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螺内酯治疗老年高血压的临床疗效及对血清炎性因子水平的影响 *

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摘要 目的:探讨螺内酯治疗老年高血压的临床疗效及对血清炎性因子水平的影响。**方法:**选择2017年6月至2018年12月我院收治的144例老年高血压患者,根据治疗方法的不同将其分为观察组80例与对照组64例。对照组给予硝苯地平治疗,观察组给予螺内酯治疗,两组均治疗观察4周,对比两组治疗前后的血清内皮素(Endothelin,ET)-1和血栓素(Thromboxane,TX)-B2含量、白介素(Interleukin,IL)-6与可溶性细胞间粘附分子(Soluble intercellular adhesion molecule,sICAM-1)水平的变化及临床疗效。**结果:**所有患者完成治疗,无严重不良反应发生。治疗后,观察组的总有效率为98.8%,显著高于对照组(85.9%, $P<0.05$)。两组治疗后24h收缩压(Systolic blood pressure,SBP)和舒张压(Diastolic blood pressure,DBP)、血清ET-1、TX-B2、IL-6与sICAM-1水平均显著低于治疗前($P<0.05$),且观察组以上指标均明显低于对照组($P<0.05$)。**结论:**螺内酯治疗老年高血压的临床疗效明显优于硝苯地平治疗,可能与其明显抑制血清与ET-1、TX-B2、IL-6与sICAM-1水平有关。

关键词:螺内酯;老年高血压;内皮素;血栓素-B2;白介素-6;可溶性细胞间粘附分子

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Efficacy of Spironolactone in the Treatment of Elderly Patients with Hypertension and Its Effect on the Serum Levels of Inflammatory Factors*

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ABSTRACT Objective: To investigate the clinical efficacy of spironolactone in the treatment of elderly patients with hypertension and its effect on the levels of serum inflammatory factors. **Methods:** From June 2017 to December 2018, 144 cases of elderly patients with hypertension were selected and divided into the observation group (80 cases) and control group (64 cases) according to different treatment methods. The control group was treated with nifedipine, and the observation group was treated with spironolactone. Both groups were treated for 4 weeks, and the levels of serum endothelin (ET)-1 and thromboxane (TX)-B2 levels, interleukin (IL)-6 and Soluble Intercellular Adhesion Molecules (sICAM) before and after treatment and clinical efficacy were compared between two groups. **Results:** All patients completed treatment without serious adverse reactions. After treatment, the total effective rate of observation group after treatment were significantly higher than that of the control group (98.8% vs. 85.9%, $P<0.05$). The 24 h systolic blood pressure (SBP) or diastolic blood pressure (DBP), serum ET-1, TX-B2, IL-6 and sICAM-1 levels in the two groups were significantly lower than those before treatment ($P<0.05$), and the above indicators in the observation group were significantly lower than the control group ($P<0.05$). **Conclusion:** The clinical efficacy of spironolactone in the treatment of elderly hypertension is significantly better than that of nifedipine, which may be related to the significant inhibition of serum and ET-1, TX-B2, IL-6 and sICAM-1 levels.

Key words: Spironolactone; Elderly hypertension; Endothelin; Thromboxane-B2; Interleukin-6; Soluble intercellular adhesion molecule

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前言

高血压主要临床表现为体循环动脉压增高,会引起患者机体发生严重的心脑肾等器官损害^[1,2],常与脂肪、糖等代谢紊乱同时并存,多发老年人,给全球公共卫生问题带来极大挑战。高血压的具体发病机制尚不明确,有一定的遗传倾向,是由多种先天与后天因素对血压的调节失代偿所致^[3,4]。高血压患者无显著

的病理学改变,主要特征为心排量增加和全身小动脉压力的增加,随着病情的发展会引起小动脉玻璃样变,逐步累及中动脉和大动脉^[5]。高血压最终治疗目的是使血压降至正常范围,减少患者肾脏及心脑血管并发症,以降低患者的病残率及病死率^[6,7]。硝苯地平可用于治疗高血压,但临床实践显示长期应用时其治疗效果并不佳^[8]。螺内酯可改变患者的血管平滑肌张力,减弱血管对去甲肾上腺素发生加压反应等作用^[9,10],且该药可拮抗醛固

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酮的保钠作用,增加钠及水的排出,进而有利于降压^[11,12]。

研究表明高血压与机体的炎症反应密切相关,ET-1、TX-B2、IL-6 与 sICAM-1 都是炎症反应重要的介质。老年高血压患者出现血压升高,会造成患者血管内皮细胞损伤,使一氧化氮分泌出现异常,影响血管的 ET-1 水平^[13]。TX-B2 是调节血小板功能的重要因子,其水平的变化与血压的调节有关。IL-6 在原发性高血压的发生、发展中发挥重要的作用,高血压患者的 IL-6 水平明显高于正常人^[14]。sICAM-1 是反应血管损伤、内皮细胞炎症的重要因子,也参与高血压的发生发展^[15]。但是国内对这几种因子对老年高血压影响的研究机制较少,因此,本研究主要探讨了螺内酯治疗老年高血压的临床疗效、安全性对血清 ET-1、TX-B2、IL-6 与 sICAM-1 水平的影响,以明确螺内酯的作用效果与具体机制。现总结报告如下。

表 1 两组一般资料的对比

Table 1 Comparison of the general data between two groups

Groups	n	Disease course (yaer)	Heart rate (time/min)	SBP (mmHg)	DBP(mmHg)	Age (year)	Gender (Male/Femal)	BMI(kg/m ²)
Observation group	80	6.69± 1.99	67.42± 2.48	157.20± 12.58	98.20± 6.93	69.28± 5.55	42/38	22.29± 2.17
Control group	64	6.58± 2.04	67.10± 3.11	156.30± 14.29	99.19± 7.10	69.28± 4.58	34/30	22.19± 3.87

1.2 治疗方法

对照组患者给予硝苯地平控释片,购自拜耳医药保健有限公司,剂量为 30 mg,1 次/d,治疗观察 4 w。观察组患者给予螺内酯治疗,口服螺内酯片(上海华联制药有限公司,国药准字 H20932442)20 mg,1 次/d,治疗观察 4 w。

1.3 观察指标

(1)两组在治疗前后使用美国生产的型号为 TONOPORT V 的 24 h 自动监测血压仪,设定每 30 min 测定血压 1 次,记录 24 h 收缩压 (Systolic blood pressure,SBP) 或舒张压(Diastolic bloodpressure,DBP)均值。(2)疗效标准:显效:DBP 下降≥ 20 mmHg 或下降≥ 10 mmHg 降至正常;DBP 下降幅度低于 10 mmHg,但可达到至正常范围为有效;治疗后 DBP 较治疗前下降幅度为 10~20 mmHg,但未达到正常范围;患者的 DBP 或 SBP 未无达到上述标准,甚至发生恶化者为无效。(3)治疗前,空腹下抽取患者的肘静脉血,抗凝后离心分离上层血清,分为两

1 资料与方法

1.1 研究对象

选择我院 2017 年 6 月 -2018 年 12 月收治的 144 例老年高血压患者,纳入标准:符合原发性高血压诊断标准;临床资料完整;年龄 60~79 岁,性别不限;患者在自愿条件下签署了知情同意书;患者近两周未接受相关治疗;本院伦理委员会批准了此次研究。排除标准:继发性高血压者;临床资料缺项者;妊娠或哺乳期妇女;心、脑、肝、肾、造血系统等患者;入院前 6 个月内曾患急性心肌梗死、脑血管意外、严重创伤患者。根据治疗方法的不同,将所有患者分为观察组(80 例)与对照组(64 例),两组患者的一般资料对比差异无统计学意义($P>0.05$),具有可比性。见表 1。

管,其中一个用于测定 ET-1 和 TX-B2 含量,试剂盒购自北京福瑞生物科技公司,检测方法为放射免疫法。另外一管用于检测 IL-6 与 sICAM-1 等炎症因子含量,检测方法为酶联免疫法,试剂盒购自天津德普生物公司。

1.4 统计学分析

所有数据均采用 SPSS23.00 软件进行统计学分析,计量与计数数据分别采用 $\bar{x} \pm s$ 及百分比表示,数据符合正态性分布,计数资料对比分析用卡方检验,计量资料对比分析用 t 检验, $P<0.05$ 时为差异有统计学意义。

2 结果

2.1 两组疗效的对比

与对照组的总有效率(85.9%)相比,观察组的总有效率(98.8%)明显较高($P<0.05$),见表 2。

表 2 两组疗效的对比(例,%)

Table 2 Comparison of the efficacy between two groups(n,%)

Groups	n	Significant effect	Effect	Non-effect	Total effect
Observation group	80	75	4	1	79(98.8%)*
Control group	64	44	11	9	55(85.9%)

Note: Compared with the control group, * $P<0.05$.

2.2 两组治疗前后动态血压的对比

所有患者完成治疗,无严重不良反应发生。两组治疗后的 24 h SBP 与 24 h DBP 都低于治疗前($P<0.05$),且观察组以上指标均显著低于对照组($P<0.05$),见表 3。

2.3 两组治疗前后血清 ET-1 和 TXB2 含量的对比

治疗后,两组的血清 ET-1 和 TXB2 含量均显著低于治疗前,且观察组明显低于对照组($P<0.05$)。见表 4。

2.4 两组治疗前后血清血清 sICAM-1 和 IL-6 含量的对比

治疗后,两组的血清 sICAM-1 和 IL-6 含量均显著低于治疗前($P<0.05$),且观察组明显低于对照组($P<0.05$)。见表 5。

3 讨论

高血压是以动脉收缩压和(或)舒张压升高为主的临床综合征,是心血管病、脑血管病和肾脏病发生和死亡的最主要危险

因素^[16]。目前,我国人口老龄化逐渐加剧,人民的生活节奏不断加快,高血压发病率逐年升高^[17]。螺内酯作为最早应用的醛固酮受体拮抗剂,在靶器官保护治疗中发挥重要作用。螺内酯阻断醛固酮与其受体结合,减少水 Na⁺ 潴留,改善机体的血管内

皮功能紊乱,从而发挥较好的降压效果^[18,19]。本研究显示两组治疗后的 24 h SBP 与 24 h DBP 都低于治疗前,观察组低于对照组,表明螺内酯能够更加的发挥降压作用,且其降压过程是一个缓慢、持久而有效的过程^[20]。

表 3 两组治疗前后动态血压的对比(mmHg, 均数± 标准差)

Table 3 Comparison of the dynamic blood pressure before and after treatment between the two groups(mmHg, $\bar{x} \pm s$)

Groups	n	24 h SBP		24 h DBP	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	80	157.20± 12.58	111.99± 14.39 ^{#*}	98.20± 6.93	72.49± 8.28 ^{#*}
Control group	64	156.30± 14.29	130.20± 17.49 [#]	99.19± 7.10	84.20± 8.11 [#]

Note: Compared with the same group before treatment, [#]*P*<0.05, compared with the control group after treatment, ^{*}*P*<0.05.

表 4 两组治疗前后血清 ET-1 和 TXB2 含量的对比(pg/mL, 均数± 标准差)

Table 4 Comparison of the serum ET-1 and TXB2 content between two groups before and after treatment (pg/mL, $\bar{x} \pm s$)

Groups	n	ET-1		TXB2	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	80	69.78± 8.22	56.30± 4.59 ^{#*}	95.78± 8.11	81.40± 8.57 ^{#*}
Control group	64	69.20± 7.28	62.48± 8.11 [#]	96.20± 7.87	89.28± 7.77 [#]

Note: Compared with the same group before treatment, [#]*P*<0.05, compared with the control group after treatment, ^{*}*P*<0.05.

表 5 两组治疗前后血清 sICAM-1 和 IL-6 含量的对比(μg/L, 均数± 标准差)

Table 5 Comparison of the sICAM-1 and IL-6 content between two groups before and after treatment(μg/L, $\bar{x} \pm s$)

Groups	n	ET-1		TXB2	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	80	648.95± 45.96	266.39± 67.10 ^{#*}	50.63± 12.85	17.66± 4.69 ^{#*}
Control group	64	650.29± 56.11	367.98± 78.11 [#]	51.00± 10.52	22.17± 4.00 [#]

Note: Compared with the same group before treatment, [#]*P*<0.05, compared with the control group after treatment, ^{*}*P*<0.05.

ET-1 是血管内皮细胞合成的体内最强的缩血管活性肽,高血压会导致患者体内的 ET-1 大量合成,并释放入血液中,其又会发挥收缩血管作用,升高血压,从而形成恶性循环^[21]。TXB2 在血压调节中发挥重要作用,高血压会减少 TXB2,导致外周血管阻力增加,升高血压^[22]。本研究表明螺内酯的应用能促进抑制 ET-1 和 TXB2 的释放。当前也有研究显示螺内酯则可以使高血压患者血清 NO 物质明显升高,抑制醛固酮在血管系统的致纤维化作用,改善患者的血管内皮功能与血管顺应性,从而改善患者脉压^[23-25]。

高血压后多数机体组织可发生炎症反应,产生炎症因子,炎症因子可影响高血压患者的预后^[26]。同时,醛固酮可诱导心肌发生炎症反应,而给予螺内酯后可使其下降,并且心肌胶原含量也相应下降^[27,28]。sICAM-1 会结合多种细胞表面成分^[29,30],IL-6 多由内皮细胞、单核细胞及成纤维细胞产生,会对炎症反应及胚胎基因进行激活,导致心肌细胞肥大^[31-33]。本研究结果显示螺内酯可显著抑制机体内的炎症因子释放。由于时间、经费等限制,本研究没有进行长时间的随访分析,研究结果可能存在偏倚,将在下一步进行深入分析。

综上所述,螺内酯治疗老年高血压的临床疗效明显优于硝苯地平治疗,可能与其明显抑制血清与 ET-1、TX-B2、IL-6 与

sICAM-1 水平有关。

参考文献(References)

- [1] Acelajado MC, Hughes ZH, Oparil S, et al. Treatment of Resistant and Refractory Hypertension[J]. Circ Res, 2019, 124(7): 1061-1070
- [2] Velasco A, Siddiqui M, Kreps E, et al. Refractory hypertension is not attributable to intravascular fluid retention as determined by intracardiac volumes[J]. Hypertension, 2018, 72(2): 343-349
- [3] Wing LMH, Gabb GM. Treatment of hypertension in older people[J]. J Pharm Pract, 2018, 48(1): 92-101
- [4] Agarwal R, Rossignol P, Garza D, et al. Patiromer to Enable Spironolactone Use in the Treatment of Patients with Resistant Hypertension and Chronic Kidney Disease: Rationale and Design of the AMBER Study[J]. Am J Nephrol, 2018, 48(3): 172-180
- [5] Ahmad KA, Banales J, Henderson CL, et al. Intravenous epoprostenol improves oxygenation index in patients with persistent pulmonary hypertension of the newborn refractory to nitric oxide [J]. J Perinato, 2018, 38(9): 1212-1219
- [6] Spence JD. Controlling resistant hypertension [J]. Stroke Vasc Neurol, 2018, 3(2): 69-75
- [7] Min JC. Increased arterial stiffness causing resistant hypertension in an adolescent with Neurofibromatosis type 1 [J]. Kosin Med J, 2018, 33(1): 105-108

- [8] Butts B, Calhoun DA, Denney TS Jr, et al. Plasma xanthine oxidase activity is related to increased sodium and left ventricular hypertrophy in resistant hypertension[J]. *Free Radic Biol Med*, 2019, 134: 343-349
- [9] Sun X, Shuai Y, Fang W, et al. Spironolactone versus observation in the treatment of acute central serous chorioretinopathy [J]. *Br J Ophthalmol*, 2018, 102(8): 1060-1065
- [10] Kong EL, Zhang JM, An N, et al. Spironolactone rescues renal dysfunction in obstructive jaundice rats by upregulating ACE2 expression[J]. *J Cell Commun Signal*, 2019, 13(1): 17-26
- [11] Attar A, Sadeghi A, Amirmoezi F, et al. Low dose spironolactone monotherapy in the management of stage I essential hypertension: a pilot randomized, double-blind, placebo-controlled trial[J]. *Acta Cardiol Sin*, 2018, 34(1): 59-65
- [12] Mortensen LA, Thiesson HC, Tougaard B, et al. The effect of spironolactone on calcineurin inhibitor induced nephrotoxicity: a multicenter randomized, double-blind, clinical trial (the SPIREN trial) [J]. *Bmc Nephrology*, 2018, 19(1): 105-114
- [13] Xu M, Lu YP, Hasan AA, et al. Plasma ET-1 Concentrations are Elevated in Patients with Hypertension - Meta-Analysis of Clinical Studies[J]. *Kidney Blood Press Res*, 2017, 42(2): 304-313
- [14] Mao SQ, Sun JH, Gu TL, et al. Hypomethylation of interleukin-6 (IL-6) gene increases the risk of essential hypertension: a matched case-control study[J]. *J Hum Hypertens*, 2017, 31(8): 530-536
- [15] Yue W, Zhou Z F. Correlation analysis of carotid intima media thickness and function in patients with H-type hypertension and acute cerebral infarction[J]. *J Hainan Med University*, 2017, 23(17): 126-129
- [16] Faconti L, Cruickshank JK, Webb AJ. Reply to comment on cardiac effects of 6 months dietary nitrate and spironolactone in patients with hypertension and with/at risk of type 2 diabetes, in the factorial design, double-blind, randomised controlled VaSera trial by faconti et al [J]. *Br J Clin Pharmacol*, 2019, 85(5): 1037-1038
- [17] Clemmer JS, Faulkner JL, Mullen AJ, et al. Sex-specific responses to mineralocorticoid receptor antagonism in hypertensive African American males and females[J]. *Biol Sex Differ*, 2019, 10(1): 24-33
- [18] Faconti L, Mills CE, Govoni V, et al. Cardiac effects of 6 months' dietary nitrate and spironolactone in patients with hypertension and with/at risk of type 2 diabetes, in the factorial design, double-blind, randomized controlled VaSera trial[J]. *Br J Clin Pharmacol*, 2019, 85(1): 169-180
- [19] Desai AS, Liu J, Pfeiffer MA, et al. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOP-CAT trial[J]. *Journal of Cardiac Failure*, 2018, 24(5): 313-320
- [20] Williams B, Macdonald TM, Morant SV, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies[J]. *Lancet Diabetes Endocrinol*, 2018, 6(6): 464-475
- [21] Hammer F, Malzahn U, Donhauser J, et al. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients[J]. *Kidney Int*, 2019, 95(4): 983-991
- [22] Imprialos KP, Bouloukou S, Kerpiniotis G, et al. Mineralocorticoid Receptor Antagonists in Essential and Resistant Hypertension[J]. *Curr Pharm Des*, 2018, 24(46): 5500-5507
- [23] Li S, Zhang X, Dong M, et al. Effects of spironolactone in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials[J]. *Medicine*, 2018, 97(35): e11942
- [24] Lu M, Wang P, Zhou S, et al. Ecdysone elicits chronic renal impairment via mineralocorticoid-like pathogenic activities[J]. *Cell Physiol Biochem*, 2018, 49(4): 1633-1645
- [25] Manolis AA, Manolis TA, Melita H, et al. Eplerenone versus spironolactone in resistant hypertension: an efficacy and/or cost or just a men's issue?[J]. *Curr Hypertens Rep*, 2019, 21(3): e22
- [26] Martin-Lorenzo M, Martinez PJ, Baldan-Martin M, et al. Urine haptoglobin and haptoglobin-related protein predict response to spironolactone in patients with resistant hypertension[J]. *Hypertension*, 2019, 73(4): 794-802
- [27] Jiang YR. Efficacy and safety of spironolactone in mono-therapy versus low doses spironolactone in combined-therapy for the treatment of idiopathic hyperaldosteronism [J]. *China Medical Abstracts (Internal Medicine)*, 2018, 35(3): 22-24
- [28] Jia L, Yin Q, Zhou L, et al. Insights into the mechanism of concomitant nucleation of form II and ethanol solvate of spironolactone in cooling crystallization[J]. *Rsc Advances*, 2018, 8(18): 9697-9706
- [29] Stavropoulos K, Papadopoulos C, Koutsampasopoulos K, et al. Mineralocorticoid receptor antagonists in primary aldosteronism [J]. *Curr Pharm Des*, 2018, 24(46): 5508-5516
- [30] Thuzar M, Law W P, Dimeski G, et al. Mineralocorticoid antagonism enhances brown adipose tissue function in humans: A randomized placebo-controlled cross-over study [J]. *Diabetes Obes Metab*, 2019, 21(3): 509-516
- [31] Trens F, Bortolamiol C, Kramberg M, et al. Pharmacological characterization of aprocitentan, a dual endothelin receptor antagonist, alone and in combination with blockers of the renin angiotensin system, in two models of experimental hypertension [J]. *J Pharmacol Exp Ther*, 2019, 368(3): 462-473
- [32] Vesely J. Spironolactone in the treatment of hypertension: a neglected molecule[J]. *Vnitr Lek*, 2018, 64(7-8): 815-820
- [33] Wang D, Wang J, Tong T, et al. Non-classical 11beta-hydroxylase deficiency caused by compound heterozygous mutations: a case study and literature review[J]. *J Ovarian Res*, 2018, 11(1): 82-90