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普罗布考联合胰激肽原酶对老年糖尿病周围神经病变患者氧化应激反应及血清 NSE 水平的影响 *

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摘要 目的:探讨普罗布考联合胰激肽原酶对老年糖尿病周围神经病变患者氧化应激反应及血清神经元特异性烯醇化酶(NSE)水平的影响。**方法:**选择2015年8月至2017年8月我院接诊的94例老年糖尿病周围神经病变患者作为本研究对象,通过随机数表法将其分为观察组(n=47)和对照组(n=47)。对照组在常规治疗基础上给予胰激肽原酶治疗,观察组在对照组基础上联合普罗布考治疗,两组均连续治疗12周。比较两组治疗后的临床疗效、治疗前后运动传导速度(MNCV)、感觉传导速度(SNCV)、多伦多临床评分系统(TCSS)评分、血清丙二醛(MDA)、超氧化物歧化酶(SOD)、过氧化氢酶(CAT)、谷胱甘肽过氧化物酶(GSH-Px)及NSE水平的变化和不良反应的发生情况。**结果:**治疗后,观察组临床疗效总有效率为93.62%(44/47),明显高于对照组[70.21%(33/47)]($P < 0.05$);两组正中神经、腓总神经MNCV、SNCV较治疗前均显著延长($P < 0.05$),且观察组正中神经、腓总神经MNCV、SNCV均明显高于对照组($P < 0.05$);两组TCSS评分各内容和总分、血清MDA、NSE水平较治疗前均显著降低($P < 0.05$),且观察组TCSS评分中症状评分、反射评分、感觉评分和总分及、血清MDA、NSE水平均明显低于对照组($P < 0.05$);两组血清超氧化物歧化酶(SOD)、过氧化氢酶(CAT)、谷胱甘肽过氧化物酶(GSH-Px)水平较治疗前均显著升高($P < 0.05$),且观察组血清SOD、CAT、GSH-Px水平均明显比对照组高($P < 0.05$)。两组治疗期间不良反应总发生率分别为10.64%(5/47)、4.26%(2/47),组间比较差异无统计学意义($P > 0.05$)。**结论:**普罗布考联合胰激肽原酶治疗老年糖尿病周围神经病变患者的效果显著优于单用胰激肽原酶治疗,可更有效改善神经病变程度,其机制可能和缓解氧化应激反应、降低血清NSE水平有关。

关键词:老年;糖尿病周围神经病变;普罗布考;胰激肽原酶;氧化应激反应;神经元特异性烯醇化酶

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Effects of Probucol Combined with Kallidinogenase on the Oxidative Stress Reaction and Serum NSE Level in the Elderly Patients with Diabetic Peripheral Neuropathy*

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ABSTRACT Objective: To study the effects of probucol combined with kallidinogenase on the oxidative stress reaction and the serum neuron specific enolase(NSE) level in the elderly patients with diabetic peripheral neuropathy. **Methods:** 94 elderly patients of diabetic peripheral neuropathy who were treated from August 2015 to August 2017 in our hospital were selected as the research objects. The patients were divided into the observation group (n=47) and the control group (n=47) according to the random number table. The control group was treated with kallidinogenase on the basis of routine treatment, while the observation group was combined with probucol on the basis of the control group, both groups were continuous treatment for 12 weeks. The clinical efficacy, the changes of motor conduction velocity (MNCV), sensory conduction velocity (SNCV), Toronto clinical scoring system (TCSS) score, oxidative stress index, serum NSE and adverse reactions of two groups before and after the treatment were compared. **Results:** After treatment, the total effective rate of observation group was 93.62% (44/47), which was significantly higher than that of the control group [70.21%(33/47)]($P < 0.05$); the MNCV and SNCV of nervi medianus and nervus peroneus communis of both groups were significantly longer than those before treatment ($P < 0.05$), which were significantly faster in the observation group than those in the control group ($P < 0.05$); the TCSS scores,

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serum MDA and NSE levels of both groups were significantly lower than those before treatment ($P < 0.05$), the symptom score, reflex score, sensation score, total TCSS score, serum MDA and NSE levels of observation group were significantly lower than those in the control group ($P < 0.05$); the superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) were significantly higher than before treatment ($P < 0.05$), which were significantly higher than those in the control group ($P < 0.05$). The total incidence of adverse reactions in the two groups was 10.64% (5/47) and 4.26% (2/47) respectively ($P > 0.05$). **Conclusion:** Probucol combined with kallidinogenase is superior to kallidinogenase alone for the elderly diabetic peripheral neuropathy with high safety, which can more effectively improve the degree of neuropathy. Its intrinsic mechanism may be related to alleviate the oxidative stress reaction and reduce the expression of serum NSE.

Key words: Elderly; Diabetic peripheral neuropathy; Probucol; Kallidinogenase; Oxidative stress reaction; Neuron specific enolase

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前言

糖尿病周围神经病变是一种糖尿病患者常见的慢性并发症,主要累积周围神经,患者出现肢体麻木、对称性疼痛、肢体敏感度降低等,严重影响其生活质量,尤其以老年人群发病率较高^[1]。该病的发病机制较为复杂,和高糖所致的代谢紊乱、神经营养障碍、血管损伤、自身免疫、氧化应激等均存在着关系,其中氧化应激发挥着极为关键的作用^[2]。神经元特异性烯醇化酶(NSE)主要由神经元细胞质和神经内分泌细胞分泌,神经特异性较高,近年来有学者发现对其的检测有助于了解糖尿病周围神经病变程度^[3]。

目前,糖尿病周围神经病变的治疗以控制血糖、血压、调脂等为主,在缓解神经功能方面效果欠佳。胰激肽原酶对血管具有扩张作用,适用于治疗微循环障碍性和神经性损伤。普罗布考是临床上较为常用的调脂药物,具有明显的抗氧化应激作用^[4,5]。但关于普罗布考联合胰激肽原酶联合用于老年糖尿病周围神经病变的相关报道仍较少。因此,本研究通过观察治疗后患者氧化应激反应和血清 NSE 水平的变化,主要探讨了普罗布考联合胰激肽原酶用于老年糖尿病周围神经病变患者的治疗作用及机制。

1 资料与方法

1.1 一般资料

选择 2015 年 8 月至 2017 年 8 月我院收治的老年糖尿病周围神经病变患者 94 例。纳入标准^[6]:①符合糖尿病周围神经病变诊断标准,确诊为糖尿病,有四肢感觉异常等表现,包括单侧或对称性肢体麻木;腱反射消失或减弱;通过神经电生理检查显示神经传导速度明显减慢;②年龄 ≥ 60 岁;③对本研究知情同意。排除标准^[7]:①合并其余神经病变;②近 3 个月内发生过糖尿病相关急性并发症;③合并肝肾功能等严重器质功能障碍;④由于药物治疗、中毒等所形成的神经病变;⑤合并癫痫、脑损伤、脑血管疾病、颅内感染、血管性痴呆、内分泌组织肿瘤等患者;⑥对研究药物过敏。通过随机数表法将所有患者分为 2 组,每组 47 例。观察组中,男 28 例,女 19 例;年龄 63~73 岁,平均 (67.77 ± 4.30) 岁,糖尿病病程 3~12 年,平均 (7.89 ± 1.54) 年。对照组中,男 26 例,女 22 例;年龄 60~74 岁,平均 (67.92 ± 4.17) 岁,糖尿病病程 3~13 年,平均 (7.76 ± 1.59) 年。研究已获得我院伦理委员会批准实施,两组一般资料比较无显著

差异($P > 0.05$),具有可比性。

1.2 治疗方法

两组均给予控制血糖、血压、血脂、饮食控制等常规处理措施,血糖控制目标为 < 7.0 mmol/L,餐后 2 h 血糖 < 10.0 mmol/L。在上述基础上,对照组再给予胰激肽原酶(规格 120 U,厂家:常州千红生化制药股份有限公司,国药准字 H19993089)治疗,剂量 240 U 口服,3 次/d;观察组在对照组基础上,联合普罗布考治疗(规格 0.125 g,厂家:齐鲁制药有限公司,国药准字 H10980054)口服治疗,剂量 0.25 g,2 次/d。两组均连续治疗 12 周。

1.3 观察指标

1.3.1 肌电图检查 于治疗前、后使用上海 MyoSystem 1400 型肌电图机,检测两组正中神经、腓总神经运动传导速度(MNCV)、感觉传导速度(SNCV)的变化。

1.3.2 多伦多临床评分系统(TCSS)评分 总共有症状评分、反射评分、感觉评分 3 部分,症状评分内容包括下肢麻木、疼痛、针刺感、乏力、走路不稳等症状,0 分表示无,1 分表示有;反射评分为评价双膝反射和踝反射,0 分表示正常,1 分表示减弱,2 分表示无反射;感觉评分包括肢体的温度觉、针刺觉、触觉、震动觉、关节位置觉,0 分表示正常,1 分表示异常;各项目总分分别为 6 分、8 分、5 分,总分 0~19 分,0~5 分表示无糖尿病周围神经病变,6~8 分表示轻度病变,9~11 分表示轻度病变, > 11 分表示重度病变。

1.3.3 氧化应激指标 采集清晨空腹静脉血 5 mL,离心速度 3000 r/min,时间 10 min,提取上层清液置于零下 40℃ 的冷冻箱内储存以备检测,丙二醛(MDA)、超氧化物歧化酶(SOD)、过氧化氢酶(CAT)、谷胱甘肽过氧化物酶(GSH-Px)的检测均使用酶联免疫吸附法(ELISA)进行,试剂盒均购于美国 R&D 公司。

1.3.4 血清 NSE 水平 使用免疫放射分析进行检测,试剂盒源自深圳晶美生物科技技术有效公司。

1.3.5 不良反应的发生情况 记录治疗期间不良反应的发生情况。

1.4 疗效评价标准

于疗程结束后评价疗效。显效:肢体麻木等症状消失,腱反射结果显示(++),通过肌电图检查结果显示正中神经、腓总神经传导速度恢复至正常,或均得到 ≥ 5 m/s 的加快;有效:肢体麻木等症状较治疗前有所缓解,腱反射结果改善但未至正常,正中神经、腓总神经传导速度较治疗前均出现加快,但加快速度 < 5 m/s;无效:未达到上述标准。以显效 + 有效为总有效率。

1.5 统计学分析

以 SPSS18.0 软件包对研究数据进行统计分析, 计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示, 组间比较采用 t 检验, 计数资料组间比较采用 χ^2 检验, 以 $P < 0.05$ 表示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, 观察组临床疗效总有效率明显高于对照组 (93.62% vs. 70.21%, $P < 0.05$), 见表 1。

表 1 两组临床疗效比较[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Excellent	Valid	Invalid	Total effective rate
Observation group(n=47)	25(53.19)	19(40.43)	3(6.38)	44(93.62)
Control group(n=47)	17(36.17)	16(34.04)	14(29.79)	33(70.21)

Note: compared with the control group, * $P < 0.05$.

2.2 两组治疗前后 MNCV、SNCV 的比较

治疗后, 两组正中神经、腓总神经 MNCV、SNCV 均较治疗

前明显加快, 且观察组正中神经、腓总神经 MNCV、SNCV 均明显快于对照组($P < 0.05$), 见表 2。

表 2 两组治疗前后 MNCV、SNCV 的比较($\bar{x} \pm s$, m/s)Table 2 Comparison of the MNCV and SNCV between two groups before and after treatment($\bar{x} \pm s$, m/s)

Groups		Nervi medianus		Nervus peroneus communis	
		MNCV	SNCV	MNCV	SNCV
Observation group (n=47)	Before treatment	42.83 $\pm$ 3.40	38.42 $\pm$ 3.17	39.84 $\pm$ 3.58	35.05 $\pm$ 2.95
	After treatment	56.02 $\pm$ 5.11* [#]	45.89 $\pm$ 3.83* [#]	50.13 $\pm$ 4.26* [#]	42.83 $\pm$ 3.49* [#]
Control group(n=47)	Before treatment	42.57 $\pm$ 3.56	38.49 $\pm$ 3.14	40.02 $\pm$ 3.42	35.12 $\pm$ 2.87
	After treatment	50.15 $\pm$ 4.52*	41.78 $\pm$ 3.49*	45.69 $\pm$ 3.85*	38.92 $\pm$ 3.16*

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

2.3 两组治疗前后 TCSS 评分比较

治疗后, 两组 TCSS 评分各内容分数均较治疗前明显降

低, 且观察组 TCSS 评分各内容分数均明显低于对照组 ($P < 0.05$), 见表 3。

表 3 两组治疗前后 TCSS 评分比较($\bar{x} \pm s$, 分)Table 3 Comparison of the TCSS scores between two groups before and after treatment($\bar{x} \pm s$, scores)

Groups		Symptom score	Reflex score	Sensory score	Total score
Observation group (n=47)	Before treatment	3.57 $\pm$ 0.52	3.78 $\pm$ 0.35	3.17 $\pm$ 0.33	10.49 $\pm$ 0.93
	After treatment	1.74 $\pm$ 0.28* [#]	1.64 $\pm$ 0.22* [#]	1.27 $\pm$ 0.12* [#]	4.62 $\pm$ 0.61* [#]
Control group(n=47)	Before treatment	3.52 $\pm$ 0.53	3.93 $\pm$ 0.33	3.23 $\pm$ 0.30	10.54 $\pm$ 0.90
	After treatment	2.49 $\pm$ 0.34*	2.71 $\pm$ 0.27*	1.79 $\pm$ 0.18*	7.04 $\pm$ 0.75*

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

2.4 两组治疗前后氧化应激指标比较

治疗后, 两组血清 MDA 水平均显著低于治疗前, 而血清 SOD、CAT、GSH-Px 水平均明显高于治疗前, 且观察组血清

MDA 水平明显低于对照组, 血清 SOD、CAT、GSH-Px 水平均明显比对照组高($P < 0.05$), 见表 4。

表 4 两组治疗前后氧化应激指标比较($\bar{x} \pm s$)Table 4 Comparison of the oxidative stress index between two groups before and after treatment($\bar{x} \pm s$)

Groups		MDA(nmol/L)	SOD(U/mL)	CAT(U/mL)	GSH-Px(U/mL)
Observation group (n=47)	Before treatment	7.54 $\pm$ 1.92	94.34 $\pm$ 15.20	3.16 $\pm$ 0.58	102.83 $\pm$ 18.36
	After treatment	4.27 $\pm$ 1.20* [#]	137.49 $\pm$ 28.37* [#]	6.38 $\pm$ 1.15* [#]	142.92 $\pm$ 27.44* [#]
Control group(n=47)	Before treatment	7.43 $\pm$ 1.99	95.11 $\pm$ 14.62	3.07 $\pm$ 0.50	103.42 $\pm$ 18.19
	After treatment	5.43 $\pm$ 1.42*	112.82 $\pm$ 20.40*	4.39 $\pm$ 0.74*	120.38 $\pm$ 23.52*

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

2.5 两组治疗前后血清 NSE 水平比较

血清 NSE 水平明显低于对照组($P < 0.05$),见表 5。

治疗后,两组血清 NSE 水平均明显低于治疗前,且观察组

表 5 两组治疗前后血清 NSE 水平的比较($\bar{x} \pm s, \mu\text{g/L}$)

Table 5 Comparison of the serum NSE level between two groups before and after treatment($\bar{x} \pm s, \mu\text{g/L}$)

Groups		NSE
Observation group(n=47)	Before treatment	19.85 $\pm$ 1.75
	After treatment	10.30 $\pm$ 1.26**
Control group(n=47)	Before treatment	19.72 $\pm$ 1.79
	After treatment	14.24 $\pm$ 1.50*

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

2.5 安全性评价

治疗期间,观察组出现 3 例胃肠道不适,1 例皮肤瘙痒,1 例乏力,对照组出现 1 例胃肠道不适,1 例皮肤瘙痒,两组不良反应总发生率分别为 10.64%(5/47)、4.26%(2/47),差异无统计学意义($P > 0.05$)。

3 讨论

相关数据显示糖尿病患者出现周围神经病变的发生率可达 7%-50%,若合并各种亚临床型神经病,可增加至 90%,老年人群由于机体免疫力的降低、糖尿病病程的延长、耐受性差等原因,疾病严重程度和治疗难度可进一步增加^[89]。研究表明氧化应激反应贯穿着糖尿病的发生、发展过程,是糖尿病周围神经病变发生的重要影响因素。机体处于氧化应激状态时,大量的活性成分产生,继而直接损伤蛋白质、DNA 等,致使神经元、血管内皮功能和结构发生紊乱^[10,11]。Kukidome D 等^[12]报道也指出氧化应激可通过经典的高血糖损伤途径对多种信号传导分子产生激活作用,改变细胞基因的表达,促使神经元功能失调并出现凋亡。因此,通过抗氧化应激、改善机体微循环、缓解微循环病变等途径治疗糖尿病周围神经病变成为目前临床学者重点关注的问题。

胰激肽原酶是动物胰腺中提取的一种蛋白水解酶,激肽原进入机体被分解后,可起到扩张血管作用,提高组织血流量,而纤溶酶被激活后可通过增加纤溶系统活性达到降低血液粘稠度的作用,已有较多报道指出其对血管病变具有较好的改善作用^[13,14]。普罗布考又被称作丙丁酚,其中含有的酚羟基极易被氧化,可消耗氧自由基、过氧自由基之类的氧化物质,Suo XQ 等^[15]将普罗布考用于进行经皮冠状动脉介入的患者,发现其可直接降低 MDA 等表达,减轻手术所致的氧化应激反应,缓解机体损伤。Liu H 等^[16]在糖尿病视网膜病变患者中使用普罗布考患者后,发现其改善视网膜病变的效果显著。

MDA、SOD、CAT、GSH-Px 是氧化应激反应的重要参考指标。其中,MDA 属氧化性物质,可反映机体氧化能力,SOD、CAT、GSH-Px 属抗氧化物质,其表达的降低也代表着机体抗氧化能力的降低^[17,18]。本研究结果显示联合用药的患者 MDA、SOD、CAT、GSH-Px 改善程度明显优于单独使用胰激肽原酶的患者,表明出两药联合可进一步促进氧化应激反应的改善,且联合用药的患者正中神经、腓总神经 MNCV、SNCV 和 TCSS

评分的改善程度也更具有优势,临床疗效高达 93.62%,提示联合用药更有助于改善神经病变程度,通过分析是由于联合用药所起到的抗氧化、改善血管内皮功能效果更佳显著,利于损伤神经的修复,因此临床疗效更显著。且联合用药并未增加药物不良反应,安全性高。

NSE 具有较高的神经特异性,当血脑屏障遭受到破坏时,其可通过血神经屏障在血液中释放入血并大量表达^[19,20]。Li J 等^[21]研究显示糖尿病周围神经病变患者血清 NSE 的表达明显比单纯糖尿病患者低,而当 NSE 高于正常值时,出现糖尿病周围神经病变的风险机率可增加 3 倍,且随着糖尿病周围神经病变的加重,NSE 浓度也随之增加,因而其可作为诊断糖尿病神经病变的补充检测指标。本研究结果显示普罗布考联合胰激肽原酶的患者血清 NSE 的降低程度明显更具有优势,通过分析是由于 NSE 的激活和组织缺血缺氧、血管损伤等存在密切关系,而普罗布考联合胰激肽原酶联合具有明显的抗氧化损伤、降低血液粘稠度等作用,有助于改善血管病变,继而减少了 NSE 在血清中的释放。

综上所述,普罗布考联合胰激肽原酶治疗老年糖尿病周围神经病变患者的效果显著优于单用胰激肽原酶治疗,可更有效改善神经病变程度,其机制可能和缓解氧化应激反应、降低血清 NSE 水平有关。

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