Clinical Evalulation of Antihypertensive Efficacy and Safety of Administration of Doxazosin Mesylate in Mild to Moderate Essential Hypertension

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ABSTRACT **OBJECTIVE:** To evaluate the efficacy and safety of administration of doxazosin mesylate in mild to moderate essential hypertension . **METHODS** In the trial ,43 patients meeting the creteria of enlistment after 2 - week wash - out periods are randomized into two groups in term of double - blind manner ,22 cases for doxazosin mesylate group ,21 cases for Terazosin hydrochloride group . The patients will recept the scheduled medication intervention and blood pressure measure in order to assess the efficacy of antihypertension . Physical examnation , electrocardiogram , hematological and urinary test will be performed for monitoring the adverse events according to the trial protocol . **RESULTS**: The rate of effectiveness of doxazosin mesylate for hypertension controling is 86 .4 % . No severe adverse events such as the cardiovascular disorders appear in the 6 - week trial except for the mild , toleratable headache in one patient . Doxazosin mesylate does not interfere with the hepatic and renal metabolism and impair their functions . **CONCLUSIONS:** Doxazosin mesylate adiministration is effective and safe in mild to moderate essential hypertension .

KEY WORDS doxazosin ,essential hypertension ,clinical trial

甲磺酸多沙唑嗪治疗轻、中度高血压的临床疗效及安全性评价

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摘要 目的:评价多沙唑嗪治疗高血压的临床疗效和安全性 。方法:采用双盲双模拟随机对照的方法观察多沙唑嗪的疗效和安全性 。经过 2 周的清洗期 ,共有 43 例病人入选(试验组 22 例 ,对照组 21 例) ,按试验流程服药及监测血压 、心率 、肝肾功能及心电图等指标 。结果:经过临床 6 周的药物治疗 ,临床有效率达 86 .4 % ,其中显效率为 68 .2 % 。对肝肾功能无影响 ,无严重不良反应 。结论:多沙唑嗪是一种有效 、安全的治疗轻 、中度高血压的药物 。

关键词 多沙唑嗪 ;高血压 ;临床验证

Alpha - adrenergic blockers , which can competatively antagonize α receptor on the membrane of peripheral vascular smooth muscular cells as well as indirectly decrease the sympathetic activities through imposing infleunce on central nervous system[1 ,2] , can reduce the increased vascular myogenic tone , hence down - regulate the blood pressure to normal level . These drugs are catagorized as one of the first - line medication interventions recommended by WHO in hypertension control .

However ,lacking of the clinical experiences ,alpha - adrenergic blockers' excellent antihypertensive effect is not recognized by the practitioners , and then result into the unsatisfied prescriptive situation . Through evaluating the efficacy and the safety of new drug , doxazosin mesylate ,in hypertension control trial ,we attemp to present one of clinical choices with high - efficacy and good - safety to modulate the patients' high blood pressure for practitioners .

1 Patients and methods

1 .1 Creteria of enlistment

Patients with essential hypertension , whose diastolic blood pressures range from 95 mmHg to 114 mmHg and systolic pressures are less then 180 mmHg ,are recruited and classified into two groups (doxazosin mesylate group/ abbreviated by D group and Terazosin hydrochloride group/ abbreviated by T group) by randomized double - blind manner . All inducted patients are exempted from the following situations : ① excessively obesity ; ② unstable angina pectoris , myocardial infaction and vascular stroke in brain in the past half a year ; ③severe heptic or renal dysfunction ; ④not well - controled diabetes mellitus ; ⑤any women in pregenence or in nursing period .

1 .2 Drugs provision

Doxazosin mesylate (2mg per tablet) is produced by conba

pharmaceutical corp Ltd Hangzhou(杭州康恩贝制药有限公司), and Terazosin hydrochloride (2mg per tablet) is manufactured by green island pharmaceutical corp Ltd Hainan(海南绿岛制药有限公司). Two drugs were provided by trial organization committee, any trial - practicers or recruitees do not know the true ingredient in the tablets which is prescribed or taken.

1.3 Trial protocol

After two - week wash - out periods, 22 cases are randomized into D group, 21 cases into T group. The patients take initial dosage of 2mg per day for 2 weeks both in trial group and in control group. The patients with uncontroled pressure (described as diastolic pressure ⩾95 mmHg) will double dosage, others with controled pressures maintain the primnary dosage. During the next consultation after 2 weeks, the above - mentioned evaluating - and - dosage increasment procedure will repeated. The maximun dosage is 4 mg per day. Efficacy was assessed in term of the sitting diastolic pressure at the end of 6 - week tial.

All patients will take physical examination, electrocardiogram, urinary test and blood chemistry for monitoring heptic and renal function, electrolyte, plasma glucose and lipids et al at the beginning and end of trial. Safety is evaluated from the recorded adverse events, blood chemistry, hematological and urinary parameters.

1.4 Evaluation creteria of antihypertensive efficacy

Cotroled: the sitting diastolic pressure is adjusted into the normal level(<95 mmHg) with decreased range ⩾10 mmHg or the reduced diastolic pressure from the baseline is more then 20 mmHg.

Showing effective: the sitting diastolic pressre is under the normal level with decreased range ⩽10 mmHg, or reduced diastolic pressure from the baseline is less then 20 mmHg but more then 10 mmHg.

Showing uneffective: can not meet the above creteria.

Fig 1 Protocol of trial

Sequence of consultation	Wash - out period / - 14days	baseline / 0 day	Administration of medication/ day					
			8^{th}	15^{th}	22^{nd}	29^{th}	36^{th}	43^{rd}
Physical examnation	+	+	+	+	+	+	+	+
Blood pressure taking	+	+	+	+	+	+	+	+
Lab parameters								
Hematological test		+						+
Haptic function		+						+
Renal function		+						+
Blood sugar		+						+
Blood lipids		+						+
Electrolyte		+						+
electrocardialgram	+							+
Medication intervention	+	+	+	#	#	#	#	#
Adverse event observation			+	+	+	+	+	+

Annotation: # - indicates the patients with uncontroled diastolic pressure who sequentially take doubled dosage (4mg per day)

1.5 Statistical analysis

Any datum or parameters are expressed by mean ±s. The mean changes in and between groups are analyzied by t test. Rate of effectiveness is analyzied by x^2 test.

2 Results

2.1 The clinical characteristics of treatment

43 cases meating the enlistment creteria were randomized into D (22 cases) or T group(21 cases). One case in each group is acquited from the following - up. 10 cases in each group need doubling the primary dosage.

2.2 Assessment of antihypertensive efficacy in D and T groups

The blood pressure datum are showed as the fig 3 in the whole period of medication intervention. 15 cases are controled, 4 cases show effective in D group, the whole rate of effectiveness [(15 + 4)/22] is 86.4 %. 12 cases, 2 cases and 66.7 % in T group respectively. There is no statistically significant difference in two groups. Blood pressures of 10 in D group and 6 in T group meet the

Fig 2 Clinical datum of patiens with essential hypertension pre - treatment

	D group /22 cases	T group /21 cases
Male/female	8/14	11/10
Age/years	51.5 ±8.9	50.6 ±6.7
Suffering years of EH/years	4.9 ±4.1	6.9 ±7.2
Systolic pressure/mmHg	149.9 ±14.4	150.7 ±12.5
Diastolic pressure/mmHg	98.4 ±6.0	99.6 ±5.7
Heart rate/bpm	77.8 ±5.8	78.8 ±12.8

latest creteria of normal pressure(<140/90 mmHg) after treatment.

Fig 3 Comparation of Blood pressures pre- and post- intermention in each group

	Systolic pressure / mmHg		Diastolic pressure/ mmHg	
	D group/ 22cases	T group/ 21 cases	D group/ 22cases	T group/ 21 cases
baseline	153.8 ±12.7	156.1 ±14.8	99.6 ±4.8	101.4 ±4.8
2 weeks post- treatment	143.9 ±13.4 *1	145.5 ±17.5 *1	92.9 ±6.8 *2	90.6 ±11.2 *2
4 weeks post- treatment	140.2 ±10.6 *2	146.7 ±13.5 *1	88.2 ±6.3 *2	89.9 ±7.9 *2
6 weeks post- treatment	136.2 ±14.2 *2	146.4 ±16.5 *1	87.2 ±6.9 *2	90.6 ±8.8 *2

Annotation: *1 $P<0.01$, *2 $P<0.05$

Fig 4 Comparation of effectivenesses of antihypertension in two groups

	D group /22 cases	T group /21 cases
Cases showing effectiveness	19(86.4 %)	14(66.7 %)
Cases showing no effect	3(13.6 %)	7(33.3 %)

Annotation: $F=0.96$ by χ^2 test. $P>0.05$ There is no statistically significant difference evident between two groups

2.3 Dosage- efficacy relationship analysis

10 cases in each group required the double dosage in the course of trial. Dosage increasement can excessively decrease the high-level pressure, the trial shows that the efficacy is positively correlative with the dosage.

2.4 Changes of heart rates in two groups

There is no signicicant changes in the heart rates before and after treatment, that indicates that the drugs don't cause the reflective heart rate increasement or tachycardia.

Fig 5 changes of heart rates in two groups in the trial

	D group /22 cases	T group /21 cases
baseline	79.8 ±13.4	81.9 ±12.1
2 weeks after treatment	81.4 ±10.6	83.5 ±8.8
4 weeks after treatment	83.9 ±9.4	84.0 ±10.2
6 weeks after treatment	83.4 ±12.5	81.7 ±11.4

Annotation: $P>0.05$. There is no statistically significant difference evident between two groups or pre- and post- treatment in each group

2.5 Safety assessment

2 cases acquit from the trial, one in D group for the allergy with the symptoms of etching and eruption papular, another for untolerated headache in T group. One case with the mild, toleratable headache in D group continues the trial. No severe adverse events such as reflective tachycardia, asthenia, flushing, pulsating headache, palpitation, dizziness, and gut symptoms occur during the study. Hematological and chemistry parameters indicate that the drug does not cast the harmful enfluences on the heptic, renal function. The plasma levels of glucose and lipids do not show the significant changes.

3 Discussion

Alpha- adrenergic blockers, which antagonize the α_1 receptor in the peripheral vascular smooth muscular cell[1], can relax the vascular myogenic tone, and sequentialy dilate the vessel beds, lower the vascular resistance in cascades, cause the blood pressure discrease eventually. Due to the little selectivity for the alph 2 receptor, the negative feedback control from sympathetic nerve terminals remains intact[2]. The clinical studies excuted by the foreign counterparts substantiate the alpha- adrenergic blockers' super properties for effective, stable and safe hypertension control[3]. More ever, Prolonged, regular medication interference wth highly selective alpha 1- adrenergic blockers in essential hypertension can reduce the low density lipoprotein- cholesterol and elevate the high density lipoprotein- cholesterol so that to improve the prognosis of patients and minimize the risk of occurrences of the cerebral or cardialvascular malign events[1].

The cause that the practitioners are not likely to prescribe the alpha- adrenergic blockers to patients afflicated by the essential hypertension is properbly ascribed to the knowledge lackage for efficacy and safety of these drugs' administration. In order to reverse this tendency, we apply the alpha- adrenergic blocker. Doxazosin mesylate, to regulate the mild to moderate hypertension in term of the randomized, double- blind manners, and simutaneously compare the efficacy of Doxazosin mesylate with that of Terazosin hydrochloride, one of alpha- adrenergic blocker with well- reputable antihypertensive ability.

Intervention of two drugs significantly reduce the blood pressure, the rate of total effectiveness of Doxazosin mesylate application in patints is 86.4 %, that of Terazosin hydrochloride is 66.7 %. Though the higher rate of effectiveness shown in the Doxazosin mesylate group, no statistically significant difference exists in two groups.

This trial presents not only the good efficacy but the well-satisfied safety of Doxazosin mesylate adiministration. Due to the symphathetic suppress and the slow- releasing technonogies, no severe adverse events such as reflective tachycardia, asthenia, flush, pulsating headache, palpitation and dizziness occur during the study. Hematological and chemistry parameters of pre- and post treatment

indicate that the drug does not interfere into the normal metabolism of liver and kidney. The long - term following - up of more cases or large - scale trial is indispensible to demonstrate the potential profits in hypercholesterolemia modulation which is not available in this small - scale pilot.

Thus, we draw the conclusion that Doxazosin mesylate adiministration is effective and safe in mild to moderate essential hypertension.

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