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卡托普利联合坎地沙坦对糖尿病肾病患者的疗效及对血浆 ET、D-D、Hcy、ADM、FIB 水平的影响 *

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摘要 目的:研究卡托普利联合坎地沙坦治疗糖尿病肾病患者的临床疗效及对血浆内皮素(Endothelin,ET)、D-二聚体(D-Dimer,D-D)、同型半胱氨酸(Homocysteine,Hcy)、肾上腺髓质素(Adrenal medulla,ADM)、纤维蛋白原(Fibrinogen,FIB)的影响。**方法:**选择 2016 年 1 月至 2017 年 8 月在我院治疗的糖尿病肾病患者 72 例,根据不同的治疗方法分为观察组和对照组。对照组采用卡托普利治疗,观察组在对照组的基础上联用坎地沙坦治疗,观察和比较两组患者的临床治疗效果,治疗前后 ET、D-D、Hcy、ADM、FIB 水平、肾功能及空腹血糖(fasting plasma glucose,FPG)、餐后 2 小时血糖浓度(2 hours Plasma Glucose,2hPG)、糖化血红蛋白(Hemoglobin A1c,HbA1C)水平的变化。**结果:**治疗后,观察组总有效率为 88.89%,明显高于对照组 69.44%($P<0.05$);观察组血浆 ET、D-D、Hcy、ADM、FIB、FPG、2hPG、HbA1C 水平、24 h 尿总蛋白及尿白蛋白排泄率均显著低于对照组($P<0.05$)。**结论:**卡托普利联合坎地沙坦治疗糖尿病肾病患者的临床疗效明显优于单用卡托普利治疗,可助于降糖、降压并有效保护患者肾脏功能。

关键词:卡托普利;坎地沙坦;糖尿病肾病;内皮素;D-二聚体;同型半胱氨酸;肾上腺髓质素;纤维蛋白原

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Clinical Efficacy of Captopril Combined with Candesartan in the Treatment of Patients with Diabetic Nephropathy and Effects on the Plasma ET, D-D, Hcy, ADM and FIB Levels*

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ABSTRACT Objective: To study the clinical efficacy of captopril combined with candesartan in the treatment of patients with diabetic nephropathy and effects on the plasma ET, D-D, Hcy, ADM and FIB levels. **Methods:** 72 cases of patients with diabetic nephropathy in our hospital from January 2016 to August 2017 were selected and randomly divided into the control group and the observation group. The control group was treated with captopril. The observation group was treated with candesartan on the basis of the control group. The clinical effects of ET, D-D, Hcy, ADM, FIB, renal function and the changes of FPG, 2hPG and HbA1C before and after treatment were observed and compared between two groups. **Results:** After treatment, the total effective rate of the observation group was 88.89%, which was significantly higher than that of the control group (69.44%, $P<0.05$). The levels of ET, D-D, Hcy, ADM, FIB, FPG, 2hPG and HbA1C in the observation group were significantly lower than those in the control group ($P<0.05$). **Conclusion:** Captopril combined with candesartan in patients with diabetic nephropathy clinical efficacy was significantly superior to captopril alone can help hypoglycemic, antihypertensive and effective protection of patients with renal function.

Key words: Captopril; Candesartan; Diabetic nephropathy; Endothelin; D-Dimer; Homocysteine; Adrenal medulla; Fibrinogen

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前言

糖尿病肾病(DN)是糖尿病患者最主要的并发症之一,是常见的继发性肾脏疾病,中老年人为高发群体,主要表现为高血压、肾功能衰竭等^[1,2]。糖尿病肾病作为一种慢性疾病,起病隐匿又无明显的临床症状,因此早期难以诊断,多数患者因未尽早得到诊断以至于延误最佳治疗时机。

随着医疗技术的进步,微量白蛋白尿被广泛应用于早期诊断糖尿病肾病的重要指标,且血浆 ET、D-D、Hcy、ADM、FIB 等指标的变化也被作为早期诊断糖尿病肾病的重要依据。临床既往常采用卡托普利治疗糖尿病肾病患者,但单一采用卡托普利已经无法满足临床治疗的需要^[3-6]。有相关文献报道在采用卡托普利用药基础上联用坎地沙坦治疗糖尿病肾病患者,其临床效果较单一用药更为显著^[7-9]。因此,本研究主要探讨了卡托普利

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联合坎地沙坦治疗糖尿病肾病患者的疗效及对血浆 ET、D-D、Hcy、ADM、FIB 水平的影响,结果报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月至 2017 年 8 月在我院进行治疗的糖尿病肾病患者 72 例。纳入标准:(1)符合相关糖尿病肾病诊断标准^[10],近 3 个月内血压控制平稳;(2)确诊为糖尿病患者;(3)病程

10 年以上。排除标准:(1)排除其他肾脏疾病;(2)排除拒绝配合检测患者;(3)排除妊娠或哺乳期妇女。将所有患者随机分为观察组及对照组,观察组 36 例患者,年龄在 34-46 岁,平均年龄(30.23±4.60)岁,病程(13.63±3.60)年,体重指数为(27.38±4.01) kg/m²;对照组 30 例,年龄在 37-51 岁,平均年龄(38.42±6.92)岁,病程(12.61±2.52)年,体重指数为(27.92±4.22) kg/m²,详见表 1。

表 1 两组患者一般临床资料的比较($\bar{x} \pm s$)

Table 1 Comparison of the general information between two groups of patients($\bar{x} \pm s$)

Group	n	m/w	age	BMI (kg/m ²)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	LDL-C(mmol/L)
Observation group	36	9/27a	57.33±8.68 ^a	27.38±4.01 ^a	125.11±19.04 ^a	79.66±12.28 ^a	2.83±0.45 ^a
Control group	36	20/16	56.81±8.23	27.92±4.22	127.10±20.22	80.45±11.50	2.91±0.42

Note: compared with the control group ^aP>0.05.

1.2 治疗方法

所有研究者均行常规心电图检测,并于检验科及放免室完成 FPG、2hPG、HbA1C 检测。对照组患者采用卡托普利(国药准字 H314689986,中美上海施贵宝制药有限公司,12.5 ng/片)12.5 mg,一日两次口服治疗。观察组在对照组的治療基础上联用坎地沙坦(国药准字 H20103244,天津武田药品有限公司,4 mg/片)4 mg,一日一次口服治疗。两组患者治疗周期均为 2 个月。

1.3 观察指标

① 治疗前后于清晨抽取静脉空腹血 6-8 mL,抗凝后离心储存于 -20 摄氏度环境中,检测糖尿病肾病患者的血糖及肾功能指标变化情况,具体方法:血糖采用免疫酶法检测;采用放射免疫法检测 ET、D-D 水平、采用高效液相色谱结合荧光检测法检测 Hcy 水平、采用 ELISA 法检测 ADM 水平、采用凝固法检测 FIB 水平,检测用试剂盒均为(上海博灿生物科技有限公司)生产。② 定时检测患者 FPG、2hPG、HbA1C 等血糖水平;③ 对治疗患者于治疗前后 1 个月采用全自动生化分析仪(济南格利特科技有限公司生产)检测其血尿素氮、血肌酐、24 h 尿总蛋白水

平,并观察治疗前后血尿素氮、血肌酐、24 h 尿蛋白水平变化;

④ 观察两组患者临床治疗效果。

疗效判定标准^[11]:显著好转:临床症状完全消失且 24 h 尿蛋白水平显著降低 50%以上,血尿素氮、血肌酐水平均明显降低 30%以上;好转:临床症状基本好转,24 h 尿蛋白水平显著降低 30%以上,血尿素氮、血肌酐水平均得到一定程度降低未达显著好转标准;无变化:患者治疗后 24 h 尿蛋白、血尿素氮、血肌酐水平无任何变化且临床症状加重。

1.4 统计学分析

选择 SPSS18.0 进行数据统计,计量资料的比较采用 t 检验,计数资料的比较采用 χ^2 检验,当 P<0.05 时表示其差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,观察组总有效率明显高于对照组(88.89% vs. 69.44%,P<0.05),详见表 2。

表 2 两组临床疗效的比较[例(%)]

Table 2 Comparison of the clinical efficacy between two groups after treatment[n(%)]

Group	n	Significant improvement	Improve	No change	Total improvement rate
Observation group	36	21(58.33) ^b	11(30.50) ^b	4(11.11) ^b	32(88.89) ^b
Control group	36	10(27.77)	15(41.66)	11(30.55)	25(69.44)

Note: Compared with the control group ^bP<0.05.

2.2 两组治疗后血浆 ET、D-D、Hcy、ADM、FIB 水平的比较

观察组治疗后血浆 ET、D-D、Hcy、ADM、FIB 水平均显著

低于对照组(P<0.05),详见表 3。

表 3 两组治疗后血浆 ET、D-D、Hcy、ADM、FIB 水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the plasma ET, D-D, Hcy, ADM and FIB between two groups after treatment($\bar{x} \pm s$)

Group	n	ET	D-D	Hcy	ADM	FIB
Observation group	36	68.55±10.14 ^b	0.14±0.01 ^b	2.42±0.30 ^b	16.44±2.51 ^b	2.60±0.41 ^b
Control group	36	106.88±15.21	0.35±0.04	3.56±0.55	35.71±5.20	3.82±0.61

Note: Compared with the control group ^bP<0.05.

2.3 两组治疗后空腹血糖(FPG)、餐后 2 小时血糖(2hPG)、糖化血红蛋白(HbA1C)水平的比较

观察组患者治疗后 FPG、2hPG、HbA1C 水平均显著低于对照组($P<0.05$), 详见表 4。

表 4 两组治疗后 FPG、2Hpg、HbA1C 水平的比较($\bar{x} \pm s$)

Table 4 Comparison of the FPG, 2Hpg and HbA1C levels between two groups after treatment($\bar{x} \pm s$)

Group	n	FPG/(mmol/L)	2hPG/(mmol/L)	HbA1C/%
Observation group	36	5.01 $\pm$ 0.79 b	5.14 $\pm$ 0.82 b	5.03 $\pm$ 0.74 b
Control group	36	8.47 $\pm$ 1.32	9.71 $\pm$ 1.51	6.78 $\pm$ 1.02

Note: Compared with the control group ^b $P<0.05$.

2.4 两组患者治疗前各项肾功能指标对比

治疗前, 两组患者的血尿素氮、血肌酐、肌酐清除率、24 h 尿总蛋白、尿白蛋白排泄率比较无明显差异($P>0.05$); 经治疗

后, 观察组患者各项肾功能指标均低于对照组且差异显著($P<0.05$)。详见表 5。

表 5 两组患者治疗前后各项肾功能指标对比分析($\bar{x} \pm s$)

Table 5 Comparison of the renal function indexes before and after treatment between two groups($\bar{x} \pm s$)

Group	time	Blood urea nitrogen (mmol/L)	Serum creatinine (μ mol/L)	Creatinine clearance rate creatinine clearance rate (mL/min)	24 h urinary total proteing/24 h)	Urinary albumin excretion rate (μ g/min)
Observation group	Before treatment	6.21 $\pm$ 0.98 ^a	77.61 $\pm$ 10.64 ^a	88.71 $\pm$ 12.14 ^a	3.15 $\pm$ 0.51 ^a	165.33 $\pm$ 25.48 ^a
	After treatment	5.68 $\pm$ 0.91 ^b	75.12 $\pm$ 11.92 ^b	80.24 $\pm$ 12.05 ^b	0.95 $\pm$ 0.12 ^b	65.25 $\pm$ 9.84 ^b
Control group	Before treatment	6.09 $\pm$ 1.01	76.98 $\pm$ 11.12	89.02 $\pm$ 11.88	3.43 $\pm$ 0.49	160.37 $\pm$ 24.81
	After treatment	5.81 $\pm$ 0.88	75.64 $\pm$ 10.82	79.65 $\pm$ 12.89	2.68 $\pm$ 0.39	72.83 $\pm$ 12.01

Note: Compared with the control group ^b $P<0.05$; Compared with the control group ^a $P>0.05$.

2.5 两组不良反应发生情况的比较

观察组出现头晕的患者 1 例、干咳 1 例、胃肠功能紊乱 2 例、鼻塞 0 例, 对照组患者出现头晕的患者 8 例、干咳 5 例、胃肠功能紊乱 6 例、鼻塞 4 例。

3 讨论

糖尿病肾病病理本质为微血管病变, 而肾小球基础为毛细血管团, 临床表现主要为蛋白尿、肾衰竭^[12-15]。目前, 卡托普利是我国用于治疗糖尿病肾病患者的首选药物。卡托普利能有效降低高血压水平并具有保护患者肾功能的作用, 但单用此药见效慢疗程长已无法满足临床的需要^[16,17]。多项研究表明坎地沙坦具有降压保护肾脏的作用, 且通过联合应用卡托普利可明显改善糖尿病肾病患者的肾脏功能、降低血浆 ET、D-D、Hcy、ADM、FIB 水平、减少疗程周期及改善预后的作用, 此类联合用药是目前临床上值得继续研究的新方向^[18,19]。

卡托普利(Captopril)作为一种血管紧张素转化酶抑制剂常被广泛用于临床治疗充血性心力衰竭等疾病^[20]。Soliman S 等^[21]认为卡托普利为血管紧张素酶抑制剂, 其作用靶点为血管紧张素酶, 从而抑制器转换为生物学效价更高的血管紧张素 II, 从而降低肾小球囊内压, 减轻蛋白尿及抑制系膜增殖、抑制肾小球毛细血管压力及防止肾小球硬化及保护肾脏的效果, 但服用该药的患者不良反应症状较多, 临床效果不佳。坎地沙坦(Candesartan)在临床上常被应用于治疗原发性高血压, 其作为一种选择性的血管紧张素 II 受体拮抗剂, 具有降低血管阻力的作用^[22]。Jia MY 等^[23]认为坎地沙坦为血管紧张素 II AT1 受体拮

抗剂, 不良反应发生率较低, 通过卡托普利及坎地沙坦联合应用于治疗糖尿病患者, 可显著抑制高血压、改善肾脏功能。本次研究患者采用联合用药患者发生头晕、干咳、胃肠功能紊乱、鼻塞等不良反应的数量明显低于单药治疗的患者。

同型半胱氨酸(Homocysteine, Hcy)作为一种含硫氨基酸, 不参与蛋白质的合成, 且在人体内的成分较少^[24]。Stiksrud B 等^[25]认为该因子与动脉粥样硬化有着密切的联系, 且与糖尿病血管病变密切相关, 通过观察糖尿病肾病患者发现, 其 Hcy 水平均明显高于正常健康人群。D-二聚体(D-Dimer, D-D)是一种降解产物, 可反映血管内血栓形成情况^[26]。Speed JS 等^[27]认为 D-D 水平升高表示浓度高病情重, D-D 水平降低表示病情得到抑制, 但是患者经过手术或者曾有外伤感染等情况也会导致 D-D 水平升高, 因此单一检测 D-D 水平无法准确判断血栓的形成状况。内皮素(endothelin, ET)是对人体血管张力及心血管系统的稳定起着重要作用的血管调节因子。Li X 等^[28]认为 ET 与糖尿病患者的血糖浓度密切相关, 即血糖越高 ET 越高呈正相关, 且 ET 升高引起肾血管收缩肾血流量减少, 导致肾小球硬化。肾上腺髓质素(adrenal medulla, ADM)广泛分布于血管内皮细胞, 对血管平滑肌细胞增殖具有一定抑制作用。Van Berkel A 等^[29]认为 ADM 在肾小管上皮可增加肾血流量, 并通过与转化因子 TGF- β 1 结合促进细胞外基质沉积, 以达到抑制肾小球硬化的目的。纤维蛋白原(Fibrinogen, FIB)作为一类凝血因子, 是形成血栓的关键因素。本次入院研究患者中, 采用卡托普利及坎地沙坦联合用药的患者 ET、D-D、Hcy、ADM、FIB 水平显著低于采用卡托普利单药治疗的患者, 提示联合用药效果较单一

用药更佳。

目前,国内外均尿素氮等指标评价肾功能的检测项目。当肾小球受损初期,血中尿素氮、肌酐水平变化不大,因此通过检测血尿素氮、肌酐水平难以早期发现肾损伤^[30]。本次研究患者入院治疗前 24 小时尿蛋白排泄量、血肌酐、尿素氮水平明显偏高,治疗后 24 小时尿蛋白排泄量、血肌酐、尿素氮水平明显降低,且联合用药患者降低更显著,其效果差异可能为联合用药的综合药力更强。研究显示糖尿病肾病患者的 FPG、2hPG、HbA1C 血糖及血压都明显偏高,采用卡托普利联合坎地沙坦治疗的糖尿病肾病患者血糖显著降低,且治疗后采用联合用药的患者总有效率 88.89%,明显高于采用卡托普利单药治疗患者的总有效率 69.44%。

综上所述,卡托普利联合坎地沙坦治疗糖尿病肾病患者的临床疗效明显优于单用卡托普利治疗,可助于降糖、降压并有效保护患者肾脏功能。

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