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甲钴胺联合血液透析治疗尿毒症患者周围神经病变的效果及对患者血清微炎症介质水平的影响

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摘要 目的:探讨甲钴胺联合血液透析治疗尿毒症患者周围神经病变的效果及对患者血清微炎症介质水平的影响。**方法:**将 86 例合并周围神经病变的尿毒症患者随机分为观察组 46 例与对照组 40 例,两组均接受血液净化治疗,观察组同时加用甲钴胺治疗。比较两组治疗前后的血清 C-反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α),白细胞介素-6(IL-6)及 IL-8 水平,肢体正中神经与腓浅神经的感觉神经传导速度(SCV)以及临床症状、体征改善情况。**结果:**治疗后,两组血清 CRP、TNF- α 、IL-6、IL-8 水平均较治疗前明显下降($P<0.05$),正中神经与腓总神经的 SCV 均较治疗前明显提高($P<0.05$),且观察组血清 CRP、TNF- α 、IL-6、IL-8 水平明显低于对照组($P<0.05$),正中神经 SCV 显著高于对照组($P<0.05$),四肢感觉减退、四肢远端麻木与烧灼感、不宁腿综合征、肢端疼痛的发生率明显低于对照组($P<0.05$)。**结论:**甲钴胺联合血液透析对尿毒症性周围神经病变的疗效明显优于单用血液透析治疗,且可显著改善机体的微炎症状态。

关键词: 甲钴胺;尿毒症;周围神经病变;微炎症

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Clinical Efficacy of Mecobalamin Combined with Blood Purification in the Treatment of Uremia Patients with Peripheral Neuropathy and its Effect on the Serum Micro Inflammatory Mediators Levels

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ABSTRACT Objective: To investigate the clinical efficacy of mecobalamin in the treatment of peripheral neuropathy and its effect on the micro inflammatory mediators of patients with uremia. **Methods:** 86 cases of patients with uremia combined with peripheral neuropathy were randomly divided into the observation group(46 cases) and the control group(40 cases). Both groups received blood purification treatment, and the observation group were added mecobalamin. The levels of serum C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-8, and sensory nerve conduction velocity (SCV) of the median nerve and superficial peroneal nerve in the extremities and improvement of clinical symptoms and signs were compared between the two groups before and after treatment. **Results:** After treatment, the levels of serum CRP, TNF- α , IL-6 and IL-8 of both groups were obviously decreased($P<0.05$), the SCV of median nerve and the peroneal nerve of both groups were obvious higher than those before treatment ($P<0.05$) and the serum CRP, TNF- α , IL-6, IL-8 levels of observation group were lower in the observation group than those of the control group ($P<0.05$). The median nerve SCV of observation group was significantly higher than that of the control group ($P<0.05$). The incidence of limb loss, numbness and burning sensation, restless legs syndrome and acral pain of observation group were significantly lower than those of the control group ($P<0.05$). **Conclusions:** Mecobalamin combined with hemodialysis was better than hemodialysis in treatment of uremic peripheral neuropathy, which could significantly improve the micro inflammatory state of patients.

Key words: Mecobalamin; Uremia; Peripheral neuropathy; Inflammation

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前言

周围神经病变是尿毒症的常见并发症,临床表现为对称性

多神经炎,以下肢损害为主,常见肌肉痉挛、麻木、烧灼、疼痛感,甚者发生"不宁腿综合征",查体可见不同程度的腱反射减退和深感觉障碍,神经电生理检查提示有感觉神经传导速度(SCV)异常^[1-3]。目前,尿毒症性周围神经病变的发病机制并不完全明确,可能与肾脏功能减退,瘦素、 β_2 微球蛋白、甲状旁腺素等中分子毒素在体内滞留以及持续微炎症状态,导致周围神经细胞水肿、坏死有关^[4-6]。

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血液净化通过清除中分子毒素以及降低炎症介质水平,对周围神经病变有一定的改善作用。甲钴胺是维生素 B12 甲基化活性制剂,可通过甲基转换反应促进核酸 - 蛋白质 - 脂质代谢,从而有助于受损神经组织修复^[7,8]。既往已有大量研究显示甲钴胺治疗糖尿病性周围神经病变的疗效好,但对尿毒症性周围神经病变是否也有相同的效果仍不明确。为此,本研究主要探讨了甲钴胺在尿毒症性周围神经病变中的应用效果,结果报道如下。

1 对象和方法

1.1 研究对象

选择 2012 年 3 月 -2016 年 3 月 86 例尿毒症患者,纳入标准:① 年龄在 16-75 岁;② 符合尿毒症诊断标准^[9],血肌酐 (Scr)>707 mmol/L,肾小球滤过率(GFR)<10 mL/L,并具有比较典型的周围神经病变表现;③ 自愿加入本项目研究,并签署知情同意书。排除标准:④ 其他原因导致的周围神经病变,如糖尿病、Guillian-Barre 综合征、维生素缺乏、药物中毒等;⑤ 合并急慢性感染性疾病、自身免疫性疾病活动期、严重心肺并发症及恶性肿瘤等;⑥ 近 12 周内有过出血或输血史;⑦ 近期内使用过免疫抑制剂、糖皮质激素、铁剂、维生素等。原发病包括:慢性肾小球肾炎 49 例,慢性肾盂肾炎 21 例,高血压肾病 10 例,多囊肾 6 例。采用随机数字法将其分为观察组 46 例与对照组 40 例,观察组男 23 例,女 23 例,年龄 18-71 岁,平均年龄(48.3±13.7)岁,透析年限(2.7±1.6)年,周围神经病变病程(1.5±0.6)年;对照组男 19 例,女 21 例,年龄 22-73 岁,平均年龄(46.3±11.4)岁,透析年限(2.4±1.9)年,周围神经病变病程(1.3±0.7)年。两组的性别、年龄、透析年限、周围神经病变病程比较差异

均无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

两组患者每周行常规血液透析(HD)3 次(国产宝法利 14 L 血液透析器),每 2 周行血液透析滤过 (HDF)1 次 (国产 REX-EED-15UC 血液透析滤过器),保证充分透析(尿素清除指数>1.3),常规低分子肝素抗凝,在此基础上观察组在每次透析后静脉推注甲钴胺注射液 (昆明金殿制药有限公司,国药准字 H20045519) 0.5 mg。观察期共 24 周。

1.3 观察指标

① 分别在治疗前后抽取空腹静脉血 5 mL,采用 ELISA 法检测血清 C- 反应蛋白(CRP)(德国 BrahmsDiagnostica 提供试剂盒)、肿瘤坏死因子- α (TNF- α),白细胞介素-6(IL-6)及 IL-8(美国 Biosource 公司提供试剂盒)。② 使用美国尼高力 Viking IV 型心电图及诱发电位仪检查肢体正中神经与腓浅神经的 SCV。③ 观察临床症状、体征改善情况,包括感觉减退、四肢远端麻木与烧灼感、不宁腿综合征、肢端疼痛等。

1.4 统计学方法

应用 SPSS 17.0 统计软件进行数据分析,计量资料均以($\bar{x} \pm s$)表示,采用 t 检验;计数资料以率表示,采用 χ^2 检验。P<0.05 为差异有统计学意义。

2 结果

2.1 两组治疗前后血清 CRP、TNF- α 、IL-6、IL-8 水平的比较

两组治疗后血清 CRP、TNF- α 、IL-6、IL-8 水平均较治疗前明显下降(P<0.05),且观察组以上指标均明显低于对照组(P<0.05),见表 1。

表 1 两组治疗前后血清 CRP、TNF- α 、IL-6、IL-8 水平的比较($\bar{x} \pm s$)

Table 1 Comparison of the serum CRP, TNF- α , IL-6, IL-8 levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	CRP(mg/L)		TNF- α (ng/L)		IL-6(ng/L)		IL-8(ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group(n=46)	102.34±22.16	89.07±14.89 [#]	89.56±15.37	52.96±11.25 [#]	70.43±9.51	56.75±10.38 [#]	135.19±42.00	70.01±1.29 [#]
Control group (n=40)	101.64±26.44	93.66±19.25 [*]	88.28±14.17	67.29±10.34 [*]	68.96±20.13	60.08±12.14 [*]	137.38±52.79	91.97±2.09 [*]

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

2.2 两组治疗前后神经传导速度比较

两组治疗后正中神经与腓总神经 SCV 均较治疗前明显提

高(P<0.05),且观察组正中神经 SCV 明显高于对照组(P<0.05),见表 2。

表 2 两组治疗前后神经传导速度比较($\bar{x} \pm s$)

Table 2 Comparison of the nerve conduction velocity between two groups before and after treatment($\bar{x} \pm s$)

Groups	Median nerve SCV		Peroneal nerve SCV	
	Before treatment	After treatment	Before treatment	After treatment
Treatment group(n=46)	35.22±6.09	48.39±5.36 [*]	31.58±4.46	38.76±5.53 [*]
Control group(n=40)	35.77±5.33	40.17±7.48 [#]	31.54±5.82	36.35±6.63 [*]

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

2.3 两组治疗后主要症状体征比较

观察组治疗后四肢感觉减退、四肢远端麻木与烧灼感、不宁腿综合征、肢端疼痛的发生率明显低于对照组(P<0.05),见表 3。

3 讨论

目前,尿毒症性周围神经病只有通过肾脏移植才能彻底治

表 3 两组治疗后主要症状体征比较[例(%)]

Table 3 Comparison of the main symptoms and signs after treatment between two groups[n(%)]

Groups	Limb loss	Acral pain	Numbness and burning sensation	Restless legs syndrome
Treatment group(n=46)	14(17.5)*	13(16.3)*	18(22.5)*	7(8.8)*
Control group(n=40)	25(31.3)	25(31.3)	32(40.0)	16(20.0)

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

愈,但这种治疗手段并不普及,绝大部分需依赖血液净化^[10,11]。而在此基础上辅以一些神经营养药物对尿毒症性周围神经病具有较好的疗效。甲钴胺是存在于血液与脑脊液中的辅酶维生素 B12,在核酸、蛋白质及卵磷脂合成过程中具有重要作用,可促进神经髓鞘形成及轴突再生^[12-14]。研究表明通过外源性补充甲钴胺能够使周围神经轴索结构蛋白输送恢复正常,从而使轴索再生,减轻髓鞘病变,改善周围神经传导速度^[15-17]。维生素 B12 需经肝脏代谢成甲钴胺才可发挥药理作用,而甲钴胺注射液无需经肝脏代谢,所以在同等剂量下,后者在血液和脑脊液中的浓度更高,而且长时间使用不会加重对肝脏的毒害性^[18,19]。

对于甲钴胺的研究目前主要集中于糖尿病周围神经病变,有研究显示甲钴胺的疗效比较理想,而也有一些研究显示甲钴胺仅能部分缓解临床症状体征,不能阻断病情进展,长时间应用不良反应明显,需要联合其它药物增进疗效^[20-22]。本研究采用甲钴胺治疗尿毒症性周围神经病变,结果显示甲钴胺联合血液净化治疗的周围神经病变患者正中神经 SCV 明显高于血液净化治疗,临床症状、体征改善情况明显优于血液净化治疗,说明规律的血液透析滤过能够清除体内代谢毒物,减轻周围神经细胞所受的损害,但作用是有限的,而外源性补充甲钴胺可进一步促进受损神经细胞及髓鞘的修复,从而显著改善患者的周围神经传导速度和四肢交感皮肤反应性,缓解肌肉麻木、疼痛、烧灼感等症状,改善患者的生活质量。

微炎症的产生与肾排泄功能直接相关,肾脏病变患者机体免疫功能紊乱,肾衰竭时对晚期糖基化终末产物的清除能力降低,同时氧化应激加重,造成炎性蛋白和炎性细胞因子大量合成、释放,自始至终都伴有炎性因子的异常表达^[23,24]。研究显示无论有无接受血液透析,慢性肾衰竭患者的 CRP 有不同程度升高,提示这类患者已处在机体免疫应答改变的异常状态,与之伴随的血清蛋白标志物发生急性时相反应,刺激单核细胞/巨噬细胞大量释放细胞因子,肝脏合成、分泌 CRP^[25,26]。而由于透析通路的慢性隐匿性感染、透析膜的生物相容性以及透析液质量等于透析过程相关因素的影响,长期血液净化治疗会导致微炎症状态加倍严重^[27,28]。肿瘤坏死因子类(TNFs)和白细胞介素类(ILs)是与肾脏病变关系最紧密的细胞因子之一,在慢性肾衰竭微炎症状态中 IL-6 是 ILs 中升高最明显的细胞因子^[29,30]。持续微炎症可使神经转氨酶活性受抑制,从而加重周围神经细胞的损害,导致神经脱髓鞘病变。因此,减轻微炎症状态有利于改善周围神经病变。本研究显示甲钴胺联合血液净化治疗的周围神经病变患者治疗后 CRP、TNF- α 、IL-6、IL-8 均明显低于血液净化治疗的周围神经病变患者,说明血液透析滤过能够一定程度降低炎症介质水平,而加用甲钴胺可促进炎症介质水平进一步降低,其中的原因可能与神经营养作用减轻了周围神经细

胞的损伤,在整体上减轻了机体氧化应激,从而使炎症介质减少有关。

综上所述,甲钴胺联合血液透析对尿毒症性周围神经病变的疗效明显优于单用血液透析治疗,且可显著改善机体的微炎症状态。

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