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普罗布考联合阿魏酸哌嗪治疗早期糖尿病肾病的效果及对血清 Cys-C、hs-CRP、TGF- β 1、 β 2-MG 水平的影响 *

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摘要 目的:探究阿魏酸哌嗪和普罗布考联合治疗早期糖尿病肾病(DN)的临床效果及对血清胱抑素 C(Cys-C)、超敏 C 反应蛋白(hs-CRP)、转化生长因子- β 1(TGF- β 1)、 β 2-微球蛋白(β 2-MG)水平的影响。**方法:**选取 2016 年 2 月~2017 年 2 月我院收治的 104 例早期 DN 患者,采用随机数字表法均分为两组。对照组给予阿魏酸哌嗪治疗,观察组给予普罗布考和阿魏酸哌嗪联合治疗。比较两组治疗后临床疗效,治疗前后血清 Cys-C、hs-CRP、TGF- β 1 水平、尿 β 2-MG 水平的变化及不良反应的发生情况。**结果:**治疗 12 周后,观察组临床总有效率为 92.3%,较对照组明显上升($P<0.05$)。与治疗前对比,两组治疗 12 周后血清 Cys-C、hs-CRP、TGF- β 1、尿 β 2-MG 水平均显著降低($P<0.01$),且观察组以上指标均显著低于对照组($P<0.01$)。两组不良反应发生率相比差异无统计学意义($P>0.05$)。**结论:**阿魏酸哌嗪和普罗布考联合治疗早期糖尿病肾病的临床疗效显著优于阿魏酸哌嗪单药治疗,且安全性较高,可能与其有效降低患者血清 Cys-C、hs-CRP、TGF- β 1 和尿 β 2-MG 水平有关。

关键词:普罗布考;阿魏酸哌嗪;早期糖尿病肾病;临床疗效

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Clinical Effect of Probucol Combined with Piperazine Ferulate on Early Diabetic Nephropathy and Its Influence on Levels of Cys-C, hs-CRP, TGF- β 1 and β 2-MG*

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ABSTRACT Objective: To investigate the clinical effect of probucol combined with piperazine ferulate on early diabetic nephropathy (DN) and its influence on levels of serum cystatin-C (Cys-C), high sensitivity c-reactive protein (hs-CRP), transforming growth factor- β 1 (TGF- β 1) and urine β 2-microglobulin (β 2-MG). **Methods:** 104 cases of patients with early DN admitted in our hospital from February 2016 to February 2017 were selected and evenly divided into two groups on a random basis. The control group was treated with piperazine ferulate, while the observation group probucol in combination with piperazine ferulate. The clinical effect, changes of serum Cys-C, hs-CRP, TGF- β 1 and urine β 2-MG levels before and after treatment as well as the incidence of adverse reactions were compared between the two groups. **Results:** The overall effective rate of the observation group at 12 weeks after treatment was 92.3%, which was higher as compared with that of the control group ($P<0.05$). The levels of serum Cys-C, hs-CRP, TGF- β 1 and urine β 2-MG levels of both groups at 12 weeks after treatment were significantly decreased as compared with those before treatment, which were obviously lower in the observation group than those of the control group ($P<0.01$). No significant difference in the incidence of adverse reaction was found between the two groups ($P>0.05$). **Conclusion:** Probucol combined with piperazine ferulate was more effective than piperazine ferulate alone in treating early DN with high safety, which may be correlated with the decrease of the serum Cys-C, hs-CRP, TGF- β 1 and urine β 2-MG levels.

Key words: Probucol; Piperazine ferulate; Early diabetic nephropathy; Clinical effect

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前言

糖尿病肾病 (diabetic nephropathy, DN) 是糖尿病(diabetes mellitus, DM)常见的微血管并发症,是 DM 患者死亡的重要原

因之一。DN 起病较为隐匿,且进展缓慢,在其早期无特异性临床表现,但若临床出现持续性尿蛋白,则病情不可逆转,肾功能发生进行性恶化,造成 DM 患者死亡^[1]。研究显示^[2-3]多种细胞因子参与 DN 的发生,其中血清胱抑素 C(cystatin c, Cys-C)、超敏

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C 反应蛋白(hypersensitivity C reactive protein, hs-CRP)、转换生长因子- $\beta 1$ (transforming growth factor- $\beta 1$, TGF- $\beta 1$)、尿 $\beta 2$ -微球蛋白($\beta 2$ -microglobulin, $\beta 2$ -MG)可能参与了 DN 的病理过程,且与患者病情的严重程度密切相关,均可作为临床治疗与评估预后的重要辅助诊断指标。阿魏酸哌嗪具有扩张微血管、抗血小板聚集的功效,可抑制系膜外基质增生以延缓肾小球硬化和保护肾脏功能的作用^[4]。普罗布考具有抗氧化、抗炎、降低尿蛋白的作用^[5]。本研究探讨阿魏酸哌嗪和普罗布考的临床效果及对血清 Cys-C、hs-CRP、TGF- $\beta 1$ 、尿 $\beta 2$ -MG 水平的影响,现报道如下。

1 资料与方法

1.1 一般资料

选取 2016 年 2 月~2017 年 2 月我院收治的 104 例早期 DN 患者,纳入标准:①符合《中国 2 型糖尿病防治指南》中制定的 DM 诊断标准^[6];②符合《慢性肾脏病临床实践指南》中制定的 DN 诊断标准,且 Mogensen 分期为 III 期^[7];③年龄 18~60 岁;④自愿参加本研究,签署知情同意书,并积极配合有关检查和治疗方案;⑤临床资料完整。排除标准:①由各种原发性肾脏疾病所致尿蛋白者;②合并严重肝肾功能不全、免疫系统、造血系统、心脑血管系统等原发性疾病者;③狼疮肾炎、紫癜肾、高血压肾损伤等继发性肾病者;④近期因使用肾毒性药物而发生尿蛋白者;⑤过敏体质或对本研究使用药物过敏者;⑥哺乳或妊娠期妇女;⑦依从性较差或精神疾病患者。

采用随机数字表法均分为两组。观察组 52 例,男 28 例,女 24 例;年龄(55.4 ± 7.5)岁;DM 病程(7.3 ± 2.6)年;DN 病程(2.1 ± 0.8)年;合并高血压 13 例。对照组 52 例,男 29 例,女 23 例;年龄(55.2 ± 7.3)岁;DM 病程(7.4 ± 2.5)年;DN 病程(2.2 ± 0.9)年;合并高血压 14 例。两组基线资料比较,差异均不显著($P > 0.05$),临床可比。本研究经我院医学伦理委员会审查同意。

1.2 治疗方法

两组患者均给予一致的常规治疗措施,具体包括:①给予患者糖尿病知识教育和用药指导;②控制饮食,给予低盐、优质低蛋白食物,根据血糖水平制定糖尿病饮食方案;③指导患者进行适量运动,注意循序渐进,以有氧运动为主;④口服胰岛素等降糖药物,使餐后 2 h 血糖 < 11.1 mmol/L,空腹血糖 < 6.1 mmol/L;⑤对于合并高血压患者给予硝苯地平控释片以控制血压在正常水平。对照组:在上述基础上,给予阿魏酸哌嗪片(湖

南千金湘江药业,国药准字 H43021825,规格:50 mg/片)治疗;具体为餐后 0.5 h 口服,4 片/次,3 次/d。观察组:在对照组基础上,加用普罗布考片(齐鲁制药,国药准字 H10980054,规格:125 mg/片)治疗,具体为早晚餐后口服,4 片/次,2 次/d,两组均以 12 周为疗程。

1.3 观察指标

1.3.1 临床疗效 判定标准^[8]:①显效:症状/体征完全消失,肾功能恢复正常,尿蛋白排泄率、糖化血红蛋白、血糖恢复至正常水平,24 h 尿蛋白定量降低 50%以上;②有效:症状/体征在一定程度上有所好转,肾功能恢复正常,尿蛋白排泄率、糖化血红蛋白、血糖有所下降但未恢复至正常水平,24 h 尿蛋白定量降低 50%以下;③无效:症状/体征无好转,各项指标均无改善。注:总有效率 = $\times 100\%$ 。

1.3.2 血清 Cys-C、hs-CRP、TGF- $\beta 1$ 水平 ①所有患者均于治疗前与治疗中各采集 5 mL/次的静脉血,离心分离血清,并保存于 -80°C 冰箱中待检;②仪器采全自动生化分析仪(日立,型号 7600-020);③Cys-C、hs-CRP 均采用免疫比浊法测定,TGF- $\beta 1$ 采用化学发光法测定,试剂盒均由上海德赛诊断系统有限公司提供;④严格按照各试剂盒配套说明书进行以上指标的检测。

1.3.3 尿 $\beta 2$ -MG 水平 ①所有患者均于治疗前与治疗中各采集晨起清洁中段尿,离心分离后取上清液,并保存于 -80°C 冰箱中待检;②尿 $\beta 2$ -MG 检测采用固相夹心酶联免疫吸附法;③试剂盒均由美国 R&D 公司提供;④严格按照各试剂盒配套说明书进行以上指标的检测。

1.3.4 不良反应 所有患者均在治疗前与治疗后进行血常规、心电图、血生化、尿常规等常规检查,治疗期间对每位患者由药物引起的不良反应均进行详细记录。

1.4 统计学分析

运用统计软件 SPSS19.0 分析处理数据,计量资料以($\bar{x} \pm s$)表示,运用 t 检验,计数资料以(%)表示,采取 χ^2 检验,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗 12 周后,观察组临床疗效总有效率为 92.3%(48/52),较对照组明显上升[76.9%(40/52), $P < 0.05$],见表 1。

表 1 两组临床疗效的比较

Table 1 Comparison of the clinical effect between two groups

Groups	n	Excellent	Effective	Invalid	Total effective rate (%)
Observation group	52	21	27	4	92.3
Control group	52	17	23	12	76.9
P					0.030

2.2 两组治疗前后血清 Cys-C、hs-CRP 水平的比较

与治疗前对比,两组治疗 12 周后血清 Cys-C、hs-CRP 均显

著降低($P < 0.01$),且观察组以上指标降低程度更显著($P < 0.01$),见表 2。

表 2 两组治疗前后血清 Cys-C、hs-CRP 水平的比较($\bar{x} \pm s$, mg/L)Table 2 Comparison of the serum Cys-C and hs-CRP levels between two groups before and after treatment($\bar{x} \pm s$, mg/L)

Groups	n	Cys-C			hs-CRP		
		Before treatment	After treatment	P	Before treatment	After treatment	P
Observation group	52	1.93± 0.54	0.79± 0.33	0.000	6.57± 0.95	2.26± 0.45	0.000
Control group	52	1.96± 0.57	1.42± 0.42	0.000	6.61± 0.98	4.20± 0.67	0.000
P		0.783	0.000		0.833	0.000	

2.3 两组治疗前后血清 TGF- β 1、尿 β 2-MG 水平的比较

与治疗前对比,两组治疗 12 周后血清 TGF- β 1、尿 β 2-MG

水平均显著下降 ($P < 0.01$), 且观察组以上指标下降更为显著 ($P < 0.01$), 见表 3。

表 3 两组治疗前后血清 TGF- β 1、尿 β 2-MG 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum TGF- β 1 and urine β 2-MG levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	n	TGF- β 1 (ng/mL)			β 2-MG (μ g/L)		
		Before treatment	After treatment	P	Before treatment	After treatment	P
Observation group	52	56.4± 8.3	26.5± 3.5	0.000	65.2± 7.4	30.2± 6.6	0.000
Control group	52	57.2± 8.5	40.2± 5.1	0.000	65.3± 7.6	45.6± 7.2	0.000
P		0.627	0.000		0.946	0.000	

2.4 两组不良反应发生情况的比较

两组治疗由药物所致的不良反应如下:观察组出现 2 例胃肠道异常,1 例咳嗽。对照组出现 2 例转氨酶异常,2 例咳嗽。两组以上症状均较轻微,经对症处理后便可好转,且均未见严重事件。观察组不良反应率为 5.8%(3/52)与对照组【7.7%(4/52)】比较差异无统计学意义($P = 0.696$)。

3 讨论

DN 为 DM 主要微血管并发症,是慢性肾衰竭的主要原因之一,DM 患者血液多呈现高凝、高聚状态,对机体内微循环产生严重影响,阻止微血管内血液物质交换,进而损伤血管壁,形成微血管并发症。据研究数据显示,25%~45%DM 患者会发展到 DN 阶段,其发病机制尚未完全阐明,目前认为其发生、发展与血流动力学异常、血脂代谢紊乱、糖代谢异常、细胞与生长因子、遗传等多重因素相关^[9]。长时间的代谢紊乱致使肾小球基底膜增厚、肾小球高滤过、肾脏肥大等,进而发展为肾小球硬化、细胞基质积聚,损失毛细血管内壁,致使肾功能发生衰竭^[10]。研究表明^[11,12]在 DN 病理过程中,慢性缺氧、高糖、蛋白尿等作用下,机体内多种细胞和生长因子参与炎症反应,促进细胞外沉积,加速间质纤维化,造成肾小管上皮细胞发生结构和功能损伤。故 hs-CRP、TGF- β 1、Cys-C 等多种细胞因子为近年来研究的热点,多种细胞因子在血流动力学、血糖、血管活性因子等多种因素的调控下,相互作用,形成 DN 病理过程细胞因子网络。早期 DN 临床症状并不明显,主要表现为微量白蛋白尿,病情进一步发展可致持续性蛋白尿、进行性肾功能降低,最终导致终末期肾病的发生^[13]。因而,对于早期 DN 应及时采取治疗措施,延缓 DN 病情进一步恶化和发展。

阿魏酸哌嗪为中药川穹提取物,临床实验显示其可有效减轻肾组织损伤,加速其修复过程,其作用机制主要在于^[14]:①抑

制胆固醇的合成,清除机体内自由基,促进肾组织损伤的修复;

②扩张微血管,缓解血液高凝、高聚状态;③抑制血小板聚集,改善肾脏血液循环;④改善肾小球高滤过作用,减轻对肾脏的损伤。另有研究发现^[15,16],普罗布考具有抗炎、抗氧化、抗衰老等多种作用,可通过多种途径保护 DM 患者肾脏,其作用机制在于分子中酚羟基易被氧化而发生断裂并与氧离子结合后形成酚氧基,可有效降低血浆中氧自由基浓度,发挥抗氧化作用。同时普罗布考可抑制炎症因子的表达,调节血脂、改善机体氧化应激状态,缓解病情^[17]。故本研究采用阿魏酸哌嗪和普罗布考联合用药方案治疗早期 DN。本研究结果显示:与采取单一阿魏酸哌嗪片治疗的对照组(76.9%)相比,加用普罗布考治疗的观察组治疗后总有效率明显升高,达 92.3%,这与耿毓汕的研究结果一致^[18],提示早期 DN 患者运用阿魏酸哌嗪片和普罗布考片联合治疗更有利于减轻或消除患者的临床症状体征、控制病情活动,促使各项指标恢复至正常水平,提升治疗效果。

hs-CRP 是一种非糖基化聚合蛋白,多由炎症分子刺激肝脏细胞合成,是反映血管炎症反应最为敏感的急性时相蛋白之一。此外,hs-CRP 具有免疫调节和免疫特异性识别功能,可有效激活机体补体系统,释放炎症介质,促进吞噬细胞反应和细胞间黏附,可作为反映机体炎症严重程度的重要指标,具有高度的敏感性和可靠性。研究显示^[19]hs-CRP 与肾脏损伤程度呈显著正相关,DN 患者因其胰岛素敏感性降低,肝脏抑制 hs-CRP 合成作用减弱,表现为血清 hs-CRP 水平的升高。Cys-C 是一种半胱氨酸蛋白酶抑制剂,广泛存在于体液和各种组织的有核细胞中,由于肾脏不分泌 Cys-C 且其是清除 Cys-C 的唯一器官,血液中 Cys-C 水平由肾小球滤过决定,且不易受其他因素的影响,因而 Cys-C 是反映肾小球滤过率的有效指标,当肾脏功能不全时则表现为 Cys-C 水平的升高^[20]。有研究显示^[21]血清 Cys-C 水平与肾脏损害程度密切相关,当肾脏存在轻微病变

时,血清 Cys-C 水平已升高且随肾脏损害程度的加重而升高。因而,血清 Cys-C 水平对于 DN 早期诊断具有重要意义,可作为其评价的有效指标。本研究中,观察组治疗后血清中 hs-CRP、Cys-C 水平均显著低于对照组;提示阿魏酸哌嗪片和普罗布考片联合治疗早期 DN 能显著降低患者血清中 hs-CRP、Cys-C 水平,减少炎症反应的发生,改善肾功能,这可能与普罗布考较强的抗炎作用有关,也是该联合方案疗效提高的重要机制之一。

TGF- β 1 是一种具有多种生物学效应的细胞因子,其最为重要的功能是调节细胞增生,对细胞增殖、分化、迁移、粘附等均具有十分显著的作用。在正常水平下,其可调节修复损伤的组织,在过量水平下,其可致慢性纤维化。另外,TGF- β 1 还可通过自身分泌作用,增强其自身生物活性,在 DN 病理过程中起着十分重要的作用。研究发现^[2],DN 患者血清 TGF- β 1 水平显著高于正常人群。在高血糖状态下,多种微循环障碍和生化异常共同参与 DN 的病理过程,包括氧化应激反应、蛋白激酶 C 的激活等,均可通过调节 TGF- β 1 水平导致肾小球硬化。在肾小球病变较轻时,小管萎缩、间质单核细胞浸润、间质纤维化均已存在。肾脏的成纤维反应与巨噬细胞、成纤维细胞及巨噬细胞合成的 TGF- β 1 有关。尿 β 2-MG 为反映肾小管损伤的特异性蛋白,是肾小管损伤标志物。已有研究证实^[23]在各种肾小球疾病中,肾小管间质病变是判断肾功能下降的重要指标。在高糖状态下肾小管发生损伤,使蛋白质等大分子过滤至肾小管,降低能量供应,促使溶酶体破裂,且产生特定成分直接损伤肾小管细胞,使其上皮细胞发生间质纤维化,增加尿 β 2-MG 表达水平^[24,25]。本研究中,观察组治疗后血清中 TGF- β 1、尿 β 2-MG 水平均显著低于对照组;提示该联合用药方案治疗早期 DN 能显著降低患者血清中 TGF- β 1、尿 β 2-MG 水平,改善肾脏间质损伤,降低尿蛋白,对肾脏起到较好的保护作用,两种药物联用具有较好的协同增效作用。同时,本研究中治疗期间两组不良反应率均较低且未见严重事件,可见在早期 DN 治疗中应用阿魏酸哌嗪片和普罗布考片联合治疗安全可靠。

综上所述,与单一用药阿魏酸哌嗪相比,早期糖尿病肾病应用阿魏酸哌嗪片和普罗布考片联合治疗具有良好协同增效作用,更能迅速缓解或消除患者临床症状体征,抑制炎症反应发生,改善肾脏间质损伤,降低尿蛋白,疗效更为显著。但对于阿魏酸哌嗪片和普罗布考联合治疗早期糖尿病肾病的具体作用机制及长期疗效与安全性,仍有待更多多中心、大样本、大规模的长期研究加以研究和论证。

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