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缬沙坦联合吡格列酮治疗早期糖尿病肾病的疗效观察

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摘要 目的:观察缬沙坦联合吡格列酮治疗早期糖尿病肾病的疗效及其对肾功能和氧化应激水平的影响。**方法:**选取 2010 年 1 月~2012 年 6 月在我院就诊的早期糖尿病肾病患者 90 例,随机分为观察组和对照组,每组各 45 例。对照组予以吡格列酮治疗,观察组在对照组的基础上予以缬沙坦治疗。观察两组治疗前后的尿白蛋白排泄率(UAER)、β2 微球蛋白(β2-MG)、血肌酐(SCr)、还原型谷胱甘肽(GSH)、丙二醛(MDA)和超氧化物歧化酶(SOD)活性水平的变化。**结果:**观察组和对照组的治疗总有效率分别为 93.33%、75.56%,观察组显著高于对照组,差异有统计学意义(X^2=4.145,P=0.042)。治疗后,两组患者的 UAER、β2-MG、SCr 和 MDA 水平均较治疗前明显降低(P<0.01),且观察组以上指标的水平显著低于对照组(P<0.01);而两组 SOD 和 GSH 水平均较治疗前明显升高(P<0.01),且观察组以上指标的水平显著高于对照组,差异有统计学意义(P<0.01)。**结论:**缬沙坦联合吡格列酮治疗早期糖尿病肾病的疗效较单用吡格列酮更好,并可显著改善患者的肾功能和降低氧化应激水平。

关键词:缬沙坦;吡格列酮;糖尿病肾病;氧化应激;疗效

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Efficacy of Valsartan Combined with Pioglitazone in the Patients with Early Diabetic Nephropathy

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ABSTRACT Objective: To observe the efficacy of valsartan combined with pioglitazone in the treatment of patients with early diabetic nephropathy and its impact on the renal function and oxidative stress. **Methods:** 90 patients with early diabetic nephropathy, from January 2010 to June 2012, were randomly divided into the observation group and control group, 45 cases in each group. The control group was treated by pioglitazone alone, while the observation group was given valsartan on the basis of control group. The urinary albumin excretion rate (UAER), β2-microglobulin (β2-MG), serum creatinine (SCr), reduced glutathione (GSH), malondialdehyde (MDA) and super oxide dismutase (SOD) were observed before and after treatment. **Results:** The total effective rate of observation group and control group were respectively 93.33%, 75.56%, which was significantly higher in the observation group (X^2=4.145, P=0.042). After treatment, the levels of UAER, β2-MG, SCr and MDA in both groups were significantly lower than those before treatment (P<0.01), which were significantly lower in the observation group than those of the control group (P<0.01). However, the levels of SOD and GSH significantly increased in both groups compared with those before treatment (P<0.01), which were significantly higher in the observation group than those of the control group (P<0.01). **Conclusion:** The treatment of valsartan combined with pioglitazone was more effective to the patients with early diabetic nephropathy than pioglitazone alone, which significantly improved the kidney function and relieved the oxidative stress.

Key words: Valsartan; Pioglitazone; Diabetic nephropathy; Oxidative stress; Efficacy

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糖尿病肾病是糖尿病患者的常见并发症之一,早期诊断和治疗糖尿病肾病是改善糖尿病患者预后的关键[1-4]。缬沙坦通过阻断肾素 - 血管紧张素 - 醛固酮系统(RAAS)的药物有效降低尿蛋白水平[5-7],起保护肾脏的作用,其降低蛋白的作用独立于降压作用,在临床上已经取得较好的疗效。吡格列酮为高度选择性和高效的二型受体 -γ(PPAR-γ)的激动剂,其主要功能是改善胰岛 β 细胞功能,降低机体的胰岛素抵抗,从而达到治疗糖尿病的作用[8,9]。临床研究表明吡格列酮降低糖尿病肾病患者的尿蛋白,保护肾功能,其机理可能与吡格列酮可以降低机体的骨桥蛋白有关[10],其确切的机理尚不清楚。我院采用缬沙坦联合吡格列酮治疗早期糖尿病肾病取得了良好的疗效,现报告如下。

1 临床资料与方法

1.1 临床资料

选取 2010 年 1 月 ~2012 年 6 月在我院就诊的早期糖尿病肾病患者 90 例,其中男 47 例,女 43 例,平均年龄 55.76±10.43(45~75)岁,平均病程 9.76± 2.87(4~19)年。纳入标准:均为 2 型糖尿病患者,符合早期糖尿病肾病诊断标准;均知情同意。

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排除标准:糖尿病合并其他严重的并发症;合并重要脏器如心肺肝脑等的损害;有高血压,冠心病,感染性疾病和肿瘤等慢性疾病;近期接受血管紧张素转化酶抑制剂(ACEI)或血管紧张素Ⅱ受体拮抗剂(ARB)治疗的患者。将患者按照随机数字法分为观察组和对照组,两组各 45 例,两组的年龄、性别、病程等一般资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 **方法**

1.2.1 **治疗方法** 两组均予以控制血糖和血压,调节血脂,抗感染、改善微循环,纠正水电解质紊乱和餐前 30min 口服吡格列酮,30mg/ 次,1 次 /d 的常规治疗。观察组在上述的基础上予以缬沙坦 80 mg 口服,1 次 /d,2 周为一个疗程。

1.2.2 **标本的保存** 治疗前和治疗后 2 周分别抽取空腹肘静脉血 3mL,注入普通塑料管内,1.8 mL 注入含 0.2 mL 3.8%枸橼酸钠的抗凝管内,标本采集后 1 h 内 3 000 r/min,离心 10 min,将血清或血浆提取后分别分装于 0.5 mL 的 EP 管内,-30℃ 保存,1 个月内检测。

1.2.3 **疗效评定标准** 显效:治疗疗程结束后,尿蛋白定量下降幅度>50%;有效:尿蛋白定量下降幅度在 20%～50% 之间;无效:下降幅度<20%。

1.2.4 **观察指标和检测方法** ①尿液指标:尿白蛋白排泄率(UAER)、尿 β2 微球蛋白(β2-MG)采用放免分析法,24 h 尿蛋白定量采用双缩脲法;②血生化指标:血肌酐(SCr)采用全自动生化分析仪测定,糖化血红蛋白采用微粒色谱法。还原型谷胱甘肽(GSH)测定采用二硫代硝基苯甲酸比色法(DNTB 法),丙二醛(MDA)测定采用硫代巴比妥酸(TBA)法。超氧化物歧化酶(SOD)活力测定采用黄嘌呤氧化酶法。

1.3 **统计学处理**

采用 SPSS19.0 软件,计量资料以均数± 标准差($\bar{X}$± S)表示,两组间比较采用 t 检验,治疗前后比较,采用配对 t 检验。计数资料采用率表示,两两比较采用 X^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 **两组临床疗效的比较**

从表 1 可知,观察组 45 例患者中,30 例显效,12 例有效,治疗总有效率为 93.33%,而对照组 45 例患者中,21 例显效,13 例有效,治疗总有效率为 75.56%,观察组显著高于对照组(X^2=4.145,P=0.042)。

表 1 两组治疗疗效的比较(例)

Table 1 Comparison of the clinical effect rate between the two groups after treatment (cases)

Group	Cases	Excellence	Good	Invalid	Total efficiency(%)
Observation group	45	30	12	3	93.33
Control group	45	21	13	11	75.56

2.2 **两组治疗前后 UAER、β_2-MG 和 SCr 水平的比较**

从表 2 可知,治疗后,两组 UAER、β2-MG 和 SCr 水平均较治疗前明显降低(P<0.01),且观察组较对照组更低(P<0.01)。

表 2 两组治疗前后 UAER、β2-MG 和 SCr 水平的比较($\bar{x}$± s)

Table 2 Comparison of the serum levels of UAER, β2-MG and SCr between two groups before and after treatment($\bar{x}$± s)

Group	Cases	UAER(μg/mL)		β2-MG(mmol/mL)		SCr(μmol/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	45	278.32± 29.65	135.65± 19.64	34.26± 9.24	23.65± 7.68	136.57± 9.67	115.67± 8.64
Control group	45	271.35± 35.24	223.84± 24.35	33.94± 8.51	29.64± 6.64	134.94± 6.97	124.67± 9.37
t		1.015	18.911	0.171	3.958	0.917	4.737
p		0.313	0.000	0.865	0.000	0.362	0.000

注:与治疗前比较,P<0.05,**P<0.01。

Note: Compared with that before treatment, *P<0.05, **P<0.01.

表 3 两组治疗前后 MDA、SOD 和 GSH 水平的比较($\bar{x}$ ± s)

Table 3 Comparison of the serum levels of MDA, SOD and GSH between two groups before and after treatment($\bar{x}$ ± s)

Group	Cases	MDA(nmol/mL)		SOD(mg/L)		GSH(mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	45	7.83± 1.38	5.37± 1.82	55.27± 12.73	87.43± 12.93	178.32± 26.32	220.73± 32.83
Control group	45	7.79± 1.26	4.19± 1.68	56.04± 11.35	75.32± 10.47	175.22± 28.81	198.46± 29.49
t		0.144	3.196	0.303	4.883	0.533	3.385
p		0.886	0.002	0.763	0.000	0.595	0.001

注:与治疗前比较,P<0.05,**P<0.01。

Note: Compared with that before treatment, *P<0.05, **P<0.01.

2.3 两组治疗前后 MDA、SOD 和 GSH 水平的比较

治疗后，两组 MDA 水平均较治疗前明显降低(P<0.01)，而 SOD 和 GSH 水平明显升高(P<0.01)，且观察组 MDA 水平较对照更低，SOD 和 GSH 水平较对照组更高 (P<0.01)。

3 讨论

糖尿病肾病重要的病理生理基础为各种致病因素导致血管紧张素 II(AT)分泌增多，引起机体的水钠潴留，肾脏系膜细胞的增生肥大，使肾脏细胞外基质增厚，肾小球滤过膜的通透性增高，最终导致蛋白尿的产生[11]。

吡格列酮为高度选择性和高效的二型受体 -γ (PPAR-γ)的激动剂，其主要功能是改善胰岛 β 细胞功能，降低机体的胰岛素抵抗，增加机体对胰岛素的敏感性，从而降低机体的血糖水平[12, 13]。同时，其可以促进肾小球基底膜蛋白多糖的合成，可以减少肾小球对蛋白的滤过作用，抑制肾小球基底膜和系膜的增生[14, 15]。缬沙坦可以选择性地作用于 AT-1 受体，阻断血管紧张素Ⅱ与 AT-1 受体的结合，从而抑制血管收缩和醛固酮的释放，产生降压作用[16, 17]。此外，缬沙坦对于阻断肾小球毛细血管的膜压升高、蛋白尿的形成具有良好的效果，可避免肾小球硬化和间质纤维化的发生[18]。本组研究表明吡格列酮联合缬沙坦治疗早期糖尿病肾病的总有效率为 93.33%，显著高于吡格列酮单一治疗，且患者的肾功能显著改善。

现有研究表明，糖尿病肾病的发病与氧化应激有关，糖尿病肾病患者的抗氧化能力下降，机体处于氧化应激状态，大量的葡萄糖及其代谢产物被氧化，产生大量的自由基，使肾小球的基底膜脂质过氧化并受损，肾小球的滤过功能发生改变[19]。由于氧化应激状体导致 Na^+-K^+-ATP 酶活性下降，导致肾小球重吸收功能发生障碍，最终导致糖尿病肾病的发生[20, 21]。本组研究表明，治疗后，吡格列酮联合缬沙坦治疗早期糖尿病肾病患者的 MDA 水平较单用吡格列酮明显降低，而 SOD 和 GSH 水平明显升高。这可能是因为缬沙坦联合吡格列酮治疗可以促进机体 SOD 和 GSH 的增加，而 MDA 水平明显下降，使机体对氧自由基的清除增加，降低机体的氧化能力，缓解糖尿病肾病的氧化应激状态，改善肾小球血管基底膜，系膜细胞和细胞外基质，促进肾小球的滤过，增加对蛋白的重吸收，从而达到缓解糖尿病肾病的作用。

总之，缬沙坦联合吡格列酮治疗早期糖尿病肾病的疗效较单用吡格列酮更好，具有更好的降低尿白蛋白和提高机体的 SOD 及 GSH 水平，具有显著改善患者的肾功能和降低氧化应激作用。

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