

# Effects of Bisoprolol with Different Drug Administration Time on the Blood Pressure of Non-dippers Hypertension

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**ABSTRACT Objective:** To investigate the effect of bisoprolol with different time on blood pressure control and circadian variability of dipper blood pressure for patients with Non-dipper hypertension. **Methods:** The patients were randomly divided into two parallel groups. All patients were treated with bisoprolol. The first group took bisoprolol at eight o'clock once-daily between 2.5mg and 10mg. The second group took bisoprolol at twenty o'clock once-daily between 2.5mg and 10mg. The efficiency of the 8 weeks' treatment and the change of the 24 hours blood pressure were detected. **Results:** The blood pressures of the patients in both groups decreased ( $P < 0.05$ ). And there was no significant difference between the two groups for the day BP decrease ( $P > 0.05$ ), but taking bisoprolol at first group had a better efficacy than that in the second group of the night BP. On the recovery diurnal rhythm of blood pressure the first group was better than that of second group ( $P < 0.05$ ). There were 10 hypertensive patients with non-dipper pattern of blood pressure changed into dipper pattern in the first group while there were 19 patients changed in the second group. **Conclusion:** Two months of treatment can control the blood pressure safe and efficacy, but taking drug at eight o'clock was better for the Non-dippers Hypertension and the diurnal rhythm of blood pressure than taking at twenty o'clock.

**Key words:** Bisoprolol; Non-dippers Hypertension; Dippers Hypertension; The diurnal rhythm of blood pressure

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## Introduction

Most of the people have the normal rhythm of blood , which is the dipper pattern. The dipper pattern shows low BP at night and high BP in the morning, and reaches a plateau in the late morning. However, some patients have no apparent nocturnal reduction in blood pressure. Patient whose blood pressure fall by less than 10 % of the day time value has been referred to as non-dippers [1-2]. Previous studies had shown that subduced nocturnal BP reduction was associated with target organ damage and cardiovascular disease [3-4]. Besides, in the early morning, a fast and steep acceleration in blood occurs, while people arising from over-night sleep. The quickly elevatory blood has been termed morning BP surge. Some study had proved that the morning blood pressure surge was significantly associated with increased frequency of damage to all target organs (brain, heart, and kidney) and a poorer prognosis for cardiovascular events [5]. So the efficiency measure of control blood pressure include clinic blood and average blood for 24 hours, even keep the blood at night descend moderately and control the morning blood pressure surge. This study was to investigate the better time in treatment of Non-dippers hypertension with bisoprolol.

## 1 Case choice and Method

### 1.1 Case choice

60 cases with Non-dipper hypertension were chosen from in-patient and out-patient in our hospital between November 1, 2008, and September 1, 2010. All the patients ceased to take antihypertensive

drug before the study for a week. The patients were randomly divided into two parallel groups. American spacelabs ambulatory blood pressure monitor was used to measure the 24 hours blood, patient whose blood pressure fall by less than 10 % of the daytime value was non-dippers. The patients affected with secondary hypertension, - ° AVB, uncontrolled hypertension (DBP > 110 mm-Hg or the SBP > 180 mmHg), brain or blood vessel suddenness, myocardial infarction or heart failure history, aortic tumour, typical angina symptoms, atrioventricular block, sick sinus syndrome and other malign arrhythmia or potential malign arrhythmia, renal or hepatic failure, serious heart and lung diseases were excluded from this study.

The ABPM was carried out on the non-dominant arm using a Spacelabs 90217 device (Spacelabs, Inc) of America. It was adopted to measure blood pressure every 30 min from 08:00 to 20:00 and from 20:00 to 08:00. All patients kept and finished their diurnal activities and avoided strenuous physical activity during the monitoring period. The average BP during diurnal or nocturnal time was calculated.

### 1.2 Methods

**1.2.1 Take medicine measure** The 60 patients were divided into two groups: Group 1, 30 patients, received the morning treatment. Group 2, 30 patient, received the night treatment. The patients of the two groups took bisoprolol 2.5 mg once a day (group 1 take medicine at eight o'clock, group 2 take medicine at twenty o'clock) for two weeks. If the blood pressure of the patients' reached the

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goal, they should keep the primary dosage for two weeks. But if the blood pressure didn't reach the goal (namely rest blood SBP  $\geq$  140 mmHg and/or DBP  $\geq$  90 mmHg), they should increase the dosage of bisoprolol from 2.5 mg to 5.0 mg. However, the patients with the dosage of 5mg for two weeks could not reach the aim should be excluded from the study.

**1.2.2 Observe target** After treatment with bisoprolol once-daily for 4 weeks, the goal of the blood pressure was less than 130mmHg systolic and 80mmHg diastolic; The average blood pressure of one day was less than 135mmHg systolic and 80mmHg diastolic ; The average blood pressure of one night less than 125mmHg systolic and 75mmHg diastolic. The goal of the blood rhythm was to recover the dipper rhythm (nocturnal blood pressure reduction by more than 10%).

**1.2.3 Statistical analysis** ontinuous variables were shown as mean  $\pm$  standard error. The differences between the two groups were

compared by Student's t-test for independent samples. A pvalue of less than 0.05 was considered to indicate statistical significance. Data management and statistical analysis were performed using SPSS17.0 software.

## 2 Results

### 2.1 The compare between the two groups

There was no significant difference on ages, sex, disease course, degree, syndrome and so on between the two groups ( $p > 0.05$ ).

### 2.2 The reduction of the blood pressure of the two groups

The table 1 indicated that both of the two methods can reduce the blood pressure ( $p < 0.05$ ), the day blood pressure was no significant difference between the two groups on the control of ( $P > 0.05$ ), but for the control of nocturnal blood pressure take the medicine at night had a better efficiency in compare with take it in morning ( $P < 0.05$ ).

Table 1 Change of the two groups' ambulatory BP after treatment

	dMSBP	dMDBP	nMSBP	nDBP	MSBP	MDBP
Bisoprolol untreatment	142 $\pm$ 2.9	79.8 $\pm$ 4.6	138 $\pm$ 2.7	79.3 $\pm$ 5.4	141.2 $\pm$ 2.5	79.7 $\pm$ 4.7
(08:00) Treatment	130.8 $\pm$ 5.4*	72.8 $\pm$ 4.2*	123.8 $\pm$ 6.7 <sup><math>\Delta</math></sup>	71.7 $\pm$ 3.5 <sup><math>\Delta</math></sup>	127.7 $\pm$ 3.3*	72.6 $\pm$ 3.4*
Bisoprolol untreatment	140.9 $\pm$ 2.2	78.1 $\pm$ 3.8	136.9 $\pm$ 3.6	79.6 $\pm$ 4.5	140.1 $\pm$ 2.1	72.6 $\pm$ 3.4
(20:00) Tntreatment	132.5 $\pm$ 4.6*	72.3 $\pm$ 3.9*	120.4 $\pm$ 5.8 <sup><math>\Delta</math></sup>	69.6 $\pm$ 4.3 <sup><math>\Delta</math></sup>	128 $\pm$ 2.8*	71.9 $\pm$ 3.4*

\*The two groups has significant difference before treatment and after treatment ( $P < 0.05$ ),  <sup>$\Delta$</sup> the two groups had significant difference at the reduction of the nocturnal blood pressure ( $P < 0.05$ ).

### 2.3 The effect of the the two groups about morning blood pressure

The table 2 indicated that take the medicine at night has a

better efficiency in compare with take it in morning ( $P < 0.05$ ), on control of the fast and steep acceleration morning blood pressure.

Table 2 Chang of the two groups' morning blood pressure after treatment

		SBP	DBP
Bisoprolol	Untreatment	150.6 $\pm$ 4.7	84.3 $\pm$ 2.8
(08:00)	Treatment	136.5 $\pm$ 3.6*	78.5 $\pm$ 3.2*
Bisoprolol	Untreatment	149.3 $\pm$ 5.0	82.8 $\pm$ 3.1
(20:00)	Treatment	133.8 $\pm$ 4.9*	75.8 $\pm$ 4.3*

\*The two groups has significant difference before treatment and after treatment on the morning blood pressure ( $P < 0.05$ ).

### 2.4 The effect of the the two groups about blood pressure rhythm

The group 1 had 11 cases changed to dipper rhythm, while go-

up 2 had 17 cases change to dipper rhythm. Taking the medicine at night has a better efficiency compared with take it in morning ( $P < 0.05$ ).

Table 3 Chang of the two groups' blood pressure rhythm after treatment

	Dipper	Non-dipper	Case
Bisoprolol (08:00)	10	18	28
Bisoprolol (20:00)	19	10	29

The two groups had significant difference ( $P < 0.05$ )

### 3 Discussion

The mean blood pressure at night was lower (by at least 10%) than that during the day, and it has been termed "the dipper". Mostly has the dipper rhythm, but there were few people lost the normal blood pressure rhythm. The subduded nocturnal blood pressure reduction was associated with target organ damage and cardiovascular disease. It had been reported that in case without or decreased nocturnal blood pressure reduction (non-dipper), the risk of cardiovascular events was higher than whose decline in blood pressure at night<sup>[6]</sup>. Additionally, patients with hypertension who had a nocturnal BP increasing compared with daytime blood pressure rising had the worst prognosis for stroke and cardiac events<sup>[7-8]</sup>. The reason may be that the non-dipper hypertension lost the normal rhythm, keep the mean blood pressure of night at high level always. The high blood pressure made the target organ at a high load, easily result in and aggravate the organ damage. Moreover, the blood pressure had a daily variation characterized by substantial reductions during sleep, a rapid rise upon awakening. The sharply rises blood pressure in the morning is the response to the activation of the sympathetic nervous system<sup>[9]</sup>. The nervous system increases cardiac output and peripheral blood vessel resistance. As a result, the blood pressure increases exceed more than 20% of their baseline values<sup>[10]</sup>. Therefore, the incidence of acute events associated with CV events, including stroke and ischemic heart disease. The relative risk was highest in the early morning period, when a rapid rise in blood pressure occurs<sup>[11]</sup>. Thus, the treatment for the non-dipper hypertension not only reduced the mean blood pressure of the 24h smoothly, control the blood pressure during the night-time and early morning is especially important. Only by this way can reduce the incidence of cardiovascular complications of hypertension. Research had shown that the non-dipper hypertension patients have higher plasma baseline values of adrenaline and noadrenaline than in dipper. This study use bisoprolol a kind of  $\beta$ -block to control the blood pressure through restrain the higher activity of sympathetic nerve.

This study indicated that taking bisoprolol with the same dose, the control of day blood pressure for the two groups had no significant difference. The reason maybe that bisoprolol is a high selective  $\beta$ -block, and possess long half-life character. It has a quick and long effect, so take once-daily can control the 24h blood pressure stably<sup>[12-13]</sup>. Taking the medicine at night had a better efficiency on decreasing the night-time blood pressure and restoring this abnormal blood pressure than taking the medicine in the morning. The reason was that the half-life of bisoprolol was 10-12h, taking it at night make the plasma values of bisoprolol at a high level at night, and at the same time the blood pressure rise<sup>[14-16]</sup>. So taking bisoprolol at night can control the blood pressure stably and restore dipper blood pressure, and even reduce incidence of acute events<sup>[17-18]</sup>. If take the drug in the morning the plasma values will be at a low level till night, the efficiency of controlling the

blood pressure will be weaker, and has a disadvantage of controlling the nocturnal blood pressure over the non-dipper hypertension. So taking drug at night has a advantage to control the nocturnal blood pressure. Therefore, the control of morning blood pressure surge is also important. In the research, it is found that taking medicine at night was better than taking in morning. Because blood pressure rise quickly in morning between six o'clock to eight o'clock, the plasma values will at the lowest level till that time, if take the drug in morning. However, take drug at night will has a higher plasma values level. So take drug at night can control the morning blood pressure surge effectually and reduced frequency of damage to all target organs (brain, heart, and kidney) and cardiovascular events<sup>[19]</sup>.

In a word, it is important to note that lower the blood pressure effectively during the day, while reducing nighttime blood pressure is more important in non-dippers than in dippers<sup>[20]</sup>. At the same time control the morning blood pressure surge is also an important thing. Take bisoprolol at night not only control the 24h blood pressure, but also change the rhythm from non-dipper to dipper and restrain the rising of the morning blood. So take bisoprolol at night is a good choice for non-dipper hypertension.

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## 不同时间服用比索洛尔对非杓型高血压血压的影响

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**摘要** 目的:观察不同给药时间分别给予比索洛尔对非杓型原发性高血压患者的降压疗效和血压节律恢复的影响。方法:选取60例非杓型高血压患者,采取随机平行对照试验,观察比索洛尔(n=30)每日早晨(8:00)给药2.5-10mg、比索洛尔(n=30)每日夜间(20:00)给药2.5-10mg治疗8周后的降压疗效。结果:两种给药方法均能降低非杓型高血压患者的全天血压(P<0.05)。两种给药方法在白天的血压控制上无显著性差异(P>0.05),但在夜间血压的控制上夜间服药降压效果具有显著性差异(P<0.05)。夜间服药在血压节律恢复方面优于早晨服药(P<0.05),早晨服药组有10例恢复杓型,夜间服药组有19例恢复杓型。结论:比索洛尔的两种给药方式均能安全有效的降压,但对于非杓型高血压患者夜间服药优于早晨服药,更有利于血压节律的恢复。

**关键词** 比索洛尔 非杓型高血压 杓型高血压 血压昼夜节律

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