary or secondary, with or without type 2 diabetes mellitus) and the antihypertensive drugs among the trials were different, representing substantial heterogeneity. Detailed information of the 6 trials was shown in Table 1.

Table 1. Baseline characteristics of the included studies.

Study	Country	N	Patients	Drug	Male/ /Female	Age	Experimental/ /Control	Study type	Duration
Farah, 2013 [8]	Israel	60	Uncontrolled hypertension with a non-dipper pattern	CCB, ACEI	40/20	50 ± 2.4	30/30	RCT, parallel design	2 months
Hermida, 2005 [15]	Spain	148	Non-dipper patients with grade 1 to 2 essential hypertension	Valsartan	50/98	53.0 ± 12.6	76/72	RCT, parallel design	3 months
Hermida, 2010 [11]	Spain	165	Untreated hypertensive subjects	ACEI, ARB	65/100	42.5 ± 13.9	82/83	RCT, parallel design	12 weeks
Hermida, 2011 [13]	Spain	661	Chronic kidney disease	CCB, ACEI, ARB, alpha--blocker, beta-blocker, diuretic and others	396/265	60.3 ± 13.6 58.5 ± 13.2	329/332	RCT, parallel design	5.4 years
Kario, 2009 [14]	Japan	450	Hypertension	Candesartan (diuretic as needed)	209/241	66.6	221/229	RCT, parallel design	6 months
Rossen, 2014 [12]	Denmark	41	Diabetes mellitus, type 2	Antihypertensive drugs	30/11	65.4 (54.1–75.2)	41/41	RCT, cross--over design	8 weeks

ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; CCB — calcium channel blockers; RCT — randomized controlled trials

Diurnal mean of SBP/DBP

All 6 studies were included in the analysis, which concerned 1,566 cases of hypertension; 779 cases were in the bedtime administration group (experimental group) and 787 cases in the morning (awaking) administration group (control group). The synthesis analysis showed that the diurnal mean of SBP in bedtime administration group was lower than the morning administration group, which reduced diurnal SBP by 1.67 mm Hg (95% CI –1.89–5.23, p = 0.36) (Fig. 2A), diurnal DBP by 1.13 mm Hg (95% CI –2.03–4.28, p = 0.48) (Fig. 2D).

Nocturnal mean of SBP/DBP

All 6 studies were included in the analysis. The synthesis analysis showed that the nocturnal mean of SBP in bedtime administration group was lower than the morning administration group, which reduced nocturnal SBP by 6.32 mm Hg (95% CI 0.62––12.01, p = 0.03) (Fig. 2B), nocturnal DBP by 3.17 mm Hg (95% CI 0.85–5.49, p = 0.007) (Fig. 2E).

24-h mean of SBP/DBP

In a research by Kario et al. [14], no 24 h mean of SBP/DBP was found, therefore 5 studies were included in the analysis, which concerned 1,116 cases of hypertension, 558 cases were in the experimental group and 558 cases in the control group. The synthesis analysis showed that the 24-h mean SBP in experimental group was lower than in the control group, which reduced 24-h SBP by 2.78 mm Hg (95% CI –0.47–6.02, p = 0.09) (Fig. 2C), 24-h DBP by 0.36 mm Hg (95% CI –1.08–1.80, p = 0.62) (Fig. 2F).

Absolute BP reduction from baseline

As the BP baselines of patients included in the researches were different, we analyzed the absolute reduction amplitude of diurnal and nocturnal BP. Three studies were taken into the analysis, which included 763 cases of hypertension, 379 cases were in the experimental group and 384 cases in the control group. There was a lack of statistically significant differences in the diurnal mean of SBP and DBP reduction from baseline between the two groups (p = 0.94/0.85) (Fig. 3A, B), but bedtime administration resulted in significant reduction from baseline in the nocturnal mean of SBP/DBP, by –4.72/–3.57 mm Hg (p = 0.01/0.05) (Fig. 3C, D).

Risk of bias in the included studies

Funnel plot was used to assess the publication bias in the literature. The overall assessment of the risk of bias is shown in Figure 4. Funnel plot demonstrated that there was no evidence of publication bias.

Discussion

The synthesis analysis showed that the level of BP in the bedtime administration group was lower than in the morning administration group, which reduced diurnal SBP by 1.67 mm Hg (95% CI –1.89–5.23, p = 0.36), diurnal DBP by 1.13 mm Hg (95% CI –2.03–4.28, p = 0.48), 24-h SBP by 2.78 mm Hg (95% CI –0.47–6.02, p = 0.09), 24-h DBP by 0.36 mm Hg (95% CI –1.08 –1.80, p = 0.62). There is no statistically significant. A recent Cochrane review [19] found evening administration lowered 24-h SBP by 1.61 mm Hg and 24-h DBP by 1.23 mm Hg, which was a statistically significant difference. In particular, the alpha-blocker doxazosin GITS (4 mg/day) [20] and the diuretic torasemide (5 mg/day) [21] evening administration reduced 24-h SBP by 5.10 mm Hg and 6.24 mm Hg, respectively and 24-h DBP by 2.70 mm Hg and 5.95 mm Hg, respectively. The two researches were excluded according to our inclusion criteria (intervention and duration).

Our meta-analysis showed that the nocturnal mean of SBP in the bedtime administration group was lower than in the morning administration group reducing nocturnal SBP by 6.32 mm Hg (95% CI 0.62–12.01, p = 0.03) and nocturnal DBP by 3.17 mm Hg (95% CI 0.85–5.49, p = 0.007). Bedtime administration resulted in significant reduction from baseline in the nocturnal mean of SBP/DBP, by –4.72/–3.57 mm Hg (p = 0.01/0.05). Hermida et al. [13] found that each 5-mm Hg decrease in mean sleep-time SBP was associated with a 14% reduction in the risk for CV events during follow-up (p < 0.001) among patients with chronic kidney disease and hypertension. Rossen et al. [12] found levels of C-reactive protein were significantly lower with bedtime administration among patients with type 2 diabetes mellitus and nocturnal hypertension (p = 0.017), which may indicate an effect on low-grade inflammation.

With the widespread use of ABPM, nocturnal hypertension usually accompanied by non-dipping status has received increasing attention. O'Brien et al. [7] reported for the first time that an abnormal circadian BP profile with a nocturnal SBP/DBP decline of less than 10/5 mm Hg led to an increased risk of stroke in 1988. Compelling evidence is now available, showing that nocturnal BP is superior to daytime BP in predicting outcomes [7]. Subsequent

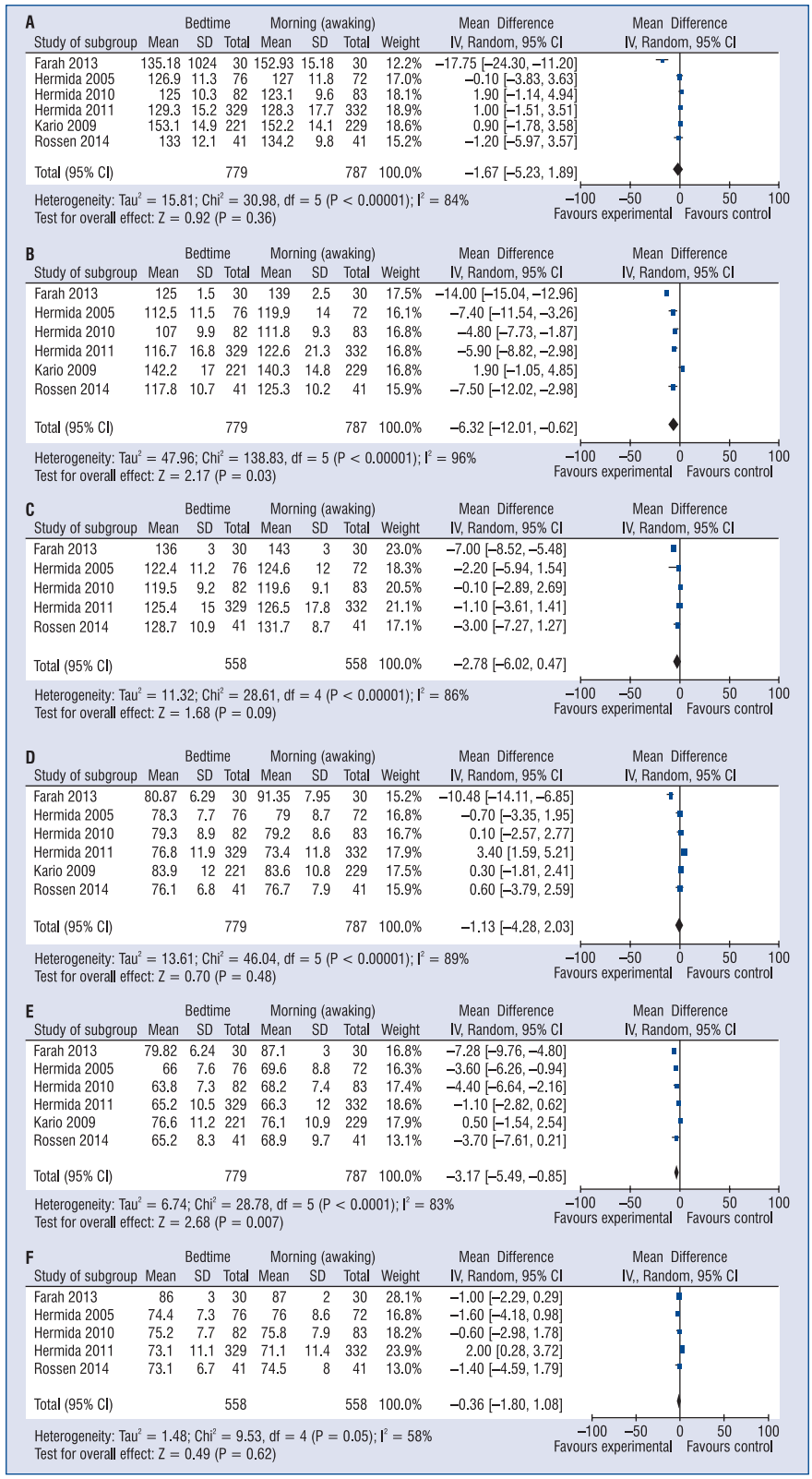

Figure 2. Forest plot showing diurnal mean of systolic blood pressure (SBP) (**A**), nocturnal mean of SBP (**B**), 24-h mean of SBP (**C**), diurnal mean of diastolic blood pressure (DBP) (**D**), nocturnal mean of DBP (**E**), 24-h mean of DBP (**F**) in the experimental group and control group; CI — confidence interval.

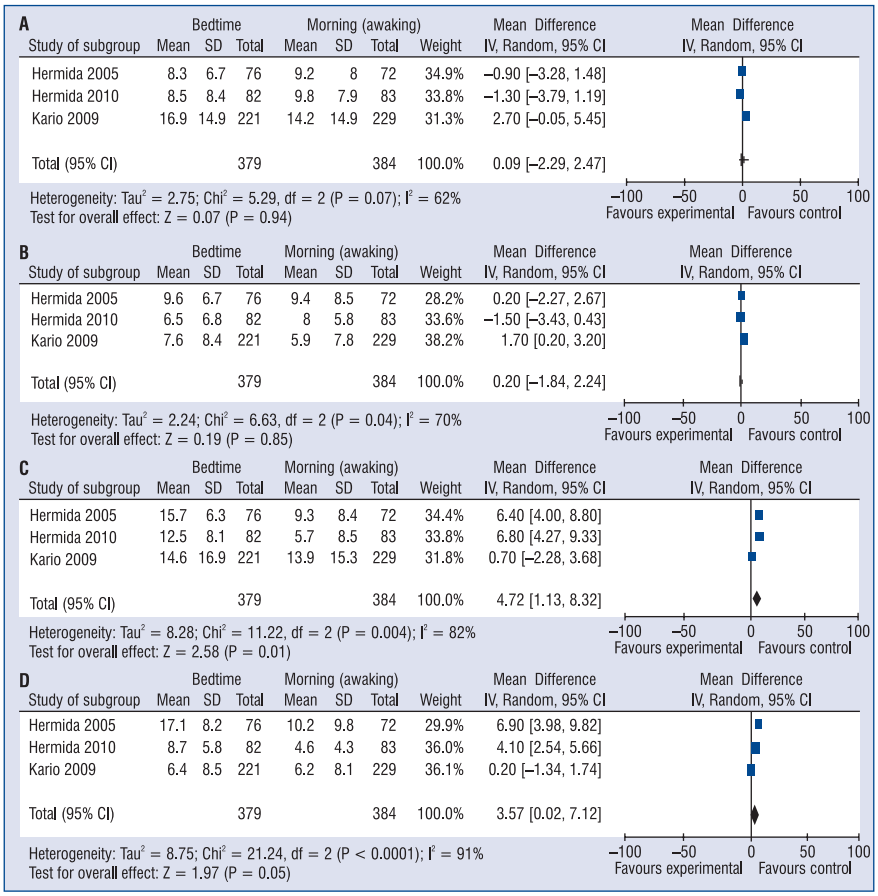

Figure 3. Forest plot showing absolute blood pressure reduction from baseline of diurnal mean of systolic blood pressure (SBP) **(A)**/diastolic blood pressure (DBP) **(B)**, nocturnal mean of SBP **(C)**/DBP **(D)** in the experimental group and control group; CI — confidence interval.

studies in different populations and hypertensive patients corroborated the fact that a diminished nocturnal fall in BP was associated with poor CV outcomes and superior to daytime BP in predicting CV events and total mortality [12]. It was found that for every increase of 10 mm Hg in mean SBP at night, the risk of death increased by 21% [7]. According to the IDACO (an International Database on Ambulatory BP in relation to Cardiovascular Outcome) database, a 16-mm Hg increase in the nocturnal SBP was associated with stroke events (HR 1.08 [1.01–1.16]; $p < 0.001$) [10]. In 1,187 essential hypertension patients followed up for 3.2 years, Krzych et al. [22] found that the occurrence of adverse CV events was nearly three times higher in non-dipper patients than dipper hypertensive patients [22].

Multiple factors alone or in combination can lead to nocturnal hypertension in 1 person. The activity of the sympathetic nervous system determines the circadian variation of BP. Nocturnal hypertension is more common in patients with diabetes mellitus, sleep disturbance, depression and anxiety disorder, and cerebrovascular diseases accompanied by elevated sympathetic nervous activity during sleep [10, 12, 23]. Bankir et al. [24] proposed a pressure natriuresis mechanism hypothesis that the relative increase in BP observed during the night is in favor of a compensatory rise in sodium excretion and the maintenance of sodium balance. In other words, the non-dipping pattern of BP at night is caused by an impaired capacity to excrete sodium due either to a reduced glomerular filtration rate or to a primary increase in tubular sodium reabsorption during daytime. Hence, BP rises at night to promote sodium excretion to maintain 24-h sodium balance [24]. An abnormal BP dipping has been reported in several clinical conditions associated with an impaired renal function (e.g., aging or renal transplantation) or an increased sodium reabsorption (e.g., primary hyperaldosteronism, ciclosporin, or administration of nonsteroidal anti-inflammatory

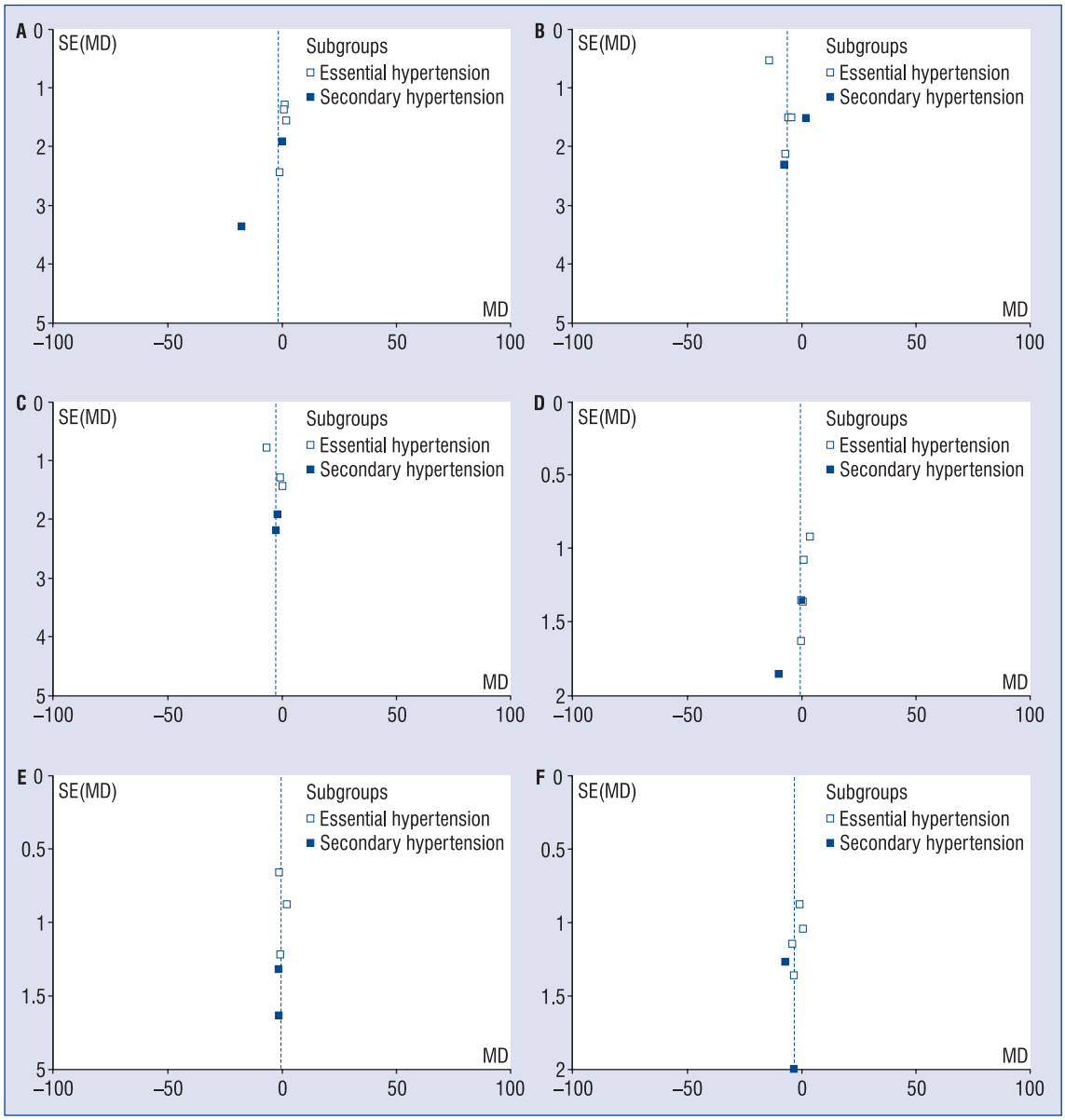

Figure 4. Funnel plot was drawn to assess the publication bias in the literature; **A.** Diurnal mean of systolic blood pressure (SBP); **B.** Nocturnal mean of SBP; **C.** 24-h mean of SBP; **D.** Diurnal mean of diastolic blood pressure (DBP); **E.** Nocturnal mean of DBP; **F.** 24-h mean of DBP.

drugs) [25]. Reduced melatonin secretion leading to disturbed BP rhythmicity-chronodisruption is also involved in the pathophysiology of nocturnal BP alterations. Non-dipping patients express a lower nocturnal surge of melatonin release, as reflected by reduced 6-sulfatoxymelatonin in urine and a lower ratio of the night/day concentration of melatonin [26]. Finally, the medications widely used in clinical conditions may have short half-life and duration of action, failing to provide a full 24 h coverage, when taken in the morning.

Nowadays, majority of hypertensive patients are treated with combination therapy, especially in patients with grade 2 or above essential hypertension and secondary hypertension to achieve an adequate BP control [27]. The influence of combination therapy in different administration time on antihypertensive efficacy studies have demonstrated that once-daily antihypertensive agents have the highest adherence compared with twice-daily or multiple daily doses. The evidence suggests that an antihypertensive medication

adherence of 80% or more appears to improve BP control and decrease the risk of developing some of the complications of hypertension [28]. Antihypertensive drugs are most often given with morning food in the traditional manner for the sake of convenience [29, 30]. An optimal once-daily hypertension therapy would not only lower BP but also normalize any blunted circadian variations in BP. Farah et al. [8] found that switching the therapy to bedtime improved BP control and helped avoid the non-dipper pattern without increasing the dose or adding more drugs.

The compliance was comparable between the two groups. In Kario's trial [14], 11 (5%) patients in the bedtime administration group and 18 (7.9%) in the morning administration group did not complete the study. In Rossen's trial [12], all patients met the criteria of compliance. No withdrawal was reported in the left trials.

The mechanisms for these observed treatment-time differences remain unclear, but it has been generally agreed that the pharmacokinetics (PK) — the study of what the body does to a drug, absorption, distribution, metabolism, and elimination — and pharmacodynamics (PD) — the study of what a drug does to the body — of the medications occurring in relation to the 24 h cyclic processes were involved in BP regulation [11, 31]. Circadian rhythms in gastric pH and emptying, gastrointestinal motility, biliary function and circulation, liver enzyme activity, and blood flow to the duodenum, kidney, and other organs, among other factors can lead to ingestion-time differences in the PK of conventional antihypertensive medications [8, 11]. In particular, the circadian pattern of the glomerular filtration rate, with a maximum during the day and a minimum at night, played a significant role [8, 11, 32]. Consequently, antihypertensive drugs were cleared more slowly overnight, potentially prolonging their duration of action when ingested at bedtime as compared to taken at awakening. Taking-time differences in the PD of antihypertensive drugs, both the therapeutic and side effects, result from the time-dependency in their PK, as well as from circadian rhythms in drug-free fraction, rate-limiting steps of key metabolic processes, receptor number and conformation, and/or second messenger and signaling pathways [11]. The result of Hermida et al.'s [11] spirapril study was consistent with the theory. The BP-lowering efficacy duration of spirapril was much longer when taken at bedtime (8 h after ingestion) than in the morning (3 h after ingestion).

At present, there is little literature on the topic and even much fewer RCTs. Three of the 6 articles included in our analysis were reported by Hermida, but the studies were conducted with independent groups of participants with different study drug, follow-up time and team. According to our pre-set inclusion criteria and the key research indicators, the overall quality of the studies included in our meta-analysis was good. The conclusion of this meta-analysis is reliable. The research is of great significance to provide a reference for the clinical physicians to make the optimized regimen of antihypertensive drugs.

Limitations of the study

Our meta-analysis had several limitations. First, the duration periods of the trials included were not long enough except for one research [13], therefore we cannot assess the relationship between nighttime BP-lowering level and protection against end-organ injury and CV morbidity and mortality in hypertension patients with different complications. Second, as there are many kinds of anti-hypertension drugs with different action mechanisms and metabolic characteristics, we need a large sample of cases and long follow-up to assess their different effects on clinical benefit of lowering nocturnal hypertension. Third, including populations of non-dipper patients (2 out of 6 included studies) could introduce an important source of bias. Due to not enough literature, if the 2 studies were excluded, the conclusion extrapolation would be even worse, therefore no analysis was conducted this paper.

Conclusions

Despite the limitations of our meta-analysis, we conclude that taking the antihypertensive drugs at bedtime demonstrated a similar reduction in the level of diurnal and 24-mean BP as morning dosing, but a significant reduction in nocturnal BP. Switching time of taking antihypertensive medicine from morning to bedtime or evening can have a better nocturnal BP control and restore or maintain the normal BP pattern which may be better for prognosis. Hypertension patients, especially those who had nocturnal hypertension or non-dipping BP pattern under the condition of evaluated BP level by 24-h-ABPM, should be suggested that they take their drugs at bedtime without changing the drug itself or the dose.

Conflicts of interest: None declared

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