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波立维联合 ARB 治疗糖尿病肾病的临床疗效及对患者尿蛋白影响*

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摘要 目的:探讨波立维联合及血管紧张素 II 受体拮抗剂(Angiotensin II receptor blockers, ARB)治疗糖尿病肾病的临床疗效及对患者尿蛋白水平的影响。**方法:**选取我院近 3 年收治的 116 例糖尿病肾病患者,按照数字随机表法将其分为研究组和对照组,每组各 58 例。对照组在常规治疗基础上给予 ARB 治疗,研究组在对照组的基础上给予波立维联合 ARB 治疗,两组患者均连续治疗 4 周,检测和比较两组治疗前后血清肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、白细胞介素-6(Interleukine, IL-6)和转化生长因子- β 1 (Transforming growth factor-beta1, TGF- β 1)、肌酐(Serum creatinine, SCr)、尿微量蛋白(Urinary microalbumin, U-malb)、24 h 尿蛋白定量(Albumin, Alb)、24 h 尿蛋白排泄率(Urinary albumin excretion rate, UAER)、血液流变学指标红细胞刚性指标(Erythrocyte deformation index, TK)、纤维蛋白原(Plasma viscosity, PF)、血浆黏度(Plasma viscosity, PV)的变化情况及治疗期间不良反应的发生情况。**结果:**治疗后,研究组血清 TNF- α 、IL-6、TGF- β 1、U-malb、Alb、UAER、TK、PF 和 PV 水平均明显低于对照组($P<0.05$);两组不良反应发生率对比无统计学差异($P>0.05$)。**结论:**波立维联合 ARB 治疗糖尿病肾病有利于减轻炎症反应,改善患者肾脏血流动力学和肾功能,且安全性高。

关键词:波立维;血管紧张素 II 受体拮抗剂;糖尿病肾病;尿蛋白

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Clinical Efficacy of Plavix and ARB in the treatment of Diabetic Nephropathy and Its Effect on the Urine Protein*

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ABSTRACT Objective: To investigate the clinical efficacy of Plavix and ARB (angiotensin II receptor antagonist) in the treatment of diabetic nephropathy and its effect on urine protein levels in patients. **Methods:** 116 patients with diabetic nephropathy admitted to our hospital in the past 3 years were divided into study group and control group according to the numerical random table method, 58 cases in each group. The control group was treated with ARB on the basis of conventional treatment, and the study group was given Plavix and ARB. The two groups were treated continuously for 4 weeks. The serum TNF- α (Tumor necrosis factor- α), interleukin-6(IL-6) and transforming growth factor-beta1 (TGF- β 1), creatinine (SCr), urinary micro Protein (Urinary microalbumin, U-malb), 24h urinary albumin quantitation (Albumin, Alb), 24 h urine protein excretion rate (UAER), blood rheology index Erythrocyte deformation index(TK), changes in fibrinogen (PF), plasma viscosity (PV) and the occurrence of adverse reactions during treatment. **Results:** After treatment, the levels of serum TNF- α , IL-6, TGF- β 1, U-malb, Alb, UAER, TK, PF and PV in the study group were significantly lower than those in the control group($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Plavix combined with ARB in the treatment of diabetic nephropathy is beneficial to reduce inflammatory reactions, improve renal hemodynamics and renal function, and is safe.

Key words: Plavix; Angiotensin II receptor blockers(ARB); Diabetic nephropathy; Urine protein

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前言

糖尿病肾病是由糖尿病导致的慢性肾脏疾病,主要临床表

现为蛋白尿,肾功能进行性受损,病程迁延难治,久治不愈,通常进展呈终末期肾病,给患者家庭及社会带来沉重负担^[1,2]。目前,糖尿病肾病尚无彻底治愈的治疗方案^[3],西医治疗以控制血

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压、血糖为主,通常首选 ARB(血管紧张素受体拮抗剂)控制血压^[4]。ARB 可阻滞 RAAS(阻滞肾素 - 血管紧张素 - 醛固酮系统),但单独应用 ARB 无法完全阻滞 RAAS,降低尿蛋白水平效果有限,并且容易产生副作用^[56]。

波立维(氯吡格雷)是一种新的抗血小板聚集药,为非竞争性二磷酸腺苷(Adenosine Diphosphate,ADP)受体拮抗剂,可选择性的抑制 ADP 与血小板表面上 ADP 的受体结合,从而抑制血小板聚集,从而起到抗凝、预防血栓等作用,可改善糖尿病肾病患者血流情况,近年来,关于波立维联合 ARB 治疗糖尿病肾病的研究越来越多^[78]。本研究系统评价了波立维联合及 ARB 治疗糖尿病肾病的效果及对患者尿蛋白水平的影响,以期为其临床应用提供一定的参考依据。

表 1 两组患者一般资料的对比

Table 1 Comparison of the general data between the two groups of patients

Groups	Cases	Sex(Male/Female)	Average age (years)	Average disease duration (years)
Research group	58	35/23	31.62± 4.13	7.64± 3.13
Control group	58	34/24	31.81± 4.21	7.81± 3.20

1.2 治疗方法

两组患者给予常规治疗,包括降压、降糖、降脂等,对照组患者在常规治疗基础上给予 ARB 治疗,替米沙坦片,生产企业:北京巨能制药有限责任公司,批准文号:国药准字 H20060285,产品规格:40 mg/s,用法用量:每次一片(40 mg),每日一次。研究组在对照组治疗基础上联合波立维治疗,生产企业:赛诺菲(杭州)制药有限公司,批准文号:国药准字 J20180029,规格:75 mg/s(波立维),用法用量:1 日 1 次,1 次 75 mg,口服给药。两组患者连续治疗 4 周,在治疗期间,均接受常规护理指导,包括饮食控制、运动锻炼、健康知识宣教等。

1.3 评价标准

观察两组患者治疗前后的炎症因子指标、肾功能指标、血液流变学指标。① 炎症因子指标。于患者治疗前及治疗 4 周后,取 5 mL 空腹静脉血,进行离心处理,取上清液,采取酶联免疫吸附法检测两组患者的炎症因子指标,包括 TNF-α(肿瘤坏死因子 α)、IL-6(白细胞介素 -6)、TGF-β1(转化生长因子 -β1)。② 肾功能指标:测定两组患者治疗前后 SCr(肌酐)、U-malb(尿微量蛋白)、Alb(24h 尿白蛋白定量)、UAER(24 h 尿蛋白排泄率),

1 资料与方法

1.1 一般资料

选取我院近 3 年收治的 116 例糖尿病肾病患者,按照数字随机表法将其分为研究组和对照组,每组患者各 58 例。纳入标准:经联合检查确诊为糖尿病肾病;对本研究药物均耐受;未伴随因感染、高血压等因素导致的蛋白尿;入选前 3 个月未使用过本研究药物;自愿参与并知晓本研究内容,签署知情同意书。排除标准:合并脏腑、系统功能障碍患者;对本研究药物不耐受;哺乳期、妊娠期妇女;合并出血倾向、泌尿系统感染患者。两组患者的性别、年龄、病程等一般资料如表 1 所示,组间对比数据无统计学差异($P>0.05$),可对比。

其中 U-malb、Alb 采取蛋白分析检测仪测定,UAER 采取放射免疫法测定。③ 血液流变学:采取血液流变仪检测两组患者治疗前及治疗 4 周后血液流变学指标,包括 TK(红细胞刚性指标)、PF(纤维蛋白原)、PV(血浆黏度)。④ 观察两组患者在治疗过程中所出现的不良反应。

1.4 统计学方法

通过 Excel 建立数据库,采取统计学软件 SPSS21.0 对全组数据进行统计学分析,炎症因子水平、肾功能指标、血液流变学指标等计量资料采取平均数±标准差($\bar{x} \pm s$)描述,组间对比数据行 t 检验;不良反应等计数资料采取百分数描述,组间对比数据行卡方检验。以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后血清炎症因子水平的对比

两组治疗前血清 TNF-α、IL-6、TGF-β1 水平对比无统计学差异($P>0.05$);治疗后,研究组血清 TNF-α、IL-6、TGF-β1 水平均明显低于对照组($P<0.05$),如表 2 所示。

表 2 两组治疗前后 TNF-α、IL-6、TGF-β1 水平的对比

Table 2 Comparison of the TNF-α, IL-6 and TGF-β1 levels before and after treatment between two groups

Groups	Cases	TNF-α(ng/L)		IL-6(ng/L)		TGF-β1(ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	58	78.19± 19.27	33.80± 10.47**	30.17± 6.01	13.49± 3.85**	78.23± 19.40	33.85± 10.46**
Control group	58	78.15± 19.30	45.79± 14.58 [#]	30.20± 6.13	19.37± 4.72 [#]	78.17± 19.38	44.96± 15.53 [#]

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

2.2 两组治疗前后 SCr、U-malb、Alb、UAER 水平的对比

两组治疗前 SCr、U-malb、Alb、UAER 对比无统计学差异($P>0.05$);治疗后,研究组 U-malb、Alb、UAER 明显低于对照组($P<0.05$),如表 3 所示。

2.3 两组治疗前后血液流变学指标对比

两组治疗前血液流变学指标(TK、PF、PV)对比无统计学差异($P>0.05$)。治疗后,研究组 TK、PF、PV 均明显低于对照组($P<0.05$),如表 4 所示。

表 3 两组治疗前后 U-malb、Alb、UAER 水平的对比

Table 3 Comparison of the U-malb, Alb, UAER levels before and after treatment between two groups

Groups	Cases	SCr(μ mol/L)		U-malb(mg/L)		Alb(mg/24 h)		UAER(g/24h)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	58	95.31 $\pm$ 15.13	56.73 $\pm$ 8.83*	224.49 $\pm$ 30.38	100.12 $\pm$ 22.83*	392.75 $\pm$ 45.21	203.21 $\pm$ 25.53*	1.53 $\pm$ 0.59	1.03 $\pm$ 0.53**
		95.32 $\pm$ 15.21	72.31 $\pm$ 9.23#	228.37 $\pm$ 30.29	132.97 $\pm$ 25.17#	392.32 $\pm$ 44.63	297.81 $\pm$ 22.75#	1.53 $\pm$ 0.60	1.39 $\pm$ 0.59#

表 4 两组治疗前后血液流变学指标的对比

Table 4 Comparison of the blood rheology indexes before and after treatment between two groups

Groups	Cases	TK((mpa/s)		PF(g/L)		PV(mpa/s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	58	5.03 $\pm$ 0.72	3.39 $\pm$ 0.47*	4.62 $\pm$ 0.72	3.12 $\pm$ 0.30*	1.98 $\pm$ 0.42	1.30 $\pm$ 0.25
Control group	58	5.01 $\pm$ 0.69	4.04 $\pm$ 0.59	4.58 $\pm$ 0.75	3.75 $\pm$ 0.43	1.97 $\pm$ 0.43	1.58 $\pm$ 0.45

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

2.4 两组不良反应发生情况的对比

所示。

两组不良反应发生率对比无统计学差异($P > 0.05$),如表 5

表 5 两组不良反应对比

Table 5 Comparison of adverse reactions between the two groups

Groups	Cases	Cough	Dizziness	Lower limb pain	Incidence rate
Research group	58	0	2	1	3(5.2)
Control group	58	1	1	0	2(3.4)

3 讨论

糖尿病肾病是一种常见的糖尿病微血管并发症,多数糖尿病肾病是 2 型糖尿病引发的^[9],相关研究表明糖尿病病程超过 10 年的糖尿病患者发生糖尿病肾病的几率较高,严重威胁患者的生命健康^[10,11]。糖尿病肾病影响进展因素有多种,包括机体血流动力学改变、高血压、遗传、血糖代谢异常、血脂等,治疗复杂,且存在一定争议^[12-14]。临床上,需尽早准确诊断患者病情,在优化血糖管理、改善生活方式等外,控制好血压、血糖是延缓糖尿病肾病进展的重要因素,减少尿蛋白可有效延缓糖尿病肾病进展^[15,16]。大量临床试验显示^[17,18]应用 ARB 能够及时控制糖尿病患者的尿蛋白量,保护患者的肾脏功能,降血压,可延缓糖尿病肾病的发生及发展。

替米沙坦片是一种血管紧张素受体阻滞剂,通过口服,可迅速被吸收,直接作用在血管紧张素 II 受体,扩张外周血管,保护肾脏,提高患者机体对胰岛素敏感性^[19,20]。波立维是一种血小板聚集抑制剂,阻断血小板活化扩增,口服波立维后,通过肝脏作用,可将其转化成活性代谢产物,控制血小板聚集^[21,22]。相关研究显示如果患者每天服用 75 mg,可抑制腺苷二磷酸诱导的血小板聚集,持续一周后,抑制作用达到稳态^[23,24]。另外,还有研究指出^[25]波立维通过抗血小板工鞣呢,降低血液粘稠度,改善患者肾脏局部血液循环,降低患者肾小球蛋白滤过,进而控制尿蛋白排泄,进而更好保护肾脏功能。

糖尿病肾病发病机制复杂,尿蛋白诱发因素多考虑和肾小球血流动力学改变,肾小球高灌注、高内压、高滤过等状态,增加蛋白毛细血管壁滤过,导致蛋白尿^[26,27]。另外,加强肾小球毛细血管机械牵张力,增加血管活性因子分泌量,增加血管通透性,加重蛋白尿^[28,29]。对此,临床治疗主要目的是改善肾小球血流动力学,改善血管通透性,改善肾功能,减轻蛋白尿^[30]。通过本次研究结果显示,两组患者治疗前炎症因子水平、肾功能指标、血流动力学指标对比无统计学差异,治疗后,研究组患者的各项指标改善程度明显优于对照组。由此说明,波立维联合 ARB 治疗可有效发挥药物优势互补的作用,具有明显降压、减少蛋白尿作用,可明显提高患者机体对胰岛素的敏感性,改善患者各项肾脏血流动力学指标,进而更好的保护肾脏,且二者联合应用并没有明显增加副作用,耐受性较好。

总而言之,波立维联合 ARB 治疗糖尿病肾病可增强临床治疗效果,有利于减轻炎症反应,改善患者肾脏血流动力学及肾功能,安全性高,值得临床推广应用。

参考文献(References)

- [1] Krairitichai U, Sarinnapakorn V, Mahannopkul R, et al. Renal Protective Effects of Combination of Diltiazem and ACEI/ARB on the Progression of Diabetic Nephropathy: Randomized Controlled Trial[J]. J Med Assoc Thai, 2017, 100(1): S40-S47
- [2] Papadopoulou-Marketou N, Kanaka-Gantenbein C, Marketos N, et al. Biomarkers of diabetic nephropathy: A 2017 update[J]. Crit Rev Clin

- Lab Sci, 2017, 54(5): 326-342
- [3] Wang XX, Levi J, Luo Y, et al. SGLT2 Protein Expression Is Increased in Human Diabetic Nephropathy [J]. J Biol Chem, 2017, 292 (13): 5335-5348
- [4] Hu ZB, Ma KL, Zhang Y, et al. Inflammation activates the CXCL16 pathway to contribute to tubulointerstitial injury in diabetic nephropathy[J]. Acta Pharmacol Sin, 2018, 39(6): 1022-1033
- [5] Zanchi C, Macconi D, Trionfini P, et al. MicroRNA-184 is a downstream effector of albuminuria driving renal fibrosis in rats with diabetic nephropathy[J]. Diabetologia, 2017, 60(6): 1114-1125
- [6] Fu Y, Wang C, Zhang D, et al. Increased TRPC6 expression is associated with tubular epithelial cell proliferation and inflammation in diabetic nephropathy[J]. Mol Immunol, 2018, 94(21): 75-81
- [7] Cardenas-Gonzalez M, Srivastava A, Pavkovic M, et al. Identification, Confirmation, and Replication of Novel Urinary MicroRNA Biomarkers in Lupus Nephritis and Diabetic Nephropathy [J]. Clin Chem, 2017, 63(9): 1515-1526
- [8] Elhorany HE, Abdellatif RN, Watany M, et al. NLRP3 expression and urinary HSP72 in relation to biomarkers of inflammation and oxidative stress in diabetic nephropathy patients [J]. Iubmb Life, 2017, 69 (8): 623-630
- [9] Hamzawy M, Saa G, Rashid L, et al. The cellular selection between apoptosis and autophagy: roles of vitamin D, glucose and immune response in diabetic nephropathy[J]. Endocrine, 2017, 58(1): 66-80
- [10] Wang ZB, Zhang S, Li Y, et al. LY333531, a PKC β inhibitor, attenuates glomerular endothelial cell apoptosis in the early stage of mouse diabetic nephropathy via down-regulating swiprosin-1 [J]. Acta Pharmacol Sin, 2017, 38(7): 1009-1023
- [11] Van Krieken R, Mehta N, Wang T, et al. Cell surface expression of 78 kDa glucose regulated protein (GRP78) mediates diabetic nephropathy [J]. Journal of Biological Chemistry, 2019, 294(19): 7755-7768
- [12] Wei W, Tu M, Huang R, et al. Serum osteoinductive factor is associated with microalbuminuria and diabetic nephropathy in type 2 diabetes[J]. Medicine, 2018, 97(31): e11759
- [13] Li XB, Li ZZ, Zhang LY, et al. 24 Danggui shaoyao powder improves diabetic nephropathy without altering blood glucose in streptozotocin-induced diabetic rats [J]. J Investig Med, 2017, 65 (7): A8. 2-A8
- [14] Cheung CY, Ma M KM, Chak WL, et al. Cancer risk in patients with diabetic nephropathy[J]. Medicine, 2017, 96(38): e8077
- [15] Ina K, Kitamura H, Nagai K, et al. Basic and clinical science posters: clinical science of nephropathy, neuropathy and retinopathy [J]. Diabetes Care, 2017, 34(S1): 54-54
- [16] Jardine M, Mahaffey K, Neal B, et al. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics[J]. Am J Nephrol, 2017, 46(6): 462-472
- [17] Tesch, Greg H. Diabetic nephropathy - is this an immune disorder? [J]. Clin Sci, 2017, 131(16): 2183-2199
- [18] Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018[J]. Am J Kidney Dis, 2018, 71(6): 884-895
- [19] Flyvbjerg, Allan. The role of the complement system in diabetic nephropathy[J]. Nat Rev Nephrol, 2017, 13(5): 311-318
- [20] Wang L, Tao T, Su W, et al. A disease model of diabetic nephropathy in a glomerulus-on-a-chip microdevice [J]. Lab Chip, 2017, 17(10): 1749-1760
- [21] Jha JC, Banal C, Okabe J, et al. NADPH Oxidase-Nox5 Accelerates Renal Injury in Diabetic Nephropathy [J]. Diabetes, 2017, 66 (10): 2691-2703
- [22] Hasan AA, Hoher B. Role of soluble and membrane-bound dipeptidylpeptidase-4 in diabetic nephropathy [J]. J Mol Endocrinol, 2017, 59(1): R1-R10
- [23] Mori KP, Yokoi H, Kasahara M, et al. Increase of Total Nephron Albumin Filtration and Reabsorption in Diabetic Nephropathy [J]. J Am Soc Nephrol, 2016, 28(1): 278-289
- [24] Imasawa T, Obre E, Nadège Bellance, et al. High glucose repatterns human podocyte energy metabolism during differentiation and diabetic nephropathy[J]. FASEB J, 2017, 31(1): 294-307
- [25] Abou-Hany HO, Atef H, Said E, et al. Crocin mediated amelioration of oxidative burden and inflammatory cascade suppresses diabetic nephropathy progression in diabetic rats[J]. Chem Biol Interact, 2018, 25(284): 90-100
- [26] Wang X, Gao L, Lin H. Mangiferin prevents diabetic nephropathy progression and protects podocyte function via autophagy in diabetic rat glomeruli[J]. Eur J Pharmacol, 2018, 824(12): 170-178
- [27] Li HY, Oh YS, Choi JW, et al. Blocking lysophosphatidic acid receptor 1 signaling inhibits diabetic nephropathy in db/db mice[J]. Kidney Int, 2017, 91(6): 1362-1373
- [28] Tao SB, Li LZ, Li L, et al. Understanding the gut-kidney axis among biopsy-proven diabetic nephropathy, type 2 diabetes mellitus and healthy controls: an analysis of the gut microbiota composition [J]. Acta Diabetol, 2019, 56(5): 581-592
- [29] Mou ZX, Feng ZG, Xu Z, et al. Schisandrin B alleviates diabetic nephropathy through suppressing excessive inflammation and oxidative stress[J]. Biochem Biophys Res Commun, 2019, 508(1): 243-249
- [30] Wang JP, Hu L, Chen Y, et al. Sitagliptin improves renal function in diabetic nephropathy in male Sprague Dawley rats through upregulating heme oxygenase-1 expression[J]. Endocrine, 2019, 63(1): 1-9