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α-硫辛酸联合前列地尔对糖尿病周围神经病变患者血清炎症因子及神经传导速度的影响*

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摘要 目的:探讨α-硫辛酸联合前列地尔对糖尿病周围神经病变患者的疗效及对血清炎症因子、神经传导速度的影响。**方法:**选取我院2015年6月-2017年6月治疗的130例糖尿病周围神经病变患者,随机分为观察组(n=65)和对照组(n=65)。其中对照组患者采用前列地尔治疗,观察组患者在此基础上联合α-硫辛酸治疗,两组患者均连续治疗2周。对两组患者的临床疗效、治疗前后的神经传导速度、血清炎症因子水平、多伦多临床神经病变评分系统(TCSS)、视觉模拟评分(VAS)、不良反应发生率等指标进行综合评价对比。**结果:**观察组临床总有效率为93.85%(61/65),高于对照组的78.46%(51/65),(P<0.05)。治疗后,两组患者腓总神经、正中神经的运动神经传导速度(MNCV)、感觉神经传导速度(SNCV)均高于治疗前,观察组高于对照组,组间比较差异显著(P<0.05)。治疗后,两组患者TCSS、VAS评分、肿瘤坏死因子-α(TNF-α)、白介素-6(IL-6)、C-反应蛋白(CRP)低于治疗前,观察组低于对照组,组间比较差异明显(P<0.05)。观察组不良反应发生率为13.85%(9/65),对照组为7.69%(5/65),组间相比差异不明显(P>0.05)。**结论:**α-硫辛酸与前列地尔联合治疗糖尿病周围神经病变,疗效满意,可显著改善患者的神经症状,降低炎症因子水平,且用药安全性好,值得在临床上进一步推广使用。

关键词:α-硫辛酸;前列地尔;糖尿病周围神经病变;炎症因子;神经传导速度

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Effects of α-Lipoic Acid and Alprostadil on Serum Inflammatory Factors and Nerve Conduction Velocity in Patients with Diabetic Peripheral Neuropathy*

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ABSTRACT Objective: To investigate the curative effect of α-lipoic acid and alprostadil on patients with diabetic peripheral neuropathy and its effect on serum inflammatory factors and nerve conduction velocity. **Methods:** 130 patients with diabetic peripheral neuropathy who were treated in our hospital from June 2015 to June 2017 were selected, and they were randomly divided into the observation group and the control group according to the random digital table method, 65 cases in each group. The patients in the control group were treated with alprostadil, and the patients in the observation group were treated with α-lipoic acid on the basis of control group, and all patients of two groups were treated for 2 weeks. The clinical efficacy, nerve conduction velocity before and after treatment, serum inflammatory factor levels, Toronto clinical neuropathy score system (TCSS), visual analogue scale (VAS) and incidence of adverse reactions were compared and evaluated between the two groups. **Results:** The total effective rate of the observation group was 93.85% (61/65), which was higher than 78.46% of the control group(51/65)(P<0.05). After treatment, motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) of common peroneal nerve and median nerve in two groups were all higher than those before treatment, and the observation group was higher than that in the control group, and the difference between the two groups was statistically significant (P<0.05). After treatment, the scores of TCSS, VAS and levels TNF-α (TNF-α), interleukin-6(IL-6) and C-reactive protein (CRP) in the two groups were all lower than those before treatment, and the observation group was lower than that in the control group, the difference between the two groups was statistically significant (P<0.05). The incidence of adverse reactions in the observation group was 13.85% (9/65), and there was no significant difference compared with the control group 7.69% (5/65), the difference between the groups was not obvious (P>0.05). **Conclusion:** α-lipoic acid combined with alprostadil is effective in the treatment of diabetic peripheral neuropathy. It can significantly improve the neurological symptoms and reduce the levels of inflammatory factors, and the safety of drug use is good, which is worthy of further promotion in clinical practice.

Key words: α-lipoic acid; Alprostadil; Diabetic peripheral neuropathy; Inflammatory factor; Neural conduction velocity

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前言

糖尿病是临床上常见的一种以血糖升高为主要病理特征的代谢性疾病，随着物质生活水平的提高及人们不规律的饮食状态，使糖尿病的发生率逐年升高，严重影响患者生命健康和生活质量[1-3]。另外，由于高血糖导致的机体代谢性的紊乱，使机体的眼、肾、心脏、血管、神经等组织器官受到损伤，引起较多的并发症[4-6]，其中周围神经病变是最常见、最复杂的一种，能致患者的神经功能受损、肢体感觉异常、剧烈疼痛等症状，严重者甚至出现糖尿病足、肢体溃疡、坏疽等现象，威胁患者的身心健康，对患者的日常生活质量造成了严重影响[7-9]。糖尿病周围神经病变的发病机制较为复杂，其中高血糖引起的代谢性紊乱诱发机体氧化应激损伤是主要的致病因素[10-12]。目前，临床上对于糖尿病周围神经病变多采用抗氧化应激和改善血管微循环药物进行治疗，能够获得良好的治疗效果。α- 硫辛酸是一种强效的抗氧化剂类药物，其能够降低患者的氧化应激反应[13]。前列地尔则是一种血管扩张剂，可改善血管的微循环[14]。因此，本研究以我院收治的糖尿病周围神经病变患者为研究对象，采用α- 硫辛酸和前列地尔联合治疗，疗效满意，现作如下报道。

1 资料与方法

1.1 临床资料

以我院 2015 年 6 月 -2017 年 6 月进行治疗的 130 例糖尿病周围神经病变患者进行研究，纳入标准：(1)所有患者均符合《中国 2 型糖尿病防治指南》中的相关诊断标准[15]，即空腹血糖≥ 7.0 mmol/L，餐后 2 h 血糖≥ 11.1 mmol/L，糖化血红蛋白≥ 6.5%；(2)所有患者均糖尿病周围神经病变的相关诊断标准，即症状表现为四肢麻木、烧灼蚁行感、针刺样疼痛以及踝膝反射减弱，神经传导速度减慢；(3)对本研究治疗药物无严重过敏反应者；(4)患者对本研究方案知情同意，并签署知情同意书。排除标准：(1)合并严重的心、肝、肾功能不全者；(2)精神状态异常者、妊娠哺乳期妇女等；(3)纳入本研究前 3 个月内服用类似治疗药物者；(4)原发性神经功能损伤者。按随机数字表法将其分为观察组和对照组，每组各 65 例。观察组男性 37 例、女性 28 例，患者年龄 38-69 岁，平均(57.21± 9.28)岁，病程 1-8 年，平均(4.02± 1.89)年。对照组男性 34 例、女性 31 例，患者年龄 36-71 岁，平均(59.42± 9.85)岁，病程 1-9 年，平均病程(4.08± 1.97)年。两组临床资料比较无差异(P>0.05)，具有可比性。

1.2 方法

所有患者治疗时均给予降血糖、控制饮食等基础治疗。对照组以前列地尔注射液(北京泰德药业股份有限公司，国药准字 H10980024，规格：2 mL:10 μg)治疗，给药方法为 2 mL 前列地尔加入到 100 mL 生理盐水中，混匀，静脉滴注给药，每日给药 1 次，连续 2 周。观察组在此基础上联合 α- 硫辛酸注射液(上海现代哈森药业有限公司，国药准字 H20056403，规格：20 mL:0.6 g)治疗，给药方法为 20 mL α- 硫辛酸加入到 250 mL 生理盐水中，混匀，静脉滴注给药，每日 1 次，连续治疗 2 周。

1.3 观察指标

对两组患者治疗前后的神经传导速度进行测量比较，采用 NeuroExam M-800C 型肌电图仪（珠海市迈康科技有限公司）测量患者的腓总神经、正中神经的运动神经传导速度(motor nerve conduction velocity，MNCV)、感觉神经传导速度(sensory nerve conduction velocity，SNCV)。采用多伦多临床神经病变评分系统(Toronto clinical scoring system，TCSS)对两组患者的神经功能症状进行评分比较，该评分系统总分为 19 分，得分越高表明患者的神经功能受损越严重。采用视觉模拟评分(visual analogue scale，VAS)对两组患者治疗前后疼痛程度进行评分，该评分系统总分为 10 分，得分越高表明患者的疼痛程度越剧烈。分别于治疗前后采集患者空腹静脉血 5 mL，低温离心 15 min，离心速度为 3000 r/min，分离得到血清后采用酶联免疫吸附试验(Enzyme-linked immunosorbent assay，ELISA)检测患者的肿瘤坏死因子 -α(tumor necrosis factor-α，TNF-α)、白介素 -6(interleukin-6，IL-6)、C- 反应蛋白(C-reactive protein，CRP)水平，试剂盒购置于赛默飞世尔科技有限公司，操作过程严格按照说明书操作规程进行。对两组患者的临床治疗效果进行评价比较，临床疗效判断标准为[16]：显效为患者症状基本消失，神经传导速度加快 >5 cm/s，VAS 评分降低 >80%；有效为患者症状有显著改善，神经传导速度加快在 0-5c m/s 之间，VAS 评分降低比例在 20%-80%；无效为患者症状无改善，神经传导速度无加快，VAS 评分降低 <20%。总有效率 = 显效率 + 有效率。对两组患者在治疗期间不良反应发生情况进行比较。

1.4 数据处理方法

以 SPSS 20.0 进行数据的统计处理，计量资料以($\bar{x}$± s)表示，行 t 检验，计数资料以率表示，行 x^2 检验，P<0.05 表示组间差异有统计学意义。

2 结果

2.1 临床疗效比较

观察组临床总有效率为 93.85%(61/65)，高于对照组的 78.46%(51/65)(P<0.05)，见表 1。

表 1 两组患者临床疗效比较[n(%)]

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

Groups	n	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	65	34(52.31)	27(41.54)	4(6.15)	61(93.85)
Control group	65	28(43.08)	23(35.38)	14(21.54)	51(78.46)
x^2 value					6.448
P value					0.011

2.2 治疗前后 MNCV、SNCV 比较

治疗前，两组患者腓总神经、正中神经的 MNCV、SNCV 比

较无差异(P>0.05)。治疗后,两组患者腓总神经、正中神经的MNCV、SNCV均高于治疗前,观察组高于对照组,组间比较差异显著(P<0.05),见表2。

表2 两组患者治疗前后MNCV、SNCV比较(cm/s,$\bar{x}\pm s$)

Table 2 Comparison of MNCV and SNCV before and after treatment in two groups of patients(cm/s, $\bar{x}\pm s$)

Groups	n	Common peroneal nerve				Median nerve			
		MNCV		SNCV		MNCV		SNCV	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	65	37.28± 2.28	43.86± 2.01*	34.79± 1.88	46.25± 2.50*	39.50± 1.94	48.83± 2.90*	37.86± 2.03	46.06± 2.48*
Control group	65	38.02± 2.39	40.37± 1.95*	35.27± 2.12	41.91± 2.30*	40.09± 2.05	43.65± 2.47*	38.49± 2.31	42.42± 2.24*
T value		1.806	10.047	1.366	10.300	1.685	10.963	1.652	8.782
P value		0.073	0.000	0.174	0.000	0.094	0.000	0.101	0.000

Note: Compare with before treatment, *P<0.05.

2.3 治疗前后TCSS、VAS评分比较

治疗前,两组TCSS、VAS比较无统计学差异(P>0.05)。治疗后,两组TCSS、VAS均低于治疗前,观察组低于对照组,组间比较差异显著(P<0.05),见表3。

表3 两组患者治疗前后TCSS、VAS评分比较(分,$\bar{x}\pm s$)

Table 3 Comparison of TCSS and VAS scores in two groups of patients before and after treatment(point, $\bar{x}\pm s$)

Groups	n	TCSS		VAS	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	65	11.59± 2.18	6.76± 1.52*	5.21± 1.33	1.47± 0.78*
Control group	65	11.92± 2.03	8.30± 1.74*	5.49± 1.38	2.42± 0.82*
T value		0.893	5.374	1.178	6.768
P value		0.373	0.000	0.241	0.000

Note: Compare with before treatment, *P<0.05.

2.4 治疗前后血清TNF-α、IL-6、CRP水平比较

治疗前,两组TNF-α、IL-6、CRP比较差异无明显差异性(P>0.05)。治疗后,两组TNF-α、IL-6、CRP均低于治疗前,观察组低于对照组,组间比较差异显著(P<0.05),见表4。

表4 两组患者治疗前后血清TNF-α、IL-6、CRP水平比较($\bar{x}\pm s$)

Table 4 Comparison of serum TNF-α, IL-6 and CRP levels in two groups of patients before and after treatment($\bar{x}\pm s$)

Groups	n	TNF-α(μg/L)		IL-6(ng/L)		CRP(mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	65	3.89± 0.98	2.92± 0.65*	353.21± 34.92	210.21± 17.04*	14.31± 4.06	5.71± 1.94*
Control group	65	3.78± 0.87	3.36± 0.74*	347.12± 32.19	256.38± 20.05*	13.47± 3.79	8.31± 2.02*
T value		0.677	2.783	1.034	14.147	1.219	7.484
P value		0.450	0.006	0.303	0.000	0.225	0.000

Note: Compare with before treatment, *P<0.05.

2.5 不良反应发生率比较

观察组不良反应发生率为13.85%(9/65),对照组为7.69%(5/65),组间比较差异无统计学意义(P>0.05),见表5。

3 讨论

糖尿病是一种长期慢性难治愈的代谢性疾病,在发病过程中易出现多种并发症,其中周围神经病变是一种常见的并发症,发病后对患者的神经功能、肢体功能造成损伤,并给患者带来难以忍受的疼痛感[17-19]。目前,对于糖尿病周围神经病变的发病机制研究显示,其致病因素主要包括高血糖引起的血糖代谢异常、自身免疫功能异常、神经营养障碍、氧化应激损伤、微血管损伤、遗传因素作用等[20,21]。其中氧化应激损伤和微循环损伤引起了研究人员的高度重视,分析可能的原因是由于糖尿病患者体内的糖、脂肪、蛋白质等物质的代谢紊乱,同时大量的糖脂

表 5 两组患者不良反应发生率比较[n(%)]

Table 5 Comparison of the incidence rate of adverse reactions between the two groups[n(%)]

Groups	n	Dizziness and nausea	Facial flush	Lower appetite	Skin sensibility	Total incidence rate
Observation group	65	2(3.08)	2(3.08)	2(3.08)	3(4.62)	9(13.85)
Control group	65	1(1.54)	2(3.08)	1(1.54)	1(1.54)	5(7.69)
x^2 value						1.281
P value						0.258

肪类物质需要经氧化代谢,使机体的氧化压力增加,线粒体活性氧水平进一步提高,体内氧化自由基增多,导致氧化应激反应出现,并增加对周围神经系统的损伤[22,23]。另外,糖尿病患者在高血糖的刺激下使得微血管出现损伤,影响患者血流动力学稳定,可使微血管堵塞引起小血管的缺血缺氧,进而导致神经缺血缺氧等损伤。因此,对于糖尿病周围神经病变患者在控制血糖的基础上增加抗氧化、改善微循环是一个较为有效的治疗途径[24]。

在本研究中,对糖尿病周围神经病变患者采用 α- 硫辛酸联合前列地尔进行注射治疗,并与单独的前列地尔治疗效果进行对比,结果显示观察组患者的临床疗效高于对照组(P<0.05),这是因为观察组为两种不同作用机制的药物同时应用,从两个不同的作用途径发挥协同相加的药理作用[25]。α- 硫辛酸为强效的抗氧化剂,其分子结构中有独特的二硫键,该药物进入患者体内后能够迅速转化为二氢硫辛酸,具有较强的还原性,能够清除抵消患者体内的氧化自由基,降低氧化应激反应,同时减轻氧化应激反应对神经功能的损伤[26]。另外,α- 硫辛酸还可纠正高血糖导致的血管内皮炎症因子的异常,增加神经血管的血流供应,以及增加神经的 Na^+-K^+-ATP 酶的活性,促进神经的能量供应恢复正常,对神经功能损伤有改善作用[27]。前列地尔为前列腺素类似物,其能增加血管平滑肌内的环磷腺苷水平,导致血管扩张,同时抑制血栓烷的合成,从而抑制血小板的聚集[28]。在本研究中,观察组患者腓总神经、正中神经的 MNCV、SNCV 均高于对照组,TCSS、VAS 评分均低于对照组(P<0.05),表明 α- 硫辛酸与前列地尔联合治疗可发挥协同作用,进一步减轻患者的症状体征,提高疗效。炎症反应是导致糖尿病周围神经病变进展的重要原因,当神经功能出现损伤时,巨噬细胞、淋巴细胞功能被激活,刺激机体分泌产生大量的炎症因子诸如 TNF-α、IL-6、CRP,导致炎症因子在病变神经处大量聚集,降低了神经组织的 Na^+-K^+-ATP 酶活性,加速了病情的进展。在本研究中,两组患者 TNF-α、IL-6、CRP 水平均低于治疗前,且观察组低于对照组(P<0.05),表明 α- 硫辛酸与前列地尔联合给药治疗对体内炎症反应的作用更强,可有效抑制周围神经损伤的病情进展恶化[29,30]。在不良反应发生的比较中,观察组与对照组患者不良反应相似,组间比较无差异性(P>0.05),表明观察组增加 α- 硫辛酸给药治疗,患者的不良反应未有显著增加,证实联合用药的安全性良好。

综上所述,与单独用药治疗相比,α- 硫辛酸与前列地尔联合治疗糖尿病周围神经病变的临床疗效更为显著,两种治疗药物通过两种不同作用机制发挥药理协同作用,进一步提高疗效,改善患者的各项神经功能和体表症状,并降低患者体内的炎症因子水平,治疗方案安全可靠,有较高的临床应用价值。

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