·临床研究·

前列地尔治疗老年糖尿病合并慢性肾脏病患者的效果分析

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【摘 要】 **目的** 探讨前列地尔联合常规治疗对老年2型糖尿病(T2DM)合并慢性肾脏病(CKD)患者的治疗效果。**方法** 入选2014年2月至2016年2月在攀枝花市中心医院内分泌科治疗的90例老年T2DM合并CKD患者,采用数字表法随机分为前列地尔组和对照组,每组45例。对照组给予常规治疗,前列地尔组在常规治疗基础上加用前列地尔10 μg/d,静脉推注,1次/d,2周为1个疗程,共治疗3个疗程。比较两组患者血脂、血糖、肝功能、肾功能等指标。所有数据采用SPSS 16.0软件进行统计学分析。计量资料用均数±标准差($\bar{x} \pm s$)表示,两组比较采用t检验。计数资料用百分率表示,组间比较用χ^2检验。**结果** 两组患者治疗前空腹血糖(FPG)、糖化血红蛋白(HbA1c)、甘油三酯(TG)、总胆固醇(TC)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、同型半胱氨酸(Hcy)、血β2微球蛋白(β2-MG)、尿白蛋白排泄率(UAER)、血肌酐(SCr)、估算肾小球滤过率(eGFR)差异均无统计学意义($P>0.05$)。治疗后,前列地尔组患者的TG、TC、LDL-C、Hcy、β2-MG、UAER显著低于对照组,差异具有统计学意义($P<0.05$)。两组患者治疗前后的凝血酶原时间(PT)、血小板(PLT)、活化部分凝血活酶时间(APTT)差异无统计学意义($P>0.05$)。两组不良反应发生率差异无统计学意义($\chi^2=0.212$, $P=0.645$)。**结论** 前列地尔联合常规治疗能显著降低老年T2DM合并CKD患者尿蛋白水平,对患者的肾功能具有一定的保护作用。

【关键词】 老年人;前列地尔;糖尿病2型;慢性肾脏病
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Efficiency of alprostadil in treatment of chronic kidney disease in elderly patients with type 2 diabetes mellitus

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【**Abstract**】 **Objective** To investigate the efficiency of alprostadil combined with conventional therapy on elderly type 2 diabetes mellitus (T2DM) patients complicated with chronic kidney disease (CKD). **Methods** A total of 90 elderly T2DM patients with CKD admitted in our hospital from February 2014 to February 2016 were recruited in this study. They were randomly divided into alprostadil group and control group ($n=45$). Conventional basic treatment was given to the patients of the 2 groups, and 10 μg/d alprostadil (once per day) was given to the alprostadil group by intravenous injection with 2 weeks as a course, for totally 3 courses. The indices of blood lipids, blood glucose, liver function and renal function were compared between the 2 groups. SPSS statistics 17.0 was used to analyze the data. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and Student's t test was employed for the comparison between groups. Enumeration data were expressed as percentage, and inter-group comparison was carried out with Chi-square test. **Results** There were no significant differences in fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), homocysteine (Hcy), blood β2-microglobulin (β2-MG), serum creatinine (SCr), and urinary albumin excretion rate (UAER) and estimated glomerular filtration rate (eGFR) between the 2 groups before treatment ($P>0.05$). After the treatment, the levels of TG, TC, LDL-C, Hcy and β2-MG and UAER were significantly lower in the alprostadil group than in the control group ($P<0.05$). No significant differences were observed in prothrombin time (PT), platelet (PLT) count, and activated partial thromboplastin time (APTT) between the 2 groups before and after treatment ($P>0.05$). There were no any differences in the incidences of adverse reaction (Chi-square = 0.212, $P=0.645$). **Conclusion** Combination of alprostadil and conventional therapy can significantly reduce urinary protein levels and exert protective effect on renal function in elderly T2DM patients with CKD.

【**Key words**】 aged; alprostadil; type 2 diabetes mellitus; chronic kidney disease

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老年2型糖尿病(type 2 diabetes mellitus, T2DM)患者由于免疫力下降、内分泌代谢调控紊乱以及器官衰老等,可以导致慢性肾脏病(chronic kidney disease,CKD)的发生。研究表明,我国T2DM合并CKD患者的发病率已大于0.05%,呈现出明显的高发态势[1,2]。早期干预T2DM合并CKD患者的肾功能,可降低尿蛋白水平,抑制肾小球氧化应激损伤,从而降低远期并发症的发生[3,4]。前列地尔(alprostadil)为前列腺素的衍生物,可通过抑制去甲肾上腺素分泌而使血管平滑肌舒张,改善微循环,增加肾的血流灌注,从而保护肾功能[5-7]。为此,本研究探讨了前列地尔联合常规方法治疗老年T2DM合并CKD患者的临床效果,为临床医师决策用药提供依据。

1 对象与方法

1.1 研究对象

入选2014年2月至2016年2月在攀枝花市中心医院内分泌科治疗的90例老年(≥65岁)T2DM合并CKD患者,采用数字表法随机分为前列地尔组和对照组,每组45例。其中前列地尔组男性26例,女性19例,年龄65~85(74.4±7.8)岁;对照组男性23例,女性22例,年龄65~85(75.0±8.7)岁。糖尿病诊断依据1999年世界卫生组织(world health organization,WHO)诊断标准[8]:空腹血糖(fasting plasma glucose,FPG)≥7.0 mmol/L;随机血糖≥11.1 mmol/L;口服葡萄糖耐量试验(oral glucose tolerance test,OGTT)后2 h血糖≥11.1 mmol/L;上述3点满足任何一点即可诊断。CKD的诊断参照美国肾脏基金会(National Kidney Foundation,NKF)发布的肾脏病诊疗指南[9],本研究纳入患者均为CKD分期3~4期。所有患者均签署知情同意书,本研究获得医学伦理委员会的批准(攀枝花市中心医院201312010号)。排除标准:(1)伴有严重高血压(收缩压>160 mmHg;舒张压>100 mmHg);(2)甲状腺和肿瘤疾病;(3)长期应用糖皮质激素;(4)伴有糖尿病酮症酸中毒、感染性疾病;(5)伴有自身免疫疾病;(6)对前列地尔有严重不良反应。

1.2 方法

对照组给予常规治疗,戒烟,调整饮食结构,低盐和低脂饮食,进行与身体状况相适应的体力活动,口服降糖药物控制血糖,调整血压及血脂,控制FPG水平为7.0 mmol/L,OGTT后2 h血糖水平为10.0 mmol/L,限制蛋白质及钠盐的摄入。给予卡托普利(国药准字:H32022823,江苏恒瑞医药股份有限公司)25 mg,3次/d,口服;辛伐他汀(国药准字:H20056876,宜昌长江药业有限公司)20 mg,1次/d,口服。前列地尔组在常规治疗基础上加用前列地尔(国药准字:H20048495,南京扬子江药业有限公司),10 μg/d,加入10 ml的无菌生理盐水注射液中,静脉推注,1次/d。2周为1个疗程,共治疗3个疗程。

1.3 观察指标

比较两组患者治疗前后FPG、糖化血红蛋白(hemoglobin A1c,HbA1c)、甘油三酯(triglycerides,TG)、总胆固醇(total cholesterol,TC)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol,HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol,LDL-C)、同型半胱氨酸(homocysteine,Hcy)、血β2微球蛋白(β2-microglobulin,β2-MG)、尿白蛋白排泄率(urinary albumin excretion rate,UAER)、血肌酐(serum creatinine,SCr)、估算肾小球滤过率(estimated glomerular filtration rate,eGFR)、凝血酶原时间(prothrombin time,PT)、血小板(platelet,PLT)、活化部分凝血活酶时间(activated partial thromboplastin time,APTT)、纤维蛋白原(fibrinogen,FIB)的变化。

1.4 统计学处理

所有数据采用SPSS 16.0软件进行统计学分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,两组比较采用t检验。计数资料用百分率表示,组间比较用χ^2检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组患者基线资料比较

两组患者的年龄、性别、体质量指数(body mass index,BMI)、吸烟情况、血压、糖尿病病程、并发症、高血压、冠心病例数方面差异均无统计学意义($P>0.05$;表1)。

2.2 两组患者疗效指标比较

两组患者治疗前FPG、HbA1c、TG、TC、HDL-C、LDL-C、Hcy、β2-MG、UAER、SCr、eGFR差异均无统计学意义($P>0.05$)。治疗后,前列地尔组患者的TG、TC、LDL-C、Hcy、β2-MG、UAER显著低于对照组,差异具有统计学意义($P<0.05$)。两组患者治疗前后的PT、PLT、APTT差异无统计学意义($P>0.05$;表2)。

2.3 两组患者不良反应比较

前列地尔组有2例出现注射部位疼痛、发红,1例出现食欲降低,对照组有2例出现轻度的恶心,上述临床症状几天后自行消失,两组不良反应发生率差异无统计学意义($\chi^2=0.212$,$P=0.645$)。

表 1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups ($n = 45$)

Item	Alprostadil group	Control group	t/χ^2	P value
Age(years, $\bar{x} \pm s$)	71.4 ± 9.8	72.0 ± 8.7	0.307	0.759
Gender(male/female, n/n)	26/19	23/22	0.403	0.525
BMI(kg/m^2, $\bar{x} \pm s$)	24.1 ± 2.2	23.8 ± 2.4	0.618	0.538
Smoking[n(%)]	12(26.67)	14(31.11)	0.216	0.624
Blood pressure(mmHg, $\bar{x} \pm s$)	128.1 ± 9.0	127.4 ± 9.2	0.365	0.716
Course of diabetes mellitus(years, $\bar{x} \pm s$)	5.6 ± 3.2	5.2 ± 2.9	0.621	0.536
Complication[n(%)]	31(68.89)	29(64.44)	0.200	0.655
Hypertension[n(%)]	12(26.67)	9(0.20)	0.559	0.455
Coronary heart disease[n(%)]	3(0.07)	2(0.04)	0.212	0.645

BMI: body mass index. 1 mmHg = 0.133 kPa

表 2 两组患者疗效指标比较

Table 2 Comparison of indices of curative effect between two groups ($n = 45$, $\bar{x} \pm s$)

Item	Alprostadil group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
FPG(mmol/L)	6.11 ± 1.05	6.09 ± 1.12	6.21 ± 1.22	6.15 ± 1.07
HbA1c(%)	8.21 ± 2.14	8.16 ± 2.00	8.52 ± 2.41	8.31 ± 2.26
TC(mmol/L)	5.81 ± 0.77	5.11 ± 0.83 *	5.74 ± 0.92	5.69 ± 0.80
TG(mmol/L)	3.14 ± 0.72	2.67 ± 0.66 *	3.20 ± 0.75	3.13 ± 0.78
HDL-C(mmol/L)	1.29 ± 0.22	1.35 ± 0.19	1.30 ± 0.18	1.32 ± 0.15
LDL-C(mmol/L)	2.11 ± 0.57	1.62 ± 0.44 *	2.25 ± 0.52	2.14 ± 0.50
Hcy(mg/L)	2.11 ± 0.52	0.94 ± 0.33 *	1.98 ± 0.56	1.33 ± 0.42
β2-MG(ug/ml)	4.48 ± 1.15	2.37 ± 0.82 *	4.50 ± 1.09	3.14 ± 1.20
UAER(ug/min)	68.41 ± 9.30	42.85 ± 8.83 *	66.72 ± 9.84	51.19 ± 9.06
SCr(umol/L)	112.4 ± 19.5	109.3 ± 20.1	109.8 ± 18.1	108.2 ± 17.4
eGFR[ml/(min · 1.73 m^2)]	40.0 ± 13.4	42.4 ± 12.8	39.2 ± 14.6	40.7 ± 14.1
PT(s)	10.56 ± 1.12	11.04 ± 1.26	10.67 ± 1.15	10.92 ± 1.30
PLT($\times 10^9$/L)	197.8 ± 45.2	192.1 ± 50.3	202.5 ± 49.1	198.6 ± 48.9
APTT(s)	34.2 ± 2.6	33.8 ± 2.9	34.9 ± 3.0	34.1 ± 2.8
FIB(g/L)	3.21 ± 0.42	3.16 ± 0.40	3.32 ± 0.39	3.20 ± 0.44

FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Hcy: homocysteine; β2-MG: β2-microglobulin; UAER: urinary albumin excretion rate; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; PLT: platele; PT: prothrombin time; APTT: activated partial thromboplastin time; FIB: fibrinogen. Compared with control group, * $P < 0.05$

3 讨 论

各种因素导致的肾功能减退,均可以促进 CKD 的发生,特别是具有合并症的人群,CKD 的发病率更高。长期的肾功能及血糖代谢紊乱可加剧血管内皮损伤,使心脑血管疾病发病率明显上升,远期致残率及入院率较高[10,11]。对于 T2DM 合并 CKD 患者进行干预,可以避免 CKD 进展至肾功能失代偿期,从而改善临床预后。一项对 115 例 CKD 合并 T2DM 患者的临床随访研究结果表明,尽管采用规范的饮食、运动及药物治疗措施,2.5% ~3.0% 的患者仍存在明显的尿蛋白,SCr 水平也持续维持在较高水平[12,13]。而前列地尔是前列腺素类衍生物,可通过交感 - 肾上腺素系统激活、稳定血小板活性和保护血管内皮细胞功能等机制发挥其在泌尿系统疾病中的防治作用[14]。前列地尔可扩张肾小球入球小动脉、降低血管阻力,增加血流灌注,同时可抑制血小板聚集、稳定炎症反应,减少肾单位基底膜的损伤及尿蛋白水平[15,16]。

已有研究表明前列地尔在糖尿病肾病及慢性肾小球肾炎等疾病中的临床应用价值,使用前列地尔可提高治疗有效率、保护残留肾单位的功能[4,17,18]。本研究结果表明,前列地尔用于 T2DM 合并 CKD 患者后,患者的 LDL-C、TC 及 TG 水平均明显改善。血脂改善可降低脂质代谢异常导致的血管内皮损伤,抑制肾入球小动脉的病变进展,但本研究并未发现治疗后血糖水平改善,一方面表明前列地尔对胰岛素分泌或胰岛素受体敏感性的改善效果不佳,另一

方面考虑可能与本研究的样本量不足有关。

Hcy是评估肾功能损伤的重要指标,水平明显下降说明肾脏滤过功能明显改善;β2-MG和UAER是评估尿蛋白水平的重要临床指标,上升往往提示肾功能恶化。前列地尔可改善肾单位的局部微循环,从而降低尿蛋白水平,延缓肾功能恶化。但本研究发现eGFR无显著变化,一方面考虑与本次研究治疗后的随访时间差别有关,另一方面考虑前列地尔对肾小球滤过率的影响较局限有关。Busch等[19]回顾性分析了54例T2DM合并CKD患者的临床资料,发现前列地尔联合常规治疗措施可降低25%患者的β2-MG水平,这与本研究的结论较一致。本研究的另一目的在于探讨前列地尔改善肾功能的同时,是否会对于凝血途径具有一定的影响。本研究结果表明APTT及PT等均未见明显变化,提示联合使用前列地尔并不影响机体的凝血功能,临床安全性较可靠。

综上所述,对于T2DM合并CKD患者,采用常规措施联合前列地尔治疗,可改善血脂代谢、降低尿蛋白水平,从而保护肾功能,且临床安全性较为可靠。但本研究的局限性在于样本量不足,缺乏多中心的前瞻性研究;缺乏对于前列地尔治疗后的临床总体有效率水平或者临床症状的改善分析,后期有待进一步研究。

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·消 息·

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自2017年1月起,我刊调整录用稿件的文末参考文献著录格式:(1)中文参考文献采用中英文双语著录,中文在前,英文在后;(2)参考文献如有“数字对象唯一标识符(DOI)”编码,应著录,列于末尾。

示例:

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