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Effects of different antihypertensive drugs on blood pressure variability in patients with ischemic stroke

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Abstract. – OBJECTIVE: Blood pressure variation is one of the factors that affects the risk of stroke recurrence and prognosis. This study investigates the effects of calcium channel blockers and beta-blockers on blood pressure variability in severe ischemic stroke patients.

PATIENTS AND METHODS: The clinical data of 24 patients with ischemic stroke in our intensive care unit were analyzed, and received amlodipine or metoprolol for more than 14 days with 24-hour ambulatory blood pressure monitoring. All patients aged 61-90 years, with GCS score ≤ 8 or associated with other organ dysfunction.

RESULTS: Among these 24 ischemic stroke patients, 12 received amlodipine and 12 received metoprolol. The observation period was divided into two phases: 1-6 days and 7-14 days. The decrease in blood pressure was faster in the metoprolol group than in the amlodipine group, while the average standard deviation was significantly greater and the smoothness index was less.

CONCLUSIONS: Metoprolol has faster onset than amlodipine and less blood pressure variability than metoprolol.

Key words:
Amlodipine, Metoprolol, Severe stroke, Blood pressure variability, Complication.

Introduction

Hypertension is the most common controllable risk factor for stroke and blood pressure reduction is effective in preventing stroke. Antihypertensives in stroke prevention are not only related to lowering blood pressure, but also on blood pressure variability (BPV)[1,2]. As shown by the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial[3], blood-pressure variability is an independent risk factor for macro-vascular or microvascular events in patients with type II diabetes mellitus. Poor prognosis is more likely to be expected in patients following severe stroke due to their critical conditions and high blood pressure variability. As described by Skalidi et al[4], brain edema is correlated to blood pressure variability in patients following stroke. A meta-analysis demonstrated that the effect of calcium channel blockers on stroke prevention was greater than its anti-hypertension effect alone, while the utility of β-antagonists in stroke prevention was not effective as an anti-hypertensive[4,5]. Antihypertensives with minimal BPV are preferable. In this study, the blood pressure lowering effects of calcium channel blockers and β-antagonists are compared in patients following severe stroke, and their effects on BPV were also investigated to provide guidance for rational drug use in clinical settings.

Patients and Methods

General data

A total of 20 males and 4 females, aged from 61 to 90 years, with the mean age of 77 ± 8 years were included in this study. Patients were admitted to the Chaoyang Hospital for severe stroke and hypertension from October, 2010 to October, 2011. Upon admission, the patients continued to receive amlodipine 2.5 mg qd or were switched to metoprolol 12.5 mg, bid, by stepwise dose titration.

Methods

Blood pressure and heart rate were documented for 14 continuous days at the exact time of day by using a Beneview T5 ECG Monitor. This included two phases: Day 1-6 (Phase-I) and Day 7-14 (Phase-II). The maximum, minimum, avera-

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ge, standard deviation, and coefficient of variation were estimated for blood pressure. Daytime was from 6:00 to 21:00 and nighttime from 21:01 to 5:59. The ratio between the average blood pressure changes computed for each hour and its standard deviation was referred to the Smoothness index. The 24-hour mean systolic blood pressure (24h SIS), 24-hour mean diastolic blood pressure (24h SID), daytime mean diastolic blood pressure (dSID), nighttime mean systolic blood pressure (nSIS) and nighttime mean diastolic blood pressure (nSID) were estimated.

Statistical analysis

All data were analyzed using the SPSS13.0 software package (SPSS Inc., Chicago, IL, USA). Mean values, standard deviations, and standard deviation and coefficient of variation, were calculated for systolic and diastolic blood pressures in both groups, and subsequently followed by an independent sample t test. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients of both groups

Patients of the metoprolol group were older than those of the amlodipine group, but there were no significant differences in gender, height and body weight between these two groups. Also, 83% patients suffered from hypertension, and nearly half were concomitant with coronary heart disease, atrial fibrillation, diabetes mellitus and smoking. There were no statistically significant differences in baseline blood pressure and APACHE scores (Table I).

Changes of 24-hour blood pressure and standard deviation for both groups

For systolic blood pressure, slow onset of the blood pressure lowering effect of amlodipine (160 mmHg and 163 mmHg) was observed in comparison to that of metoprolol (149 mmHg and 133 mmHg) for both phases ($p < 0.05$). However, the standard deviation (18 and 11) and coefficient of variation (12 and 7) for the former regimen were lower than the standard deviation (24 and 23), and the coefficient of variation (16 and 17) for the latter ($p < 0.05$). Similar results were observed for the diastolic blood pressure. For heart rate, similar results were observed for the 24-hour average rates of phase-I, while the heart rate of amlodipine group was slower than that of metoprolol group. However, the coefficient of variation is smaller in phase-I than in phase-II, with a p value < 0.05 (Table II).

Smoothness index

The smoothness index of the amlodipine group was higher than that of metoprolol group during the different phases, with all values > 1, suggesting favorable blood pressure variability. For systolic blood pressure, the 24-hour, daytime and nighttime blood pressures were higher than those of metoprolol group (< 1) and these differences were statistically significant. For diastolic blood pressure, the mean values of the amlodipine group were also higher than those of the metoprolol group.

Discussion

Hypertension is a risk factor for many diseases, but its mechanism to induce target organ

Table I. Baseline characteristics of patients of both groups.

Parameters	Amlodipine group (n=12)	Metoprolol group (n=12)	*p* value
Proportion of males [n (%)]	83.3	83.3	1.000
Age (years)	72.67±5.71	80.50±8.33	0.013
Body height (cm)	169.5±8.99	168.0±7.53	0.558
Body weight (kg)	72.41±10.30	68.71±11.03	0.414
Hypertension [(%)]	83	83	1.000
Coronary heart disease [(%)]	33	50	0.680
Atrial fibrillation [(%)]	42	42	1.000
Diabetes mellitus [n (%)]	33	50	0.680
Smoking history [n (%)]	58	67	-
Baseline blood pressure	195/92	194/93	-
APACHE II score	22.74±4.70	21.05±5.77	0.166

Table II. Changes of 24-hour blood pressure and standard deviation for both groups.

		Phase I (days 1-6)					Phase II (days 7-14)				
		Mean	Max	Min	SD	CV	Mean	Max	Min	SD	CV
SBP	Amlodipine group (n=12)	160.0	172.1	149.1	18.8	11.7	163.3	173.1	151.0	11.6	7.13
	Metoprolol group (n=12)	149.1	154.7	145.4	24.1	16.2	133.9	138.9	124.9	23.2	17.3
	p value	0.000			0.00	0.00	0.000			0.000	0.000
DBP	Amlodipine group (n=12)	77.4	84.3	69.0	11.2	14.4	79.7	83.5	76.5000	7.3022	9.1641
	Metoprolol group (n=12)	78.9619	81.1034	75.4118	10.7970	13.6682	72.1241	74.6818	69.9000	9.7891	13.5759
	p value	0.087			0.474	0.286	0.000			0.000	0.000
HR	Amlodipine group (n=12)	86.5242	92.5556	82.7778	12.4232	14.3824	82.7233	88.7000	77.4444	9.6585	11.7183
	Metoprolol group (n=12)	86.9854	91.4828	83.1176	16.7397	19.2274	88.6886	93.5500	84.1429	12.3123	13.8993
	p value	0.378		0.000	0.000	0.000				0.000	0.003

injury and cardiovascular events is still unclear. The effects of antihypertensives on blood pressure variation and daytime blood pressure peak are not well elucidated. In some guidelines, only elevation of mean blood pressure other than intermittent increase of blood pressure could be considered as hypertension. For patients with hypertension, the blood pressure variation has been omitted during treatment and no observation was conducted for long-term prognosis. In patients with critical conditions at admission following stroke, the presence of hypertension disease is frequently observed. Appropriate use of antihypertensives and improved prognosis are challenges for many clinicians.

Table III. Smoothness index of the blood pressure in two groups

	Amlodipine group	Metoprolol group	*p*
24hSIS	1.018±0.124	0.935±0.139	0.029
24hSID	1.022±0.153	0.959±0.174	0.183
dSIS	1.052±0.197	0.945±0.184	0.040
dSID	1.035±0.183	1.023±0.182	0.818
nSIS	1.212±0.148	0.998±0.233	0.000
nSID	1.065±0.288	1.038±0.246	0.921

Importance of blood pressure variation

Average blood pressure is a strong predictor for vascular events. Concurrently, blood pressure variation is also a factor based on increasing epidemiological evidence[6]. In ASCOT-BPLA trial, SBP variation and SBP peak were more predictive for stroke than mean blood pressure[7]. Moreover, effects of antihypertensives concomitant with orthostatic hypotension are more likely to be expected in the elderly, due to poor vascular stability, resulting in vascular events. Routine monitoring of mean blood pressure seemed to be of limited utility[8]. It has been demonstrated that large SBP variation was associated with end organ injury[6]. For the occurrence of stroke following TIA, the risk of patients with well controlled mean blood pressure and high BPV was higher by five folds than those with low BPV[1,7]. Therefore, exacerbation of SBP variation has been correlated to the high incidence of cerebrovascular events. Control of blood pressure variation seemed to be beneficial to patient outcomes.

Selection of antihypertensives

In 1998, Parati et al[9] proposed the concept of the smoothness index to reflect the stability of the blood pressure lowering effect. Higher smoothness index was associated with steadier blood pressure lowering effect and lower BPV. Its repeatability was superior to peak/trough ratio. Therefore, it was critical to choose appropriate antihypertensives with stable blood pressure lowering effect, low BPV and high smoothness index. In this study, the onset of amlodipine was slow, with significant lower SD and coefficient of variability and higher smoothness index in comparison to metoprolol. Calcium channel blockers were associated with arterial stiffness reduction, vasodilation, arterial compliance improvement, and BPV decrease prior to vascular remodeling, and resulting in reduction of blood flow induced cerebral pulsation and stroke incidence[10]. β-antagonists might induce unstable orthostatic blood pressure which has been identified to be one of causes of BPV aggravation, but rare events were reported in the case of calcium channel blockers[11]. Metoprolol could reduce the heart rate, which was associated with poor prognosis. However, no definite conclusion was made in this study[1].

In patients with severe stroke and concomitant multiple-organ dysfunction, metoprolol was associated with a reduction of cardiac autonomic nervous activity in patients with cerebral infarction. There were improvements of the sympathetic and parasympathetic balances to some extents, and a reduction in sudden cardiac death. Thus, the benefits were demonstrated for this medication[12].

Conclusions

The risk of stroke could not be predicted by routine blood pressure control. However, blood pressure variation seemed to be a better predictor in the real-world setting. Higher smoothness index is considered as the best parameter to reflect variation changes. BPV control is an important factor associated with successful stroke prevention[13]. Calcium antagonists reduces blood pressure variability to its maximum extent and results in a favorable prognosis. In comparison, in addition to their heart rate lowering effects, β-antagonists could produce BPV exacerbation in response to increasing doses. This is a negative factor for stroke treatment.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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