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阿魏酸钠联合缬沙坦对糖尿病肾病患者的疗效及对肾脏纤维化的影响*

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摘要 目的:研究阿魏酸钠联合缬沙坦对糖尿病肾病(diabetic kidney disease, DKD)患者的治疗效果及对肾脏纤维化的影响。**方法:**选择 2017 年 1 月~2018 年 12 月山西医科大学附属晋中医院收治的 101 例糖尿病肾病患者,随机分为两组。两组均低蛋白饮食,口服他汀类药物调脂,口服降糖药和(或)胰岛素控制血糖。对照组加服缬沙坦 80 mg/d 治疗,观察组服缬沙坦联合静脉滴注 0.3 g 的阿魏酸钠,每天 1 次。两组均连续治疗 1 个月。观察两组肾功能指标、血糖指标以及肾脏纤维化指标的变化。**结果:**治疗后,观察组的治疗总有效率 92.00%(46/50),显著高于对照组[68.63%(35/51)]($P<0.05$)。治疗后,两组患者血清的纤维化相关指标 III 型前胶原(procollagen type III, PC III)和 IV 型胶原(type IV Collagen, C IV)均明显降低($P<0.05$),且观察组的明显低于对照组($P<0.05$);治疗后,两组的空腹血糖(fasting plasma glucose, FPG)、餐后 2 h 血糖(2 h plasma glucose, 2 h PG)、血尿素氮(blood urea nitrogen, BUN)、血肌酐(serum creatinine, SCr)、 β_2 -微球蛋白(β_2 -Microglobulin, β_2 -MG)、24 h 尿白蛋白排泄率(24 h urine microalbumin excretion, 24 h UAER)均明显降低($P<0.05$),且观察组的指标均显著低于对照组($P<0.05$),两组肾小球滤过率(GFR)增高($P<0.05$),且观察组指标明显高于对照组($P<0.05$)。**结论:**阿魏酸钠联合缬沙坦对 DKD 患者有较好的疗效,能明显延缓机体肾脏纤维化的进展速度,进而有效改善肾功能。

关键词:阿魏酸钠;缬沙坦;糖尿病肾病;肾功能;血糖;肾脏纤维化

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Effect of Sodium and Valsartan Coadministration on Diabetic Kidney Disease and Renal Fibrosis*

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ABSTRACT Objective: To investigate the effect of sodium ferulate and valsartan combined therapy on diabetic kidney disease (DKD) and renal fibrosis. **Methods:** One hundred and one cases of patients with DKD who were treated in Jinzhong Hospital affiliated to Shanxi Medical University from January 2017 to December 2018 were studied. They were divided into two groups randomly. Both groups were treated with low protein diet, statins, oral hypoglycemic drugs and/or insulin to control blood glucose. The control group was also treated with valsartan 80 mg/d. The observation group was given 0.3 g sodium ferulate intravenously once a day in addition to valsartan. Both groups were treated continuously for 1 month. Renal function, blood glucose and index of renal fibrosis were detected. **Results:** After treatment, the total effective rate in the observation group was 92.00%(46/50), which was significantly higher than that of the control group[68.63%(35/51)]($P<0.05$). After treatment, serum fibrosis related indicators PCIII and C IV levels in both groups were significantly reduced ($P<0.05$), and those in the observation group were significantly lower than that of the control group ($P<0.05$). After treatment, the fasting plasma glucose, 2 h plasma glucose, blood urea nitrogen, serum creatinine, β_2 -microglobulin and 24 h urine microalbumin excretion of the two groups were significantly reduced ($P<0.05$), and the changes of the above index in the observation group were more obviously than that of the control group ($P<0.05$). The GFR level of the two groups were increased ($P<0.05$), and the changes of the above index in the observation group were more obviously than that of the control group ($P<0.05$). **Conclusion:** Sodium ferulate and valsartan combined therapy was effective for the treatment of DKD, and could significantly delay renal fibrosis, and thus protect renal function.

Key words: Sodium Ferulate; Valsartan; Diabetic Nephropathy; Renal Function; Blood Glucose; Renal Fibrosis

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前言

糖尿病肾脏疾病(diabetic kidney disease, DKD)是糖尿病常见的微血管并发症,病理学方面的变化主要表现为肾小球硬化和肾小管-间质纤维化^[1,2]。DKD患者病情发展到后期,会出现严重的肾功能衰竭,预后比较差^[3-5]。目前,DKD的发病机制尚未明确,存在高血糖学说、炎症介质学说以及高血脂学说,临床上主要通过控制血糖、降压、调节血脂等延缓其进展^[6,7]。血管紧张素 II 1 型受体阻断剂可选择性地作用于血管紧张素 II 受体的 AT1 亚型,抑制血管紧张素与之结合,起到扩张血管,降低血压的作用,同时这类药物能降低肾小球内压力,发挥降压之外的肾脏保护作用^[8]。阿魏酸钠不但有显著的扩张血管效果,还能降低红细胞聚集性及血液黏度,改善微循环。临床上已有将阿魏酸钠和缬沙坦联用的研究,但是还没有关于其联合应用对肾脏纤维化影响的报道。本研究创新性地分析了阿魏酸钠联合缬沙坦对 DKD 患者肾脏纤维化的影响。

1 资料与方法

1.1 一般资料

选择 2017 年 1 月~2018 年 12 月山西医科大学附属晋中医院收治的 101 例糖尿病肾病患者,均符合 DKD 的诊断标准^[9],没有其他的肾脏疾病、异常出血和炎症感染等疾病,均知情同意。排除标准:(1)1 个月内使用过阿魏酸钠和缬沙坦治疗者;(2)原发性高血压和原发性肾脏病患者;(3)具有心脏、肝脏和肺部等病史;(4)患有严重的泌尿系统感染者。用抽签法随机分为两组。观察组 50 例,男 27 例,女 23 例;年龄 37~80 岁,平均(57.14±15.26)岁;病程 3~10 年,平均(5.29±1.13)年;血肌酐 108.32~175.50 μmol/L,平均(143.27±27.35)μmol/L。对照组 51 例,男 27 例,女 24 例;年龄 37~80 岁,平均(57.33±16.89)岁;病程 3~10 年,平均(5.27±1.09)年;血肌酐 109.05~174.01 μmol/L,平均(142.89±26.24)μmol/L。两组的基线资料比较差异均无统计学意义,具有可比性($P>0.05$)。

1.2 治疗方法

两组均低蛋白饮食,口服他汀类药物调脂,口服降糖药和(或)胰岛素控制血糖。对照组口服缬沙坦(北京诺华制药有限公司,国药准字 H20040217) 80 mg/d 治疗,观察组联合静脉滴注 0.3 g 的阿魏酸钠(成都亨达药业有限公司,国药准字 H51023583),每天 1 次。

两组均持续治疗 1 个月。

1.3 观察指标

疗效判断^[9]:显效:相关症状及体征消失,且 24 h 尿蛋白定量降低 50 %以上;有效:相关症状及体征显著缓解,且 24 h 尿蛋白定量降低在 30 %~50 %;无效:相关症状及体征基本无改善,甚至加重。总有效率=(显效+有效)/总数×100%。

治疗前后,空腹采集 5 mL 静脉血,检测血清血尿素氮(blood urea nitrogen, BUN)、空腹血糖(fasting plasma glucose, FPG)、餐后 2 h 血糖(2 h plasma glucose, 2 h PG)、血肌酐(serum creatinine, SCr)、IV 型胶原(type IV Collagen, CIV)和 III 型前胶原(procollagen type III, PCIII)水平。其中,SCr 采取 ELISA 法进行检测,2 h PG 以及 FPG 采取葡萄糖氧化酶法进行检测,BUN 采取放射免疫法进行检测,PCIII 以及 CIV 采取增强化学发光免疫分析法进行检测。留取患者治疗前后 24 h 尿,采用美国 Beckman Coulter 公司生产的 AU5800 全自动生化分析仪检测肾小球滤过率(GFR)、24 h 尿白蛋白排泄率(24 h urine microalbumin excretion, 24 h UAER)和 β₂-微球蛋白(β₂-microglobulin, β₂-MG)的水平。

1.4 统计学分析

应用 SPSS 21.0 进行统计学分析,计量资料用($\bar{x} \pm s$)表示,计数资料用%表示,组间比较分别行 t 检验和 χ^2 检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 疗效比较

治疗后,观察组的治疗总有效率 92.00 % (46/50),显著高于对照组[68.63 % (35/51)],差异有统计学意义($P<0.05$),见表 1。

表 1 两组临床疗效比较[例(%)]

Table 1 Comparison of the clinical effect [n (%)]

Groups	n	Excellence	Effective	Invalid	The total effective rate
Control group	51	23(45.10)	12(23.53)	16(31.37)	35(68.63)
Observation group	50	30(60.00)*	16(32.00)*	4(8.00)*	46(92.00)*

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

2.2 两组肾间质纤维化程度比较

治疗前,两组的 PC III 和 C IV 水平比较差异无统计学意义($P>0.05$);治疗后,两组的 PC III 和 C IV 等肾脏纤维化指标均较治疗前明显降低($P<0.05$),且观察组明显低于对照组($P<0.05$),见表 2。

2.3 两组肾功能指标和血糖指标对比

治疗前,两组的 FPG、2 h PG、BUN、SCr、β₂-MG、24 h UAER、GFR 水平对比差异无统计学意义($P>0.05$);治疗后,两组的 FPG、2 h PG、BUN、SCr、β₂-MG、24 h UAER 均明显降低($P<0.05$),且观察组的上述指标显著低于对照组($P<0.05$),两组

GFR 增高($P<0.05$),且观察组指标明显高于对照组($P<0.05$),见表 3。

3 讨论

长期的高血糖会造成患者的内分泌功能发生异常,引起全身的各器官受到损伤,特别是肾脏,容易导致肾小球硬化和肾小管-间质纤维化,表现为尿蛋白量显著增多,如果未及时发现,耽误了最佳的治疗时机,会逐渐发展为 DKD,严重影响其正常的工作和生活,对社会和家庭造成负担^[10-13]。

表 2 两组治疗前后的肾脏纤维化指标比较($\bar{x} \pm s$)

Table 2 Comparison of the renal fibrosis indexes between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n		PC III (ng/mL)	C IV (ng/mL)
Control group	51	Before treatment	71.43 $\pm$ 18.27	51.48 $\pm$ 12.79
		After treatment	65.23 $\pm$ 11.64 [#]	48.22 $\pm$ 10.33 [#]
Observation group	50	Before treatment	72.59 $\pm$ 17.34	52.38 $\pm$ 13.41
		After treatment	61.27 $\pm$ 10.03 ^{*#}	44.26 $\pm$ 10.13 ^{*#}

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

表 3 两组肾功能指标和血糖指标比较($\bar{x} \pm s$)

Table 3 Comparison of renal function indexes and blood glucose indexes between the two groups($\bar{x} \pm s$)

Groups	n		FPG (mmol/L)	2 h PG (mmol/L)	BUN (mmol/L)	SCr (μ mol/L)	β 2-MG (mg/L)	24 h UAER (mg/24 h)	GFR (ml/min)
Control group	51	Before treatment	10.34 $\pm$ 1.72	14.39 $\pm$ 1.27	12.97 $\pm$ 1.54	143.27 $\pm$ 27.35	4.17 $\pm$ 1.13	337.46 $\pm$ 59.31	49.21 $\pm$ 3.34
		After treatment	7.34 $\pm$ 1.13 [#]	10.13 $\pm$ 1.25 [#]	10.03 $\pm$ 3.27 [#]	118.32 $\pm$ 34.39 [#]	3.38 $\pm$ 1.04 [#]	309.87 $\pm$ 34.53 [#]	58.47 $\pm$ 4.25 [#]
Observation group	50	Before treatment	10.26 $\pm$ 1.39	14.42 $\pm$ 1.36	12.98 $\pm$ 1.49	142.89 $\pm$ 26.24	4.18 $\pm$ 1.15	336.28 $\pm$ 58.44	48.57 $\pm$ 3.29
		After treatment	6.52 $\pm$ 1.07 ^{*#}	8.36 $\pm$ 1.07 ^{*#}	6.71 $\pm$ 2.14 ^{*#}	94.27 $\pm$ 30.36 ^{*#}	2.14 $\pm$ 0.72 ^{*#}	177.43 $\pm$ 22.39 ^{*#}	76.96 $\pm$ 5.63 ^{*#}

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

DKD 的发病机制可能与以下因素相关:(1) 血液流变学的变化,包括血沉加快以及血液黏稠度的增加造成血流明显减慢,导致局部组织缺氧,内皮损伤以及血管基底膜增厚,使肾微血管发生闭塞,进而升高滤过压^[14-16]。(2)血流动力学的变化,主要是肾小球内的高压、高滤过以及高灌注,与胰岛素样生长因子、高血糖、一氧化氮以及胰高血糖素等有关^[17,18]。(3)脂质代谢出现紊乱,脂质代谢的过程中,重要酶类的活性发生变化,使患者常常并发高脂蛋白血症以及高脂血症,这是出现血管病变的一个重要基础^[19,20]。(4)环境因素以及遗传因素^[21]。及时进行防治对延缓 DKD 的疾病进展具有重要的意义。

常规的降压和降血糖药物等对糖尿病肾病的疗效欠佳,无法很好的改善其症状^[2]。阿魏酸钠是以当归和川芎等中药为主要材料的钠盐,能竞争性地抑制机体内的内皮素受体,改善肾小球的高滤过,进而明显降低尿蛋白,有效保护肾脏^[22]。多项研究均发现,阿魏酸钠能有效抑制肿瘤生长因子- β 和内皮素,常被用于治疗肾小球疾病和糖尿病性血管病变^[23,24]。缬沙坦能扩张出球小动脉大于扩张入球小动脉,降低肾小球内的压力,改善肾脏的血流动力学,明显降低尿蛋白的排泄率,从而对肾脏产生保护效果^[25-27]。本研究中,观察组的治疗有效率明显高于对照组;治疗后,观察组的 FPG、BUN、2 h PG、SCr、 β 2-MG、24 h UAER 明显低于对照组,GFR 明显高于对照组,与 Xu^[28]等学者的研究类似,缬沙坦联合阿魏酸钠治疗 DKD 患者疗效显著,并且显著减少 24 h UAER。与本研究不同的是,该学者发现缬沙坦联合阿魏酸钠能够降低 DKD 患者的血清 Cys C、PEDF、VEGF 水平,可能是通过改善糖尿病肾脏异常血管新生发挥肾脏保护效应。两组治疗后 SCr 明显降低,主要原因是两组治疗后肾小球动脉显著扩张,降低了肾小球内的压力,增加了 GFR,

从而减低了患者 SCr、 β 2-MG、24 h UAER。本研究表明阿魏酸钠联合缬沙坦能明显提高 DKD 患者的疗效,有效改善肾功能指标和血糖指标。其原因为将阿魏酸钠和缬沙坦联合使用一方面能有效的控制糖尿病肾病患者的血压,降低肾小球内的压力,另一方面也在改善肾小球的血流动力学,改善患者的肾功能衰竭情况,进而提高疗效。

DKD 患者血浆内的内皮素水平显著升高,可以刺激血管紧张素 II 受体拮抗剂的生成,促进血管的收缩,增加肾脏纤维化指标 PCIII 和 CIV 水平的表达,促进肾小球系膜细胞外间质堆积及细胞增殖,使肾小球的硬化速度加快^[29-31]。治疗后,观察组的 PCIII 和 CIV 水平明显低于对照组,表明阿魏酸钠联合缬沙坦能明显降低肾脏纤维化,改善肾功能。其原因与阿魏酸钠具有双重保护内皮、拮抗内皮素、平衡纤溶机制、调节血管舒缩功能、抗炎、对抗血小板活性以及调节免疫等多种药理作用有关。Dai H^[32]等发现在 DKD 小鼠模型中,通过特异性抗体阻断 CTGF 可减少蛋白尿,防止 DKD 小鼠中肾小球 CTGF 和 β -catenin 的过度表达。研究表明 CTGF 抗体可减少 β -catenin 的过表达,这可能为 CTGF 抑制 DKD 的机制提供新的思路。

综上所述,阿魏酸钠联合缬沙坦对 DKD 患者有较好的疗效,能明显延缓机体肾脏纤维化的发生速度,进而有效改善肾功能。目前,国外对于糖尿病肾病的研究主要集中在寻找新的药物治疗的靶点和诊断方法。而本研究主要是创新性地将阿魏酸钠与缬沙坦联合一起治疗糖尿病肾病,通过肾脏纤维化指标、肾功能指标和血糖指标的对比,取得了显著的疗效,为以后治疗 DKD 提供了新的治疗方向,同时也为寻找 DKD 的致病机制和药物治疗靶点提供生物学指标。本研究也存在一定的不足,样本量少,同时也没有对阿魏酸钠联合缬沙坦对 DKD 治疗

的不良反应及作用机制进行深入研究, 后续需要进一步深入研究。

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症,本组病例中的微瘤型类癌为此表现,术前考虑为慢性炎症改变伴局部支气管扩张及结石,术后病理显示局部支气管扩张、炎症伴微小类癌结节。

典型和非典型类癌均可能合并肺门或纵隔淋巴结肿大(炎症淋巴结肿大或转移),其中,非典型类癌淋巴结转移更常见,本组中有1例为右肺门旁肿块,不均匀强化,伴右肺门、纵隔多发淋巴结转移。

周围型肺类癌较少,约占20%,表现为肺内的孤立结节。这些结节通常为圆形或卵圆形,边缘光滑或轻度分叶。典型的肺类癌生长缓慢,因此在生长缓慢的孤立性肺结节的鉴别诊断中要考虑到类癌的诊断。CT能显示直径为5 mm或更小的肿瘤,并且可以显示结节与邻近小气管的关系。

3.4 肺类癌的鉴别诊断

3.4.1 中央型肺癌 中央型肺癌临床更常见,表现为肺门部肿块及肿瘤远端阻塞性肺气肿、肺炎及肺不张改变,与中央型肺类癌相似,但肺癌肿块常沿支气管管壁浸润性生长,导致支气管腔内腔呈锥形、鼠尾状狭窄、闭塞,肺癌肿块常强化较弱、不均匀,边缘不清,钙化少见,少见支气管腔内结节或“冰山征”,罕见伴有支气管扩张或粘液嵌塞。

3.4.2 肺硬化性血管瘤 主要表现为肺周围或肺门单发圆形或类圆形肿块或结节,密度多较均匀,边缘光滑锐利,生长缓慢,与周围型类癌难以鉴别,但硬化性血管瘤钙化少见,增强后可见贴边血管征、尾征、肺动脉为主征。需要注意的是硬化性血管瘤可以同时合并类癌。确诊需要病理诊断。

3.4.3 错构瘤 生长缓慢、边缘清楚,少毛刺,可以有浅分叶,密度不均,可有钙化和脂肪密度,与周围型类癌难以鉴别,但错构瘤强化往往较弱,极少合并支气管扩张等征象。

总之,肺类癌为少见的具有神经内分泌功能的肺实体肿瘤,包括恶性度较低的典型类癌和恶性度较高的非典型类癌,影像学具有一定的特征性。典型的肺类癌影像学表现为支气管内结节或肺门肿块,肿块呈圆形或卵圆形,或略呈分叶状,血供丰富,常见钙化,可同时合并阻塞性肺气肿、肺炎,肺不张、支气管扩张等间接征象;而周围型类癌表现为肺内孤立结节,生长较缓慢,确诊最终依赖病理诊断。

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