

· 临床研究 ·

小剂量左氨氯地平、替米沙坦及氢氯噻嗪同时或不同时给药降压及逆转非杓型高血压的临床分析

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【摘要】目的 探讨小剂量左氨氯地平、替米沙坦及氢氯噻嗪同时或不同时给药降压及逆转非杓型血压的效果。**方法** 选择300例收缩压(SBP) < 180mmHg, 舒张压(DBP) 91~109mmHg, 年龄 > 45岁的非杓型高血压患者, 随机分为两组, I组(不同时给药组)晨服替米沙坦40mg和氢氯噻嗪10mg, 晚服左氨氯地平2.5mg; II组(同时给药组)以上3种药物均晨服, 所有病例治疗前及治疗8周后进行动态血压监测。**结果** (1)治疗8周后, I组和II组的24h SBP/DBP分别降低14.92/9.96和15.04/10.66mmHg, 日间SBP/DBP分别降低13.90/10.60和16.06/11.70mmHg, 均较治疗前明显降低($P < 0.01$);两组24h和日间SBP/DBP治疗后差异无统计学意义($P > 0.05$)。(2)I组夜间SBP/DBP降低25.44/19.48mmHg, 与治疗前相比差异非常显著($P < 0.01$)。(3)II组夜间SBP/DBP降低17.68/14.76mmHg, 与治疗前差异也有统计学意义($P < 0.05$)。(4)治疗后夜间SBP/DBP降幅I组较II组差异更明显($P < 0.01$)。(5)I组逆转率为88.16%, II组为55.41%, 两组比较差异有统计学意义($P < 0.01$)。**结论** 小剂量左氨氯地平、替米沙坦及氢氯噻嗪两种服药方法均能有效地控制24h血压和日间血压, 而不同时给药能更好地逆转非杓型高血压。

【关键词】 左氨氯地平; 替米沙坦; 氢氯噻嗪; 高血压; 时间治疗学

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Efficacy of small dosed levamlodipine, telmisartan and hydrochlorothiazide given at the same or different time points on anti-hypertension and reverse of non-dipper hypertension: clinical analysis of 300 cases

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【Abstract】 Objective To determine the efficacy of small doses of levamlodipine, telmisartan and hydrochlorothiazide given at the same or different time points on anti-hypertension and reverse of non dipper hypertension. **Methods** Three hundred over-45-year-old patients with non-dipper hypertension [systolic blood pressure (SBP) < 180mmHg and diastolic blood pressure (DBP) ranging from 90 to 109mmHg] admitted in our out- and in-patient departments from May 2011 to October 2013 were prospectively subjected in this study. They were randomly divided into 2 groups, group I (the drugs were given at different time, 40mg telmisartan and 10mg hydrochlorothiazide were given in the morning, while 2.5mg levamlodipine at night), and group II (all 3 drugs were given at the morning). All cases received ambulatory blood pressure monitoring before and in 8 weeks after treatment. **Results** In 8 weeks after the treatment, the 24-hour SBP/DBP was reduced by 14.92/9.96mmHg and 15.04/10.66mmHg respectively for groups I and II, while the daytime SBP/DBP was decreased by 13.90/10.60mmHg and 16.06/11.70mmHg, respectively. These indices were all significantly lower than before treatment ($P < 0.01$), but there was no difference between the 2 groups ($P > 0.05$). The nighttime SBP/DBP was reduced by 25.44/19.48mmHg in group I and by 17.68/14.76mmHg in group II, and both were significantly lower than before treatment ($P < 0.01$, $P < 0.05$). The reversion of non-dipper hypertension was 88.16% and 55.41% for the 2 groups, with significant difference between them ($P < 0.01$). **Conclusion** No matter small doses of levamlodipine, telmisartan and hydrochlorothiazide are given at the same or different time points, they effectively control the 24-hour and daytime blood pressures. But the drugs given at different time points can reverse non-dipper hypertension better.

【Key words】 levamlodipine; telmisartan; hydrochlorochiazide; hypertension; chronotherapeutics

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在生理状态下人体血压一直在不断地波动, 正常人及部分高血压患者的血压夜间比白天低10%~20%, 称为杓型, 部分高血压患者的血压夜间与白天相差<10%, 甚至夜间高于白天称为非杓型^[1]。习惯上人们称此类高血压为非杓型高血压。研究表明, 无论患者血压的平均水平如何, 夜间血压下降幅度减少或无明显下降者, 发生心脑血管并发症的可能性显著增加^[2,3]。目前降压药物品种繁多, 联合用药方式各异, 服用时间说法不一^[4]。因此需要大家探索一些安全、有效、价格适宜, 便于推广的联合治疗方案。本文探讨小剂量左氨氯地平、替米沙坦及氢氯噻嗪同时或不同时给药对非杓型高血压的降压作用及对血压昼夜节律的影响。

1 对象与方法

1.1 研究对象

选取河北医科大学附属哈励逊国际和平医院2011年5月至2013年10月门诊及住院高血压患者1200多例, 符合《中国高血压防治指南2010》的诊断标准^[5]。停药1~2周进行24h动态血压监测, 根据结果除外杓型血压, 超杓型血压及清晨高血压患者, 另除外继发性高血压、心肌病、心脏瓣膜病及影响脉压的疾病患者。该类患者无脑心肺疾患, 无血脂紊乱、糖尿病及甲状腺疾病。符合入组标准, 即收缩压(systolic blood pressure, SBP)<180mmHg, 舒张压(diastolic blood pressure, DBP)91~109mmHg, 年龄>45岁, 即中老年年轻中度的非杓型高血压患者300例, 随机分为两组。入选病例的基线指标见表1。本研究获医院伦理委员会批准, 参加患者均签署知情同意书。

1.2 方法

1.2.1 动态血压测量方法 采用美国航空实验室的90217型(Spacelabs, Inc)无创动态血压监测仪进行24h动态血压测量。袖带束缚于受试者左上臂, 患者休息15~30min后启动第1次血压测定, 进行昼(06:00~22:00)夜(22:00~06:00)24h动态血压监测, 每30min自动测量1次, 同时保持日常工作和活动。全天有效血压读数>85%, 每小时夜间有效读数无缺漏。排除不符合上述判读血压时间及读者数。

1.2.2 药品 左氨氯地平: 施慧达药业集团(吉林)有限公司生产, 批号: H19991083; 替米沙坦: 浙江金立源药业有限公司生产, 批号: H20041252; 氢氯

表1 入选病例的基线指标

Table 1 Baseline data of selected patients ($\bar{x} \pm s$)

Item	Group I (n = 152)	Group II (n = 148)
Age(years)	51.61 ± 6.72	51.82 ± 6.91
oSBP(mmHg)	154.32 ± 14.38	153.86 ± 12.66
oDBP(mmHg)	98.48 ± 8.26	97.84 ± 8.14
24h SBP(mmHg)	141.16 ± 15.68	140.92 ± 15.88
24h DBP(mmHg)	92.64 ± 7.76	92.42 ± 7.84
dSBP(mmHg)	143.34 ± 15.62	143.68 ± 15.34
dDBP(mmHg)	95.42 ± 7.52	95.38 ± 7.96
nSBP(mmHg)	137.82 ± 17.24	138.18 ± 16.86
nDBP(mmHg)	90.94 ± 8.82	91.92 ± 8.48
TC(mmol/L)	4.41 ± 0.73	4.46 ± 0.71
TG(mmol/L)	1.36 ± 1.12	1.38 ± 1.14
HDL-C(mmol/L)	1.44 ± 0.33	1.46 ± 0.34
LDL-C(mmol/L)	2.92 ± 0.51	2.95 ± 0.52
FBG(mmol/L)	4.96 ± 1.20	5.06 ± 1.21

Group I: the drugs were given at different time; Group II: the drugs were given at the same time; oSBP: office systolic blood pressure; oDBP: office diastolic blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; dSBP: daytime SBP; dDBP: daytime DBP; nSBP: nighttime SBP; nDBP: nighttime DBP; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FBG: fasting blood glucose

噻嗪: 山西云鹏制药有限公司生产, 批号: H20058629。

1.2.3 治疗方法 对符合入组标准的患者采用完全随机设计分组法分为两组: 不同时给药组(I组), 152(男100, 女52)例, 晨服替米沙坦40mg和氢氯噻嗪10mg, 晚服左氨氯地平2.5mg; 同时服药组(II组), 148(男99, 女49)例, 上述3种药物均晨服, 各药量同I组。清晨服药时间为7:00~10:00, 晚上服药时间为19:00~22:00。治疗8周后再次进行24h动态血压监测。

1.3 统计学处理

采用SPSS10.0统计软件处理, 计量资料用 $\bar{x} \pm s$ 表示, 两组间比较采用独立样本t检验, 治疗前后均数比较用配对t检验; 计数资料比较用 χ^2 检验, 以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 治疗后血压的变化

治疗8周后, I组和II组的24hSBP/DBP分别降低14.92/9.96mmHg和15.04/10.66mmHg, 日间SBP/DBP分别降低13.90/10.60mmHg和16.06/11.70mmHg, 均较治疗前明显降低($P < 0.01$); 两组24h和日间SBP/DBP治疗前后差异无统计学意义; I组夜间SBP/DBP降低25.44/19.48mmHg, 与治疗前相比差异

显著 ($P < 0.01$) ; II 组夜间 SBP/DBP 降低 17.68/14.76 mmHg, 与治疗前差异也有统计学意义 ($P < 0.05$; 表2)。

2.2 夜间血压下降幅度的变化

治疗8周后夜间SBP/DBP降幅 I 组较 II 组更明显 ($P < 0.01$); 组内比较 I 组SBP/DBP降幅更大 ($P < 0.01$), II 组降幅也有统计学差异 ($P < 0.05$; 表3)。

2.3 逆转非杓型血压例数的变化

按照SBP昼夜差值百分比 $< 10\%$ 确定为非杓型血压, I 组逆转率为88.16% (134/152), II 组为55.41% (82/148), 两组比较差异有统计学意义 ($P < 0.01$)。

3 讨论

替米沙坦是非肽类血管紧张素 II (angiotensin II, AT II) 受体拮抗剂 (angiotensin receptor blocker, ARB), 能选择性地与AT II 1型受体结合而阻断其作用, 从而发挥降压效应。该药半衰期长, 具有缓和持久的降压效果, 起效平稳, 口服吸收好, 生物利用度高, 不受食物影响, 长期应用可升高血钾^[5,6]。

氢氯噻嗪属噻嗪类利尿剂, 主要通过利钠利尿减低高血容量负荷发挥降压作用。小剂量氢氯噻嗪 (6.25~25 mg) 对代谢影响很小, 与其他降压药物[尤其是血管紧张素转换酶抑制剂 (angiotensin converting

enzyme inhibitor, ACEI) 或ARB] 合用可显著增加后者的降压作用, 该药长期服用可引起低血钾^[5,7]。

左氨氯地平为新一代长效二氢吡啶类钙离子通道阻滞剂 (calcium channel blocker, CCB), 口服吸收, 谷峰比值较高。氨氯地平 (amlodipine) 有左旋和右旋两种对应体, 右旋氨氯地平几乎无疗效, 因此, 等量的左氨氯地平的疗效是氨氯地平的2倍。与氨氯地平相比, 去掉了其右旋体, 减轻了不良反应, 安全性更高^[8,9]。

近年来, 国内学者也在不断探索各种联合治疗方案或复方制剂。朱鼎良等^[10]认为奥美沙坦酯/氢氯噻嗪复方片剂其降压作用和降压有效率明显优于奥美沙坦酯单药治疗, 且具有良好的安全性。替米沙坦联合苯磺酸氨氯地平与单用苯磺酸氨氯地平相比, 不仅能有效控制血压, 而且还能逆转高血压引起的左室肥厚^[11]。

除此之外, 高血压的时间治疗学已倍受国内外学者的重视, 它是根据血压昼夜形态采取合理的时间进行药物治疗^[6]。国内学者根据各种药物的特性, 针对不同类型的高血压, 采取不同时间给药, 均取CCB + ACEI (ARB) + 噻嗪类利尿剂组成的联合方案最为常用。本文选用了左氨氯地平、替米沙坦得了良好效果^[6,12,13]。

《指南》^[4]提出3药联合治疗方案, 即二氢吡啶类和氢氯噻嗪联合, 均为小剂量, 减少副作用, 增强疗效, 并采用不同时给药的方法, 从而避免3药血药浓度在同一时间段达到峰值。而不同时给药组,

表2 两组不同服药方法患者血压组内及组间比较
Table 2 Comparison of blood pressure between two groups

		(mmHg, $\bar{x} \pm s$)		
Group	Item	24h	Daytime	Nighttime
I	btSBP	141.16 $\pm$ 15.68	143.34 $\pm$ 15.62	137.82 $\pm$ 17.24
	atSBP	126.24 $\pm$ 12.74	129.44 $\pm$ 13.12	112.38 $\pm$ 13.26
	btDBP	92.64 $\pm$ 7.76	95.42 $\pm$ 7.52	90.94 $\pm$ 8.82
	atDBP	82.68 $\pm$ 7.82	84.82 $\pm$ 7.74	71.46 $\pm$ 8.52
II	btSBP	140.92 $\pm$ 15.88	143.68 $\pm$ 15.34	138.18 $\pm$ 16.86
	atSBP	140.92 $\pm$ 15.88	127.62 $\pm$ 12.84	120.50 $\pm$ 12.82**
	btDBP	92.42 $\pm$ 7.84	95.38 $\pm$ 14.96	91.20 $\pm$ 8.48
	atDBP	81.76 $\pm$ 8.26	83.68 $\pm$ 7.92	76.44 $\pm$ 8.68**

Group I: the drugs were given at different time; Group II: the drugs were given at the same time; btSBP: systolic blood pressure before treatment; atSBP: systolic blood pressure after treatment; btDBP: diastolic blood pressure before treatment; atDBP: diastolic blood pressure after treatment. Compared with Group I, ** $P < 0.01$.

表3 两组不同服药方法患者夜间血压下降程度的比较
Table 3 Comparison of decline degree of nighttime blood pressure between two groups

		SBP		DBP	
Group	Time point	Nighttime decline (mmHg)	Percentage of nighttime decline(%)	Nighttime decline (mmHg)	Percentage of nighttime decline(%)
I	Before treatment	15.52 $\pm$ 4.26	3.85 $\pm$ 3.32	4.48 $\pm$ 3.08	4.69 $\pm$ 3.16
	After treatment	17.06 $\pm$ 8.24**	13.18 $\pm$ 7.46**	13.36 $\pm$ 8.52**	15.75 $\pm$ 8.76**
II	Before treatment	5.50 $\pm$ 4.12	3.83 $\pm$ 3.20	4.18 $\pm$ 3.26	4.38 $\pm$ 3.18
	After treatment	7.12 $\pm$ 5.64	5.58 $\pm$ 4.32	7.24 $\pm$ 5.44*	8.65 $\pm$ 5.74*

Group I: the drugs were given at different time; Group II: the drugs were given at the same time; SBP: systolic blood pressure; DBP: diastolic blood pressure. Compared within the group, * $P < 0.05$; ** $P < 0.01$

晚服左氨氯地平使其夜间的血药浓度更高,其降压作用更强,有利于夜间血压的控制。从结果看,治疗后日间血压Ⅰ组略高于Ⅱ组(但无统计学意义),考虑与白天左氨氯地平浓度较低有关。替米沙坦和氢氯噻嗪晨服即能增效,又能减少电解质紊乱发生,还能避免晚服致夜尿增多,造成夜间血压波动上升。

研究表明,非杓型高血压患者晚服左氨氯地平不仅在纠正夜间血压高负荷方面有优势,且在全天血压及白天血压控制方面也具有较好的收益,同时能显著提高非杓型血压患者的夜间血压达标率^[10,14]。

通过本研究,我们认为该组方案既符合指南的最佳联合方案,又采用不同时服药的方式,更好地控制全天血压,并有效地逆转非杓型血压,对减少中老年高血压患者心脑血管病的发生将具有重要的临床意义。但是,其他组合方式、服药时间的安排、治疗病例数量、不同血压类型的选择以及随访时间还需要大家进一步探索,制定出适合不同人群的多种治疗方案,以更好提高高血压的控制率,降低致残率和致死率。

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