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百令胶囊联合左卡尼汀对维持性血液透析患者氧化应激、T 淋巴细胞亚群及营养状态的影响 *

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摘要 目的：探讨百令胶囊联合左卡尼汀对维持性血液透析（MHD）患者氧化应激、T 淋巴细胞亚群及营养状态的影响。**方法**：选取我院于 2015 年 6 月至 2017 年 4 月期间接受 MHD 治疗的慢性肾衰竭患者 72 例为研究对象。按照数表法将患者随机分为对照组（n=36）和实验组（n=36）。两组患者均行 MHD 治疗，实验组患者在此基础上给予百令胶囊联合左卡尼汀治疗，疗程均为 6 个月。比较两组治疗前、治疗 6 个月后的氧化应激指标：血浆丙二醛（MDA）、血浆谷胱甘肽过氧化物酶（GSHPx）、血浆总高半胱氨酸（tHcy）水平，免疫功能指标：$CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$，营养状态指标：血红蛋白（Hb）、白蛋白（Alb）、前白蛋白（PA）、总胆固醇（TCh）、三酰甘油（TG）、脂蛋白（a）[Lp（a）]。**结果**：两组患者治疗 6 个月后 MDA、tHcy 水平下降，且实验组低于对照组（*P<0.05*）；治疗 6 个月后实验组患者 GSHPx 水平高于治疗前与对照组（*P<0.05*），而对照组 GSHPx 水平与治疗前相比差异无统计学意义（*P>0.05*）。治疗 6 个月后，实验组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平高于治疗前及对照组，而 $CD8^+$ 低于治疗前及对照组（*P<0.05*）。实验组治疗 6 个月后 Hb、Alb、PA 水平高于治疗前及对照组，而 Lp（a）低于治疗前及对照组（*P<0.05*），实验组患者 TCh、TG 水平与治疗前比较差异无统计学意义（*P>0.05*）；对照组治疗 6 个月后 Hb、Alb、PA、TCh、TG、Lp（a）水平与治疗前比较差异均无统计学意义（*P>0.05*）。**结论**：百令胶囊联合左卡尼汀可减轻 MHD 患者氧化应激反应，调节 T 淋巴细胞亚群，同时改善患者营养状况，值得临床推广应用。

关键词：百令胶囊；左卡尼汀；维持性血液透析；氧化应激；T 淋巴细胞亚群；营养状态

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Effects of Bailing Capsule Combined with Levocarnitine on Oxidative Stress, T Lymphocyte Subsets and Nutritional Status in Patients with Maintenance Hemodialysis*

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ABSTRACT Objective: To investigate the effects of Bailing Capsule Combined with Levocarnitine on oxidative stress,T lymphocyte subsets and nutritional status in patients with maintenance hemodialysis (MHD). **Methods:** 72 patients with chronic renal failure treated with MHD in our hospital from June 2015 to April 2017 were selected as the subjects. The patients were randomly divided into control group (n=36) and experimental group (n=36) in accordance with the number table method. The two groups were treated with MHD, the experimental group were given Bailing Capsule combined with Levocarnitine on this basis, the course of treatment was 6 months. Oxidative stress indicators: plasma malondialdehyde (MDA), plasma glutathione peroxidase (GSHPx), plasma total homocysteine (tHcy) level, Immune function indicators: $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$, nutritional status indicators: hemoglobin (Hb), albumin (Alb), prealbumin (PA), total cholesterol (TCh), three acylglycerol (TG), lipoprotein (a) [Lp (a)] were compared before and 6 months after treatment. **Results:** The levels of MDA and tHcy decreased 6 months after treatment in the two groups,and the experimental group was lower than that of the control group (*P<0.05*). The level of GSHPx in the experimental group 6 months after treatment was higher than that before the treatment and the control group (*P<0.05*). There was no significant difference in the level of GSHPx in the control group compared with that before the treatment (*P>0.05*). The level of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in the experimental group 6 months after treatment was higher than before reatment and the control group,while the $CD8^+$ was lower than that before treatment and the control group (*P<0.05*). The level of Hb, Alb and PA in the experimental group 6 months after treatment were higher than before treatment and the control group, while the Lp (a) was lower than before treatment and the control group (*P<0.05*). There was no significant difference in the level of TCh and TG between the patients in the experimental group and before treatment (*P>0.05*). There was no significant difference in the level of Hb, Alb, PA, TCh, TG, Lp (a) after 6 months of treatment in the control group compared with before treatment (*P>0.05*). **Conclusion:** Bailing Capsule Combined with L-carnitine can alleviate oxidative stress in

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patients with MHD, the regulation of T lymphocyte subsets, and improve the nutritional status of the patients, it is worthy of clinical application.

Key words: Bailing capsule; Levocarnitine; Maintenance hemodialysis; Oxidative stress; T lymphocyte subsets; Nutritional status

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前言

维持性血液透析(maintenance hemodialysis,MHD)多用于治疗各种终末期肾脏疾病,是临床应用较为广泛的肾脏替代疗法之一,可帮助患者有效的排出因肾功能障碍而无法清除的代谢废物[1-3]。尽管该治疗方式可改善肾脏疾病患者的临床症状,延长生存期,但 MHD 通常只能清除小分子物质,并不能真正的代替正常肾脏所有复杂的代谢以及内分泌功能,所以肾脏疾病患者在经过长期反复的透析治疗后,易引发多种 MHD 并发症,如慢性炎症、免疫功能下降等[4-6]。另有相关研究报道指出[7],行 MHD 治疗的患者通常存在不同程度的营养不良状态。因此,寻找有效的防治手段以改善 MHD 患者的氧化应激状态,维持患者正常免疫功能及营养状态具有积极的临床意义。百令胶囊是采用生物工程方法分离的冬虫夏草菌种经低温发酵精制而成,可有效改善肾小管功能损伤[8]。左卡尼汀是一种机体必需营养素,具有促进脂类代谢的功效,对多种系统疾病均有较好的治疗效果[9,10]。本研究通过采用百令胶囊与左卡尼汀联合治疗,分析上述治疗方式对 MHD 患者氧化应激、T 淋巴细胞亚群及营养状态的影响,旨在为 MHD 患者临床治疗及预后提供数据支持,现作如下报道。

1 资料与方法

1.1 一般资料

选取我院于 2015 年 6 月至 2017 年 4 月期间接受 MHD 治疗的慢性肾衰竭患者 72 例为研究对象。纳入标准:(1)所有患者透析龄均≥ 6 个月,透析频率每周 2-3 次;(2)近期内无急慢性感染、心力衰竭及手术史者;(3)入院前未使用过相关降脂类药物治疗者;(4) 所有患者及其家属知情同意并签署知情同意书。排除标准:(1)伴有免疫缺陷疾病者;(2)合并肿瘤、甲状腺疾病者;(3)使用过糖皮质激素或者免疫抑制剂者;(4)并发 2 型糖尿病、病毒性肝炎者。按照数表法将患者随机分为对照组(n=36)和实验组(n=36),其中对照组男 17 例,女 19 例,年龄 45-67 岁,平均(55.26± 3.48)岁;病程 1-10 年,平均(5.26± 1.47)年;透析龄 7-28 月,平均(20.18± 2.69)月;原发病:慢性肾炎 8 例,糖尿病肾病 9 例,高血压肾损害 7 例,多囊肾 5 例,缺血性肾病 6 例,梗阻性肾病 1 例。实验组男 20 例,女 16 例,年龄 46-70 岁,平均(54.28± 3.89)岁;病程 1-9 年,平均(4.88± 1.65)年;透析龄 6-30 月,平均(19.48± 3.01)月;原发病:慢性肾炎 9 例,糖尿病肾病 7 例,高血压肾损害 5 例,多囊肾 7 例,缺血性肾病 5 例,梗阻性肾病 3 例。两组患者一般资料比较差异无统计学意义(*P>0.05*),均衡可比。本研究经医院伦理委员会批准同意。

1.2 方法

1.2.1 治疗方法 采用德国费森尤斯医药用品有限公司生产的透析机、聚砜膜透析器,有效膜面积 1.5 m^2,透析液流量 500 mL/min,血流速度 180-240 mL/min,低分子肝素抗凝,所有患者均进行 1 周 3 次的 MHD 治疗,单次透析时间均为 4h,透析期间两组均常规控制血压、血糖,纠正贫血,并根据患者病情给予相关对症干预治疗。实验组在上述治疗的基础上加用百令胶囊与左卡尼汀联合治疗:口服百令胶囊(杭州中美华东制药有限公司,国药准字 Z10910036,每粒装 0.5 g),4 粒 / 次,3 次 /d;静脉注射左卡尼汀 (海南通用康力制药有限公司, 国药准字:H20070286,规格:0.5 g),每次透析后将 1.0 g 左卡尼汀溶于 20 mL 生理盐水中进行注射。两组患者疗程均为 6 个月。

1.2.2 血标本采集与检测 分别于治疗前、治疗 6 个月后采集所有患者清晨空腹静脉血 15 mL,均分为三份。血标本之一 3000 r/min 离心 10 min,取上清液置于 -70℃ 冰箱中待测。血浆丙二醛(malondialdehyde,MDA)水平检测采用硫代硫酸巴比妥法,血浆谷胱甘肽过氧化物酶(glutathione peroxidase,GSHPx)水平检测采用分光光度法,血浆总高半胱氨酸(total homocysteine,tHcy)水平检测采用 HPLC 法,试剂盒均购自上海捷门生物科技有限公司,严格按照说明书进行操作。血标本之二以 1500 r/min 离心 5 min,离心半径 6 cm,弃上清,采用 BD 流式细胞仪测定 T 淋巴细胞亚群 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平。血标本之三用于检测营养状态指标,包括血红蛋白(hemoglobin,Hb)、白蛋白(albumin,Alb)、前白蛋白(prealbumin,PA)、总胆固醇(total cholesterol,TCh)、三酰甘油(three acyl glycerol,TG)、脂蛋白(a)[lipoprotein,Lp(a)],采用 1650 全自动生化分析仪进行检测。

1.3 观察指标

氧化应激指标:比较两组治疗前、治疗 6 个月后的 MDA、GSHPx、tHcy 水平;免疫功能:比较两组治疗前、治疗 6 个月后的 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平;营养状态:比较两组治疗前、治疗 6 个月后的 Hb、Alb、PA、TCh、TG 以及 Lp(a)。

1.4 统计学方法

数据分析采用 SPSS24.0 软件进行,计量资料以 ($\bar{x}\pm s$)表示,实施 t 检验,计数资料以率或百分比表示,实施 x^2 检验,检验标准设置为 α=0.05。

2 结果

2.1 两组患者治疗前、治疗 6 个月后氧化应激指标比较

两组患者治疗前 MDA、GSHPx、tHcy 水平比较差异无统计学意义(*P>0.05*);两组患者治疗 6 个月后 MDA、tHcy 水平下降,且实验组低于对照组(*P<0.05*);治疗 6 个月后实验组患者 GSHPx 水平高于治疗前与对照组(*P<0.05*),而对照组 GSHPx 水平与治疗前相比差异无统计学意义(*P>0.05*);详见表 1。

2.2 两组患者治疗前、治疗 6 个月后 T 淋巴细胞亚群比较

两组患者治疗前 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平比较

表 1 两组患者治疗前、治疗 6 个月后氧化应激指标比较($\bar{x}\pm s$)

Table 1 Comparison of oxidative stress indicators before and after 6 months after treatment in two groups ($\bar{x}\pm s$)

Groups	Time	MDA(nmol/L)	GSHPx(μmol/L)	tHcy(μmol/L)
Control group(n=36)	Before treatment	5.18± 1.55	75.31± 1.25	28.56± 3.65
	6 months after treatment	4.16± 0.48*	74.16± 3.23	21.17± 3.25*
Experimental group(n=36)	Before treatment	5.01± 1.04	74.37± 1.12	29.98± 3.87
	6 months after treatment	3.43± 0.15*&	87.09± 2.74*&	18.03± 3.16*&

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

差异无统计学意义（$P>0.05$）；治疗 6 个月后，实验组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平高于治疗前及对照组，而 $CD8^+$ 低于治疗前及对照组（$P<0.05$）；治疗 6 个月后对照组患者 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平与治疗前比较差异无统计学意义（$P>0.05$）；详见表 2。

表 2 两组患者治疗前、治疗 6 个月后 T 淋巴细胞亚群比较($\bar{x}\pm s$)

Table 2 Comparison of T lymphocyte subsets before and after 6 months after treatment in two groups ($\bar{x}\pm s$)

Groups	Time	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	$CD4^+/CD8^+$(%)
Control group(n=36)	Before treatment	52.38± 6.43	33.79± 5.69	33.51± 6.45	0.93± 0.38
	6 months after treatment	53.78± 6.71	35.18± 6.55	32.14± 5.68	1.07± 0.26
Experimental group(n=36)	Before treatment	51.43± 7.12	34.08± 6.58	33.63± 5.12	0.98± 0.35
	6 months after treatment	59.93± 7.56*&	39.01± 6.34*&	28.78± 5.51*&	1.41± 0.25*&

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

2.3 两组患者治疗前、治疗 6 个月后营养指标比较

两组患者治疗前 Hb、Alb、PA、TCh、TG、Lp(a)水平比较差异无统计学意义（$P>0.05$）；实验组治疗 6 个月后 Hb、Alb、PA 水平高于治疗前及对照组，而 Lp(a)低于治疗前及对照组（$P<0.05$），实验组患者 TCh、TG 水平与治疗前比较差异无统计学意义（$P>0.05$）；对照组治疗 6 个月后 Hb、Alb、PA、TCh、TG、Lp(a)水平与治疗前比较差异均无统计学意义（$P>0.05$）；详见表 3。

表 3 两组患者治疗前、治疗 6 个月后营养指标比较($\bar{x}\pm s$)

Table 3 Comparison of nutritional status before and after 6 months after treatment in two groups ($\bar{x}\pm s$)

Groups	Time	Hb(g/L)	Alb(g/L)	PA(mg/L)	TCh(mmol/L)	TG(mmol/L)	Lp(a)(mg/L)
Control group (n=36)	Before treatment	82.43± 10.12	33.98± 5.27	248.32± 28.12	4.42± 1.41	1.68± 1.34	289.89± 145.09
	6 months after treatment	84.01± 9.83	34.59± 6.02	253.89± 29.55	4.51± 1.12	1.72± 1.33	291.18± 153.23
Experimental group (n=36)	Before treatment	81.83± 10.73	33.37± 6.34	247.14± 29.87	4.52± 1.33	1.73± 1.22	286.93± 152.23
	6 months after treatment	93.74± 11.28*&	39.12± 5.98*&	290.43± 30.65*&	4.01± 1.08	1.70± 1.45	256.59± 173.06*&

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

3 讨论

随着透析治疗次数的增加，MHD 患者残余肾功能不断衰退，易引发多方面的不利影响，如微炎症状态、营养不良以及免疫力下降等，对患者的生活质量、透析效果以及生存率产生了极大的影响[11-13]。因此，对 MHD 患者透析后实施综合干预具有积极的临床意义。左卡尼汀作为一种氨基酸的衍生物，广泛存在于体内不同的组织细胞中，有相关研究报道已证实左卡尼汀作为抗氧化剂，可促进脂肪进行分解代谢，协助细胞维持生理活动的能量生成[14-16]。百令胶囊主要成分包含虫草酸、19 种氨基酸、多种维生素以及微量元素等，可发挥补肺肾、益精气的作用，目前临床多用于肾脏疾病患者以补充血浆必须氨基酸，改善营养情况，继而延缓肾衰发展[17-18]。肾脏疾病患者由于长期的 MHD 治疗，致使体内左卡尼汀水平普遍低于正常水平，并伴有不同程度的营养不良症状[19-21]。

氧化应激是由于活性氧、抗氧化防御机制平衡失调所造成的组织损伤，可对患者体内蛋白质、脂质以及碳水化合物分解造成影响[22,23]。目前临床常用的氧化应激标志物有 MDA、tHcy 以及 GSHPx，MDA 是体内引发过氧化作用的最终毒性产物，GSHPx 是人体内重要的生物酶，其活性降低表明机体抗氧化能力受损，tHcy 则可以增强脂质过氧化[24-26]。本次研究结果表明两组患者治疗 6 个月后 MDA、tHcy 水平下降，且实验组低于对照组，实验组患者治疗 6 个月后 GSHPx 水平高于治疗前与对照组（$P<0.05$）。表明经百令胶囊与左卡尼汀联合治疗后，MHD 患者氧化应激状态得到明显缓解，这与左卡尼汀可阻断蛋白激酶 C 以及 NADPH 途径有关，进而改善氧化应激反应。

本次研究结果还显示治疗 6 个月后对照组患者 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平与治疗前比较差异无统计学意义（$P>0.05$），表明单独应用 MHD 治疗并不能改善肾脏疾病患者免疫功能状况。而实验组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平高于治疗前及对照组，$CD8^+$ 低于治疗前及对照组（$P<0.05$），提示百令胶囊联合左卡尼汀可调节 T 淋巴细胞亚群，改善免疫功能状况。相关研究报道左卡尼汀可上调 $CD3^+$、$CD4^+$ 以及 $CD4^+/CD8^+$ 的比值，进而改善患者免疫功能，这与本研究结果基本一致[27]。左卡尼汀对免疫功能的改善作用机制如下：（1）左卡尼汀可促进中性粒细胞吞噬、杀菌，同时可改善患者红细胞免疫功能；（2）左卡尼汀可促进脂肪酸氧化，使胰岛素抵抗及蛋白质代谢得到改善，促进 T 淋巴细胞分化生长，并减少凋亡；（3）左卡尼汀可抑制炎症因子生长，清除过多的氧自由基作用，继而增强 T 淋巴细胞功能[28]。另外由于百令胶囊成分与天然虫草基本一致，具有抑制甲状旁腺激素分泌的功能，同时还可提供肾脏疾病患者体内所需的多种氨基酸，继而改善患者营养状态[29]。本次结果表明实验组治疗 6 个月后 Hb、Alb、PA 水平高于治疗前及对照组，而 Lp(a)低于治疗前及对照组（$P<0.05$），以上结果均表明经百令胶囊联合左卡尼汀治疗后，MHD 患者营养状态明显得到改善，Hb、Alb、PA 等指标显著升高，这可能与百令胶囊的药理活性有关，促使患者体能以及主观感受得到明显改善[30]。

综上所述，MHD 患者采用百令胶囊与左卡尼汀联合治疗后，可减轻氧化应激反应，进而改善患者营养状态，还可通过调节 T 淋巴细胞亚群改善患者免疫功能状况，对延长 MHD 患者生存期具有积极的临床意义。

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