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Original Article

Therapeutic effect and prognostic life quality of renal denervation therapy and nifedipine combined with metoprolol tartrate in the treatment of resistant hypertension

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Abstract: Objective: This study aimed to explore the therapeutic effect and prognostic life quality of renal denervation therapy (RDN) and nifedipine combined with metoprolol tartrate in the treatment of resistant hypertension. Methods: 90 cases with resistant hypertension in our hospital were randomly divided into observation group and control group with 45 cases in each group. The observation group was treated with RDN and nifedipine combined with metoprolol tartrate, while the control group was treated with RDN and nifedipine. The therapeutic effect, the systolic and diastolic blood pressure before and after treatment, and the incidence of adverse reactions were observed. The prognostic life quality was evaluated by SF-36. The risk factors of ineffective treatment were analyzed by multivariate Logistic regression. Results: SBP and DBP in the two groups after treatment were lower than those before treatment (P<0.05). SBP and DBP after treatment, as well as total incidence of adverse reactions in the observation group were lower than those in the control group (P<0.05). The total effective rate and scores of eight dimensions in the observation group was higher than those in the control group (P<0.05). The univariate analysis showed that there were obvious differences in age, course of disease, BMI, diabetes, hyperlipidemia, blood glucose, white blood cell count and treatment methods between the two groups (P<0.05). The multivariate Logistic regression analysis showed that the course of disease, BMI, blood glucose and LDL-C were the risk factors of ineffective treatment. Conclusion: RDN and nifedipine combined with metoprolol tartrate have better antihypertensive effect and therapeutic effect, lower incidence of adverse reactions, and higher prognostic life quality in the treatment of resistant hypertension. The course of disease, BMI, blood glucose and LDL-C are the risk factors of ineffective treatment.

Keywords: Renal denervation therapy, nifedipine, metoprolol tartrate, resistant hypertension, prognostic life quality

Introduction

There are about 270 million hypertensive patients in China. The prevalence of hypertension is increasing year by year [1]. In the study of Lu et al. [2], the awareness rate, treatment rate and control rate of 1.73 million hypertensive patients were 36%, 22.9% and 5.7%. Even if three kinds of antihypertensive drugs are combined reasonably, it is still difficult to lower the blood pressure to a reasonable level [3]. Therefore, three kinds of drugs or more are used to treat the resistant hypertension generally [4]. Pimenta et al. [5] found that the risk of other cardiac and cerebrovascular diseases in the patients with resistant hypertension was twice as that in the patients with new-onset hypertension. In addition, if blood pressure

does not reach a reasonable level for a long time, there is a risk of target organ damage [6].

Many studies have shown that the renal denervation therapy (RDN) could effectively lower blood pressure in patients with resistant hypertension [7, 8]. Bartuś et al. [9] reported that RDN was performed on 32 patients with resistant hypertension and 30% of patients was controlled below 140/90 mmHg, and no complications or adverse events were observed within 2 years. Nifedipine can effectively dilate small arteries by inhibiting calcium ions entering vascular smooth muscle cells and cardiac myocytes, thus rapidly and continuously decreasing systemic blood pressure and increasing myocardial oxygen delivery. Therefore, nifedipine showed good therapeutic effect and safety [10, 11]. Metoprolol tartrate is a β-receptor blocker. Some reports suggested that metoprolol tartrate can reduce the incidence and mortality of cardiovascular diseases in young hypertensive patients, and improve sudden cardiac death and myocardial infarction [12, 13]. However, the efficacy and prognosis of RDN and nifedipine combined with metoprolol tartrate in the treatment of resistant hypertension remain unclear.

Therefore, RDN and nifedipine combined with metoprolol tartrate was applied to treat resistant hypertension, and the therapeutic effect and prognostic life quality were observed. This study aimed to provide the evidence and direction for clinical practice.

Materials and methods

Clinical data of patients

90 patients with resistant hypertension form August 2017 to February 2018 in our hospital were collected. 45 patients were treated with RDN and nifedipine combined with metoprolol tartrate as the observation group. Among them, 33 were male and 12 were female, with the average age of 51.6 ± 9.4 years old. Another 45 patients were treated with RDN and nifedipine as the control group. Among them, 29 were male and 16 were female, with the average age of 52.4 ± 10.5 years old. This study was approved by the Medical Ethics Committee. All patients signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: all patients were diagnosed with resistant hypertension according to pathology. The diagnostic criteria were in accordance with the Hypertension Guideline developed by American Heart Association and American College of Cardiology in 2017 [14]. The patients with stable physical condition can undergo RDN. The clinical data of the patients were complete, and they cooperate with the treatment and follow-up. Exclusion criteria: patients with severe liver and kidney dysfunction; patients with other malignant tumors; patients with severe cardiovascular and cerebrovascular diseases; patients with severe inflammation; patients receiving previous renal artery intervention therapy; patients with renal atherosclerosis; and pregnant or nursing women.

Main drugs

Nifedipine (Shantou Jinshi Pharmaceutical Co., Ltd. of Sinopharm Group, Medicine H44021-513). Metoprolol Tartrate (Heilongjiang Green Pharmaceutical Co., Ltd., Medicine H200662-66).

Treatment schedule

The renal angiography was performed on all patients. The radiofrequency ablation was performed from catheter to double renal arteries within 3-6 weeks for two minutes. The ablation was rotational and regressive. After operation, the same nursing scheme was adopted in both groups: nifedipine was taken orally for 10 mg/time and 3 times/day. On this basis, the patients in the observation group were treated with metoprolol tartrate orally with 90 mg/time/day for 3 months.

Efficacy evaluation [15]

The effective treatment is that the mean systolic blood pressure was less than 140 mmHg, or the difference of systolic blood pressure is more than 20 mmHg before and after treatment. Others are the ineffective treatment.

Outcome measures

Main outcome measures: the systolic and diastolic blood pressures before and after treat-

Table 1. Clinical data of patients

	Observation group (n=45)	Control group (n=45)	t/x^2 value	*P* value
Gender			0.829	0.362
Male	33 (73.33)	29 (64.44)		
Female	12 (26.67)	16 (35.56)		
Age (year)	51.6 ± 9.4	53.4 ± 10.1	0.875	0.384
Course of disease (year)	13.2 ± 6.4	14.5 ± 7.8	0.864	0.390
BMI (kg/m^2)	23.73 ± 1.82	24.82 ± 1.97	1.226	0.224
Diabetes			0.458	0.499
Yes	16 (35.56)	13 (28.89)		
No	29 (64.44)	32 (71.11)		
Hyperlipemia			0.241	0.624
Yes	10 (22.22)	12 (26.67)		
No	35 (77.78)	33 (73.33)		
History of smoking			0.443	0.506
Yes	17 (37.78)	14 (31.11)		
No	28 (62.22)	31 (68.89)		
History of alcoholism			0.257	0.612
Yes	9 (20.00)	11 (24.44)		
No	36 (80.00)	34 (75.56)		
Residence			1.029	0.311
City	37 (82.22)	33 (73.33)		
Rural	8 (17.78)	12 (26.67)		
SBP (mmHg)	168.87 ± 14.63	172.59 ± 17.25	1.103	0.273
DBP (mmHg)	113.47 ± 12.64	109.83 ± 11.49	1.429	0.156
Uric acid (μmol/L)	252.93 ± 54.41	237.23 ± 46.62	1.470	0.145
Blood glucose (mmol/L)	6.47 ± 2.21	6.22 ± 1.96	0.568	0.572
Urea nitrogen (mmol/L)	5.17 ± 2.62	5.39 ± 2.81	0.384	0.702
Creatinine (μmol/L)	84.86 ± 13.74	89.29 ± 15.31	1.445	0.152
White blood cell count ($\times 10^9/L$)	6.58 ± 1.37	6.75 ± 1.43	0.576	0.566
LDL-C (mg/dl)	137.58 ± 24.37	145.54 ± 27.53	1.452	0.150

Remarks: BMI: Body mass index; SBP: systolic pressure; DBP: diastolic pressure; LDL-C: Low density lipoprotein cholesterol.

ment in the two groups, the evaluation of therapeutic effect in the two groups, the life quality of the patients assessed with the 36-item Short-Form Health Survey (SF-36), and the scores of various dimensions of SF-36 after treatment.

Secondary outcome measures: the adverse reactions after treatment in both groups.

Statistical methods

In this study, SPSS20.0 (Chicago SPSS Co., Ltd.) medical statistical analysis software was utilized to analyze the collected data. GraphPad Prism 7 (San Diego GraphPad Software Co., Ltd.) was utilized to draw pictures for the collected data. The enumeration data were expressed by X^2 using chi-square test. The measurement data were expressed by means ± standard deviation (Means ± SD). All measurement data were in accordance with the normal distribution. Independent t-test was applied for comparison between the two groups. Paired t test was used for comparison within the two groups. $P<0.05$ indicates that there was statistically significant difference.

Results

Clinical data

The clinical data of the two groups were collected and compared. The results revealed that there were no significant differences in gender, age, course of disease, BMI, history of

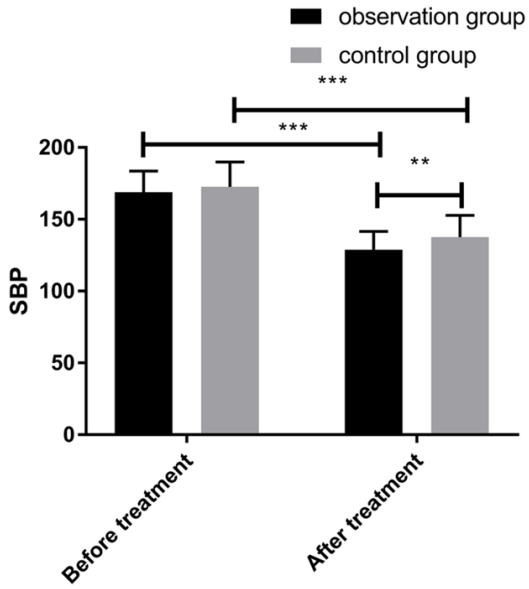

Figure 1. Changes of SBP in the two groups before and after treatment. The SBP in the observation group after treatment was lower than that before treatment (t=14.623, P<0.001), and the SBP in the control group after treatment was lower than that before treatment (t=11.245, P<0.001). After treatment, the SBP in the observation group was lower than that in the control group (t=2.956, P=0.004).

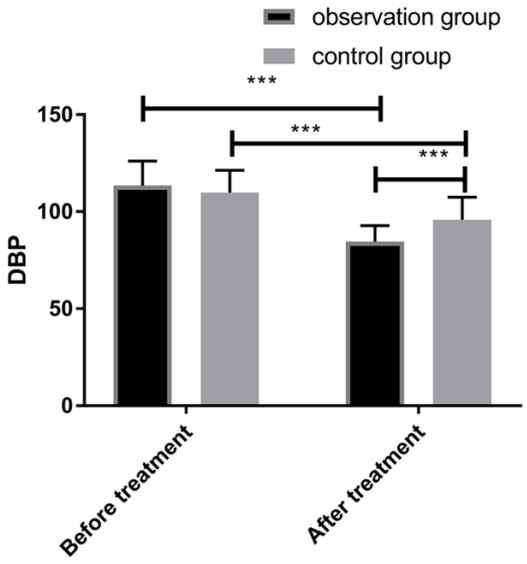

Figure 2. Changes of DBP in the two groups before and after treatment. The DBP in the observation group after treatment was lower than that before treatment (t=14.225, P<0.001), and the DBP in the control group after treatment was lower than that before treatment (t=7.624, P<0.001). After treatment, the DBP in the observation group was lower than that in the control group (t=5.289, P=0.004).

diabetes, hyperlipidemia, smoking and alcoholism, residence, SBP, DBP, uric acid, blood glucose, urea nitrogen, creatinine, white blood cell count, and LDL-C between the two groups (P>0.05) (**Table 1**).

Comparison of SBP and DBP levels between the two groups after treatment

Comparing the levels of SBP and DBP between two groups before and after treatment, it was found that after treatment, the levels of SBP and DBP in the observation group were 128.76 ± 12.76 mmHg and 84.52 ± 8.24 mmHg, and the levels of SBP and DBP in the control group were 137.52 ± 15.24 mmHg and 95.79 ± 11.68 mmHg. The levels of SBP and DBP in the two groups after treatment were lower than those before treatment (P<0.05). After treatment, the levels of SBP and DBP in the observation group were lower than those in the control group (P<0.05) (**Figures 1** and **2**).

Adverse reactions of the two groups after treatment

Comparing the adverse reactions of the two groups after treatment, it was found that the total incidence of adverse reactions in the observation group was lower than that in the control group (P<0.05) (**Table 2**).

Evaluation of therapeutic effect in the two groups after treatment

Comparing the therapeutic effect in the two groups after treatment, it was found that the total effective rate of the observation group was higher than that of the control group (P<0.05) (**Table 3**).

SF-36 scores of the two groups after treatment

According to the SF-36 scores of the two groups, the life quality of the patients was evaluated. It was found that the scores of eight dimensions in the observation group were higher than those in the control group (P<0.05) (**Table 4**).

Univariate analysis of therapeutic effect

According to the therapeutic effect of patients, the patients were divided into effective group (n=63) and ineffective group (n=27). The clinical data of the two groups were collected for univariate analysis. It was found that there

Table 2. Adverse reactions after treatment in two groups

	Observation group (n=45)	Control group (n=45)	x^2 value	*P* value
Dizziness	2 (4.44)	5 (11.11)		
Limb weakness	1 (2.22)	2 (4.44)		
Facial flushing	2 (4.44)	5 (11.11)		
Lower limb edema	1 (2.22)	3 (6.67)		
Nausea	2 (4.44)	2 (4.44)		
Total incidence of side effects	8 (17.78)	17 (37.78)	4.486	0.034

Table 3. Evaluation of therapeutic effect of the two groups after treatment

	Observation group (n=45)	Control group (n=45)	x^2 value	*P* value
Ineffective	8 (17.78)	19 (42.22)	4.286	0.038
Effective	37 (82.22)	26 (57.78)		

Table 4. SF-36 scores of two groups after treatment

	Observation group (n=45)	Control group (n=45)	t value	*P* value
Physical Functioning	73.37 ± 16.93	65.46 ± 17.25	2.195	0.031
Role-Physical	59.76 ± 16.64	51.37 ± 22.15	2.032	0.045
Bodily Pain	74.84 ± 12.75	64.64 ± 15.36	3.428	0.001
General Health	65.40 ± 9.28	54.33 ± 12.85	4.685	<0.001
Vitality	67.74 ± 16.26	57.49 ± 13.86	3.218	0.002
Social Functioning	58.77 ± 12.94	52.46 ± 13.65	2.250	0.027
Role-Emotional	71.46 ± 15.24	63.45 ± 14.85	2.525	0.013
Mental Health	57.94 ± 17.15	51.27 ± 15.92	2.027	0.046

were statistical differences in age, course of disease, BMI, history of diabetes and hyperlipidemia, blood glucose, white blood cell count and treatment methods between the two groups (P<0.05), and there was no obvious difference in gender, history of smoking and alcoholism, residence, SBP, DBP, uric acid, urea nitrogen, creatinine and white blood cell count (P>0.05) (**Table 5**).

Multivariate analysis of therapeutic effect

The indicators with differences in univariate analysis were assigned (**Table 6**). The multivariate Logistic regression analysis revealed that age, diabetes, hyperlipidemia and treatment method were not the independent risk factors of ineffective treatment, while course of disease (OR: 4.274, 95% CI: 3.378-5.262), BMI (OR: 0.310, 95% CI: 0.120-0.799), blood glucose (OR: 1.872, 95% CI: 1.317-2.058), and LDL-C (OR: 1.072, 95% CI: 1.032-1.317) were the independent risk factors of ineffective treatment (**Table 7**).

Discussion

The resistant hypertension has always been an uncontrollable disease. Some studies have reported that sympathetic nerve dysfunction and excessive secretion of epinephrine could participate in and lead to the occurrence and development of hypertension [16]. Based on this principle, RDN combined with corresponding antihypertensive drugs has been developed to lower blood pressure in patients with resistant hypertension [17, 18]. As β-receptor blocker could lower blood pressure and reduce the risk of cardiovascular events, it was utilized in combination treatment for hypertension [19]. However, some studies have suggested that the use of β-receptor blocker during the perioperative period of non-cardiac surgery can prevent nonfatal cardiac infarction, but may increase the risk of stroke, death, hypotension and bradycardia [20]. Therefore, this study explored whether RDN and nifedipine combined with metoprolol tartrate could affect the therapeutic effect, safety and prognosis of patients.

Firstly, the systolic and diastolic blood pressures of the two groups after treatment were compared. It was found that the systolic and diastolic blood pressures of the two groups after treatment were lower than those before treatment, and the systolic and diastolic blood pressures of the observation group were lower than those of the control group. It was suggested that our treatment achieved the therapeutic effect and lowered the blood pressure of patients, but the antihypertensive effect of RDN and nifedipine combined with metoprolol tartrate was better than that of RDN and nifedipine alone. Then the adverse reactions of the

Table 5. Univariate analysis

	Effective group (n=63)	Ineffective group (n=27)	t/x^2 value	*P* value
Gender			0.484	0.487
Male	42 (66.67)	20 (74.07)		
Female	21 (33.33)	7 (25.93)		
Age (year)	49.6 ± 9.7	54.4 ± 10.3	2.112	0.038
Course of disease (year)	11.3 ± 7.5	15.6 ± 6.8	2.561	0.012
BMI (kg/m^2)	22.54 ± 2.03	26.35 ± 1.73	8.511	<0.001
Diabetes			6.805	0.009
Yes	15 (23.81)	14 (51.85)		
No	48 (76.19)	13 (48.15)		
Hyperlipemia			5.546	0.019
Yes	11 (17.46)	11 (40.74)		
No	52 (82.54)	16 (59.26)		
History of smoking			0.677	0.411
Yes	20 (31.75)	11 (40.47)		
No	43 (68.25)	16 (59.26)		
History of alcoholism			0.306	0.590
Yes	13 (20.63)	7 (25.93)		
No	50 (79.37)	20 (74.07)		
Residence			1.224	0.269
City	47 (47.60)	23 (85.19)		
Rural	16 (25.40)	4 (14.81)		
SBP (mmHg)	169.66 ± 15.21	172.23 ± 17.01	0.709	0.480
DBP (mmHg)	109.27 ± 11.35	112.45 ± 13.05	1.164	0.248
Uric acid (μmol/L)	235.96 ± 48.22	254.21 ± 51.39	1.613	0.110
Blood glucose (mmol/L)	6.02 ± 2.14	6.97 ± 1.64	2.060	0.042
Urea nitrogen (mmol/L)	5.23 ± 2.66	5.34 ± 2.72	0.179	0.859
Creatinine (μmol/L)	85.34 ± 13.96	88.42 ± 15.20	0.934	0.353
White blood cell count ($\times 10^9$/L)	6.41 ± 1.36	6.78 ± 1.44	1.162	0.248
LDL-C (mg/dl)	131.58 ± 22.16	150.54 ± 30.48	3.309	0.001
Treatment method			6.402	0.011
Separate treatment	26 (41.27)	19 (70.37)		
Combined treatment	37 (58.73)	8 (29.63)		

Table 6. Assignment list

	Evaluation
Age	Data are continuous variables using raw data analysis
Course of disease	Data are continuous variables using raw data analysis
BMI	Data are continuous variables using raw data analysis
Diabetes	Yes =1, No =0
Hyperlipemia	Yes =1, No =0
Blood glucose	Data are continuous variables using raw data analysis
LDL-C	Data are continuous variables using raw data analysis
Treatment method	Combined treatment =1, Separate treatment =0
Therapeutic effect	Ineffective =1, Effective =0

two groups after treatment were compared. The total incidence of adverse reactions in the observation group was lower than that in the control group, which also revealed that RDN and nifedipine combined with metoprolol tartrate could reduce the incidence of adverse reactions. Comparing the therapeutic effect of the two groups, the total effective rate of the observation group was higher than that of the control group. It was also suggested that RDN and nifedipine combined with metoprolol tartrate may be more conducive to improving the therapeutic effect. SF-36 was applied to

Table 7. Multivariate analysis

	B	S.E,	Wals	Sig.	Exp (B)	EXP (B) 95% C.I.	
						Lower limit	Upper limit
Course of disease	0.478	1.762	6.107	0.016	4.274	3.378	5.262
BMI	0.267	0.483	5.876	0.015	0.310	0.120	0.799
Blood glucose	0.572	0.498	5.724	0.002	1.872	1.317	2.058
LDL-C	0.142	0.019	5.278	0.024	1.072	1.032	1.317

Remarks: B: Constant term; SE: standard deviation; Wals: Chi square value; Sig: *P* value; Exp (B): Dominance ratio; 95% C.I. of EXP (B): Advantage ratio 95% confidence interval.

evaluate the life quality of the two groups after treatment. It was found that the scores of eight dimensions in the observation group were higher than those in the control group, indicating that RDN and nifedipine combined with metoprolol tartrate had better effect on improving the prognostic life quality of the patients. In the study of Zhang et al. [21], the high and low doses of metoprolol tartrate were utilized to treat patients with chronic heart failure. It was found that both doses could improve heart function, motor function, life quality and mental state of patients. There was no significant difference of therapeutic effect between the two doses. It was also proved that metoprolol tartrate could improve the life quality of patients, and the effect of metoprolol tartrate on improving the life quality of patients with hypertension may not be affected by the dose.

Finally, according to the therapeutic effect, the Logistic regression was utilized to analyze the risk factors of ineffective treatment. It was found that the course of disease, BMI, blood glucose and LDL-C were the risk factors of ineffective treatment. In the study of Tsioufis et al. [22], 79 patients with resistant hypertension were treated with RDN. The decreases of blood pressure in 6 months and 12 months were observed, and analyzed by Logistic regression. It was found that age, body mass index (BMI), and blood pressure were the predictors of treatment. There are some differences in the results, but it is more conducive to predicting the therapeutic effect of patients. It was speculated that our observation time was shorter than theirs, other different drugs were combined for treatment, and routine examination indicators such as blood glucose and LDL-C were included.

However, there are still some shortcomings in this study. Firstly, there are many drugs used in the treatment of hypertension. There are many kinds of calcium antagonists and β-receptor blockers, such as cilnidipine and atenolol. It is not clear whether the use of other drugs will affect our results, which required the addition of more other drug treatment groups in the subsequent studies. Secondly, the patients with hypertension need long-term medication treatment, and our study time may be relatively short. Therefore, the subsequent studies should increase the follow-up time to further study the changes of various indicators. Finally, as there was no obvious difference in the therapeutic effect of RDN, there were some controversies. Therefore, it still needs a larger sample size of further study to demonstrate the therapeutic effect of RDN [23, 24].

In conclusion, RDN and nifedipine combined with metoprolol tartrate have better antihypertensive effect and therapeutic effect, lower incidence of adverse reactions, and higher prognostic life quality in the treatment of resistant hypertension. The course of disease, BMI, blood glucose and LDL-C are the risk factors of ineffective treatment.

Disclosure of conflict of interest

None.

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