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硫辛酸联合缬沙坦治疗早期糖尿病肾病的疗效及安全性分析

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摘要 目的:探讨硫辛酸联合缬沙坦治疗早期糖尿病肾病的疗效及安全性。**方法:**选取了 80 例糖尿病肾病患者,按随机数字表法分为两组,对照组(39 例)给予缬沙坦治疗,观察组(41 例)给予缬沙坦和硫辛酸治疗。通过观察并记录患者治疗前后超敏 C 反应蛋白(hs-CRP),尿蛋白排泄率(UAER),尿 β_2 微球蛋白(β_2 -MG),血清丙二醛(MDA),总抗氧化能力(T-AOC),超氧化物歧化酶(SOD)水平及治疗期间不良反应情况,评价硫辛酸联合缬沙坦治疗早期糖尿病肾病的疗效及安全性。**结果:**治疗前两组 hs-CRP,UAER, β_2 -MG 差异无统计学意义($P>0.05$),经 2 个疗程药物治疗后两组各指标均明显降低。使用硫辛酸联合缬沙坦治疗的患者,治疗后上述指标降幅更明显($P<0.05$),治疗前,两组 SOD、MDA、T-AOC 水平差异无统计学意义($P>0.05$),治疗后两组 SOD、T-AOC 水平均显著增加,MDA 水平显著降低($P<0.05$)。组间比较,观察组 SOD、T-AOC 水平高于对照组,MDA 水平低于对照组($P<0.05$);治疗期间,两组不良反应率无统计学意义($P>0.05$)。**结论:**硫辛酸联合缬沙坦能显著减少糖尿病肾病患者尿蛋白水平,改善机体氧化应激状态,用药安全,值得临床推广使用。

关键词:硫辛酸;缬沙坦;糖尿病肾病;氧化应激;尿蛋白

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Analysis of Efficacy and Safety of Lipoic Acid and Valsartan in the Treatment of the Early Diabetic Nephropathy

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ABSTRACT Objective: To discuss the efficacy and safety of lipoic acid and valsartan in the treatment of the early diabetic nephropathy. **Methods:** 80 patients with diabetic nephropathy were randomly divided into two groups. The patients in control group (39 cases) were given valsartan, and the patients in observation group (41 cases) were given valsartan and lipoic acid. The efficacy and safety of lipoic acid and valsartan in the treatment of the early diabetic nephropathy was evaluated by UAER, hs-CRP, β_2 -MG, SOD, T-AOC, MDA levels and the incidence of adverse reactions were detected during treatment. **Results:** Before treatment, there were no statistical significance in the level of hs-CRP, UAER, β_2 -MG between two groups ($P>0.05$). After 2 courses of treatment, the indexes were decreased in two groups ($P<0.05$). After treating with lipoic acid and valsartan, the indexes were decreased obviously ($P<0.05$). Before treatment, there were no statistical significance in the level of SOD, MDA, T-AOC between two groups ($P>0.05$). After treatment, the SOD, T-AOC level was increased in two groups ($P<0.05$), and the MDA level was decreased in two groups ($P<0.05$). The SOD and T-AOC level of observation group was higher than that of the control group and the MDA level of observation group was lower than that of the control group ($P<0.05$). There were no statistical significance in incidence of adverse reactions between two groups ($P>0.05$). **Conclusions:** The combination of lipoic acid and valsartan can significantly reduce the level of urinary protein and improve the oxidative stress state in patients with diabetic nephropathy with good safety, worthy of clinical application.

Key words: Lipoic acid; Valsartan; Diabetic nephropathy; Oxidative stress; Urinary protein

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前言

糖尿病肾病是内分泌科常见疾病,患者机体代谢复杂且紊乱,若发展到肾脏末期,治疗困难,严重影响着患者的生活质量

[1]。临床治疗糖尿病肾病以改善患者氧化应激状态和降低尿蛋白为主,可起到延缓肾功能衰竭,达到保护肾脏的作用[2]。硫辛酸具有较强的氧化能力,可以调节机体抗氧化能力,缬沙坦具有保护肾脏,减少尿蛋白的作用[3],两药物联用,可起到协同作用。既往研究中,仅针对糖尿病肾病患者氧化应激或尿蛋白水平某一方面进行检测,未能全面评估影响肾功能的指标[4,5]。为此我院自 2011 年 3 月-2016 年 3 月选取了 80 例糖尿病肾病患者,观测报道如下。

1 资料与方法

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1.1 病例资料

选取糖尿病肾病患者 80 例, 年限 2011 年 3 月 -2016 年 3 月, 均为我院住院治疗患者, 入组标准: ① 入组患者均符合糖尿病肾病的诊断标准^[9]; ② 空腹血糖 6-8 mmol/L, 餐后 2 h 血糖 10-12 mmol/L; ③ 经本院伦理委员会同意, 治疗前每位患者均签署书面知情书。排除标准: 血管及神经并发症、精神类疾病、急慢性感染患者。按随机数字表法分为两组, 对照组患者 39 例, 给予口服缬沙坦片, 其中, 男 26 例, 女 13 例, 年龄 45.78±12.28(30-64)岁, 观察组患者 41 例, 给予缬沙坦和硫辛酸, 男 24 例, 女 17 例, 年龄 46.53±13.35(31-62)岁。两组病例资料相比, 差异没有统计学意义(P>0.05)。

1.2 给药方案

对照组: 口服缬沙坦 (鲁南贝特制药有限公司, 规格: 80 mg, 批准文号: 国药准字 H20090092), 80 mg/次, 1 次/d。观察组: 在对照组治疗基础之上, 给予硫辛酸注射液(重庆药友制药有限责任公司, 规格: 6 mL:0.15 g, 批准文号: 国药准字 H20066706), 600 mg/d, 0.9% 250 mL 氯化钠注射液静脉滴注治疗, 治疗 7 d 为 1 个疗程, 共计 2 个疗程。

1.3 观察指标

UAER, β2-MG: 采用化学发光法测定患者治疗前后 UAER, β2-MG 水平, 所用仪器为化学发光免疫分析仪(西门子医学诊断产品有限公司, 型号: IMMULITE 2000) 及其配套的

UAER, 尿 β2 微球蛋白(β2-MG)检测试剂盒。

hs-CRP: 取患者肘静脉血 5 mL, 1500 r/min 离心 5 min 后分离血清, 采用全自动生化分析仪(东芝医疗系统有限公司, 型号: TBA-2000FR)测定。

SOD, T-AOC, MDA: SOD 采用羟胺法测定, T-AOC, MDA 采用比色法测定, 所用仪器为紫外可见分光光度计(上海天美, 型号: UV1000); SOD, T-AOC, MDA 测定所需配套试剂均由上海酶联生物科技有限公司提供。

不良反应: 治疗期间, 观察并记录不良反应事件, 包括头痛、恶心、乏力、呼吸困难等症状。

1.4 统计方法

采用 SPSS 17.0 统计软件分析, 数据以 $\bar{x} \pm s$ 表示, 组内治疗前与治疗后相比采用配对 t 检验, 组间比较采用两独立样本 t 检验, 计数资料采用秩和或卡方检验, 以 P<0.05 为差异有统计学意义。

2 结果

2.1 hs-CRP, UEAR, β2-MG 比较

治疗前两组 hs-CRP, UEAR, β2-MG 差异无统计学意义(P>0.05), 经 2 个疗程药物治疗后两组各指标均明显降低(P<0.05)。使用硫辛酸联合缬沙坦治疗的患者, 治疗后上述指标降幅更明显(P<0.05), 见表 1。

表 1 两组 hs-CRP, UEAR, β2-MG 对比 ($\bar{x} \pm s$)

Table 1 Comparison of hs-CRP, UEAR, β2-MG level between two groups ($\bar{x} \pm s$)

Groups		hs-CRP(mg/L)	UEAR(μg/min)	β2-MG(μg/d)
Observation group (n=41)	Before treatment	3.46±1.38	186.4±18.5	123.2±12.2
	After treatment	1.82±0.96 [*]	122.8±16.8 [*]	73.1±11.1 [*]
Control group (n=39)	Before treatment	3.36±1.97	187.1±17.9	124.1±13.6
	After treatment	2.26±1.14 [*]	156.7±17.6 [*]	95.4±14.1 [*]

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

2.2 氧化应激指标比较

治疗前, 两组 SOD, MDA, T-AOC 水平差异无统计学意义(P>0.05), 治疗后两组 SOD, T-AOC 水平均显著增加, MDA 水

平显著降低(P<0.05)。组间比较, 观察组 SOD, T-AOC 水平高于对照组, MDA 水平低于对照组(P<0.05), 见表 2。

表 2 两组氧化应激指标比较 ($\bar{x} \pm s$)

Table 2 Comparison of oxidative stress indicators between two groups ($\bar{x} \pm s$)

Groups	n	SOD(U/mL)	MDA(μmol/L)	T-AOC(U/mL)
Observation group (n=41)	Before treatment	81.1±9.1	4.91±0.36	7.14±1.36
	After treatment	92.4±11.5 [*]	4.16±0.34 [*]	8.86±1.73 [*]
Control group(n=39)	Before treatment	83.3±10.2	5.02±0.31	7.18±1.66
	After treatment	84.6±12.4 [*]	4.82±0.28 [*]	7.35±1.42 [*]

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

2.3 不良反应比较

治疗期间, 观察组 2 例头痛, 恶心 1 例, 乏力 1 例, 停药后症状自行缓解, 不良反应率 9.7%; 对照组出现 1 例头痛, 2 例

呼吸困难, 停药后症状缓解, 不良反应率 7.7%。两组不良反应率无统计学意义(P>0.05)。

3 讨论

糖尿病肾病是临床常见的一种糖尿病并发症,发病隐匿,病程长,影响肾功能^[7]。2型慢性糖尿病患者体内糖代谢紊乱,体内血糖长期处于高水平状态,高血糖可激活肾素-血管紧张素-醛固酮系统,引起肾小球高灌注和高滤过以及肾小球基底膜增厚和通透性增加^[8-10]。高血糖还能破坏体内抗氧化系统,导致过多超氧化物产生,影响肾功能。目前,糖尿病肾病的治疗策略主要是在严格控制血糖和血压的基础上对其发病机制进行干预^[11,12]。

缬沙坦属于血管紧张素Ⅱ受体抑制剂,对Ⅰ型受体具有高度选择性,能抑制肾小球系膜细胞增生、肥大,减弱胶原蛋白合成、纤维细胞增生,防止肾小球进一步硬化,从而起到肾脏保护作用^[13]。然而治疗糖尿病肾病的关键是要控制机体微量尿蛋白,除了在饮食方面控制外,服用缬沙坦也能有效降低机体尿蛋白^[14]。另一方面,消除体内过多的超氧化物也能显著减轻糖尿病肾病症状, α -硫辛酸是一种强氧化剂,人体可自行生物合成。糖尿病患者宜适量补充硫辛酸,以提高体内抗氧化能力,抑制脂质过氧化,减少糖尿病肾病及神经病变的发生率^[15]。

hs-CRP与肾脏早期受损有关, β 2-MG是人体白细胞抗原分子的一个 β 轻链,对诊断肾功能衰竭具有重要的临床意义,肾脏受损时,患者体内 β 2-MG水平急速升高^[16]。UEAR与尿蛋白有关,糖尿病肾病患者UEAR常处于高水平状态^[17]。本研究中,治疗前两组hs-CRP、UEAR、 β 2-MG差异无统计学意义,治疗后两组hs-CRP、UEAR、 β 2-MG等指标均显著降低($P<0.05$)且观察组上述指标显著低于对照组($P<0.05$)。说明硫辛酸联合缬沙坦能显著治疗早期糖尿病肾病,减少蛋白尿,延缓肾功能衰竭。段纬喆等^[18]将硫辛酸与替米沙坦联合用于早期2型糖尿病肾病的治疗,可使患者体内UEAR及 β 2-MG大幅下降,与本研究结果一致。氧化应激方面,本研究选取SOD、T-AOC、MDA作为观察指标。当机体氧化应激水平升高时,产生的自由基损害糖类、蛋白质、脂质代谢,使其发生过氧化,MDA作为脂质的过氧化中间产物,可使生物大分子交联成异常的大分子而破坏其结构和功能,测量其量可以反映肾脏细胞的损伤程度^[19]。T-AOC可以反映自由基产生程度,T-AOC水平降低时,机体炎症、肿瘤、糖尿病等疾病发病风险增加^[20]。SOD是存在于机体中的一种金属酶,可与体内超氧自由基发生歧化反应,降低机体氧化应激水平。SOD水平越高,说明机体清除氧自由基的能力越强^[21]。疗前,两组SOD、MDA、T-AOC水平差异无统计学意义($P>0.05$),治疗后两组SOD、T-AOC水平均显著增加,MDA水平显著降低($P<0.05$)。组间比较,观察组SOD、T-AOC水平高于对照组,MDA水平低于对照组($P<0.05$)。提示硫辛酸联合缬沙坦联用可以发挥协同作用,改善患者氧化应激状态,延缓肾脏损伤。林杏娟等^[22]研究发现采用硫辛酸联合缬沙坦治疗糖尿病肾病,治疗后患者SOD、T-AOC水平升高,MDA水平降低。与本研究结果相一致。进一步研究发现,两组不良反应率无统计学意义($P>0.05$),说明联合用药不会增加不良反应风险。

硫辛酸联合缬沙坦能显著减少糖尿病肾病患者尿蛋白水平,改善机体氧化应激状态,用药安全,值得临床推广使用。

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