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重组人促红细胞生成素对血液透析患者营养状况和免疫功能的影响*

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摘要 目的:研究重组人促红细胞生成素对血液透析患者营养状态和免疫功能的影响。**方法:**选取 2015 年 8 月至 2016 年 4 月在我院进行维持性血液透析的患者共 139 名,随机分为对照组和观察组。对照组患者接受常规铁剂、叶酸等辅助治疗;观察组患者在常规治疗的基础上加用重组人促红细胞生成素。比较两组患者治疗前后血红蛋白、红细胞压积、营养状况(前白蛋白和转铁蛋白)以及免疫功能(CD4⁺细胞、CD8⁺细胞、CD4⁺/CD8⁺细胞和免疫球蛋白)等指标。**结果:**两组患者治疗前血红蛋白、红细胞压积、营养状况指标和免疫功能指标比较均没有统计学差异($P>0.05$)。治疗 12 周后,两组患者治疗后的血红蛋白、红细胞压积、前白蛋白、转铁蛋白均较治疗前显著升高($P<0.05$),且观察组患者以上指标较对照组升高更为明显($P<0.05$)。对照组患者治疗后的 CD4⁺细胞比例较治疗前明显升高($P<0.05$),但 CD8⁺细胞和 CD4⁺/CD8⁺细胞比例没有显著变化($P>0.05$),而观察组治疗后这三类细胞的比例均较治疗前明显升高($P<0.05$)。观察组治疗后 IgA、IgM 和 IgG 浓度均较治疗前显著提升($P<0.05$),而对照组只有 IgA 和 IgM 浓度在治疗后有明显提高($P<0.05$),但仍显著低于观察组($P<0.05$)。**结论:**重组人促红细胞生成素能有效纠正血液透析患者的贫血情况,改善其营养状况并提高其免疫功能。

关键词:重组人促红细胞生成素;血液透析;营养状况;免疫功能

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Impact of Recombinant Human Erythropoietin on the Nutritional Status and Immunity of Patients Undergoing Hemodialysis*

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ABSTRACT Objective: To investigate the effect of recombinant human erythropoietin on the nutritional status and immune function of hemodialysis patients. **Methods:** A total of 139 patients undergoing hemodialysis in our hospital from August 2015 to April 2016 were involved in this study. They were randomly divided into two groups, the control group and the observation group. Patients in the control group were given regular adjuvant therapy, such as oral iron and folic acid. And those in the observation group were given rhuEPO besides regular adjuvant therapy. The hemoglobin (Hb), hematocrit (Hct), nutritional status (prealbumin, PA and transferrin, TFR) and immunity function (including the ratio of CD4⁺ cells, CD8⁺ cells and CD4⁺/CD8⁺ cells, and immunoglobulin) in two groups were compared before and after corresponding treatment. **Results:** There was no statistically significant difference in the hemoglobin, hematocrit, nutritional status and immune function between the two groups ($P>0.05$). After treatment for 12 weeks, the hemoglobin and hematocrit, prealbumin and transferrin were significantly increased ($P<0.05$). After treatment, the above indexes in the observation group were significantly higher than those in the control group ($P<0.05$). The levels of prealbumin and transferrin were significantly higher in the two groups than in the control group ($P<0.05$), but the levels of prealbumin and transferrin in the observation group were significantly different from those in the observation group ($P<0.05$). ($P<0.05$), but the ratio of CD4⁺/CD8⁺ cells showed no significant change ($P>0.05$); while the proportion of CD4⁺ cells in the control group was significantly higher than that before treatment. The ratio of these three types of cells after treatment had significantly increased compared with before treatment ($P<0.05$). The IgA, IgM and IgG concentrations in the treatment group were significantly higher than those in the control group ($P<0.05$), only IgA and IgM in the control group was significantly increased after treatment ($P<0.05$), but were still lower than the observation group ($P<0.05$). **Conclusion:** Recombinant human erythropoietin could effectively correct the anemia of hemodialysis patients, improve the nutritional status, and improve the immune function.

Key words: Recombinant human erythropoietin (rhuEPO); Hemodialysis; Nutritional status; Immunity

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前言

慢性肾功能不全是指各种原因造成的慢性进行性肾实质损害,致使肾脏明显萎缩,不能维持其正常的基本功能,临床出现以代谢产物滞留、水、电解质、酸碱平衡失调,全身各系统受累为主要表现的临床综合征^[45]。对于严重的慢性肾功能不全患者,血液透析(Hemodialysis, HD)是目前最重要的治疗方式。血液透析是将体内血液引流至体外,经过透析器清楚血液中的代谢废物、多余的电解质、酸碱产物、水分等,再将过滤后的血液重新输注回人体体内,以体外透析器替代病变的肾脏功能,维持患者体内的代谢、水电解质及酸碱平衡^[67]。虽然血液透析可以帮助慢性肾功能不全患者排泄代谢产物,但在血液透析维持期间,也会出现很多急性或者慢性的并发症,贫血、营养不良等都是其中最为常见的并发症^[189]。重组人促红细胞生成素是一种人工合成的激素,在临床上被逐渐应用及推广,在肾性贫血患者中取得很好的疗效^[2]。为了进一步研究重组人促红细胞生成素对血液透析患者营养状态和免疫功能的影响,我们选取了2015年8月至2016年4月间在我院进行维持性血液透析的患者进行研究,比较患者治疗前后红细胞、营养状况和免疫功能的变化,现报道如下。

1 资料和方法

1.1 临床资料

选取2015年8月至2016年4月在我院行维持性血液透析的慢性肾功能不全患者共139例,其中男性72例,女性67例,年龄43-67岁,平均51.47性慢性岁。入组标准:(1)符合2012年国际肾脏病组织公布的《KDIGO慢性肾评估与管理临床实践指南》中对慢性肾病毒毒症期的诊断标准^[3],即肾小球滤过率(Glomerular filtration rate, GFR)小于15 mL/(min × 1.73 m²);(2)患者已接受规律性血液透析治疗大于6个月,每周透析2-3次,每次4小时;(3)合并有肾性贫血,血红蛋白<85 g/L,血清铁蛋白<200 μg/L;(4)了解本次研究内容,自愿参加本次研究。排除标准:(1)怀疑有其他原因引起的贫血;(2)合并有其他器官系统严重病变或恶性肿瘤;(3)合并有急性感染。随机将患者分为观察组和对照组,对照组65例,其中男性33例,女性32例,年龄52.3男性感染岁,原发病为慢性肾小球肾炎25例,糖尿病性肾病17例,高血压性肾病12例,间质性肾炎9例,多囊肾2例;观察组74例,男性39例,女性35例,年龄50.9组肾炎病岁,原发病为慢性肾小球肾炎31例,糖尿病性肾病19例,高血压性肾病16例,间质性肾炎7例,多囊肾1例。两组患

者年龄、性别、原发病、肾功能指标等一般病情资料比较,差异没有统计学意义($P>0.05$),具有可比性。

1.2 方法

1.2.1 治疗方法 对照组患者接受常规口服铁剂、叶酸等辅助治疗。观察组患者在接受常规治疗的同时,加用重组人促红细胞生成素(沈阳三生制药有限责任公司,规格:4000 IU/支,国药准字:201603047v),皮下注射,每次4000 U,每周2次,连续治疗12周。两组患者均接受血液透析治疗,每周3次,每次4小时。治疗期间禁止输血或使用免疫抑制剂。

1.2.2 血常规检测 采取患者静脉血,采用UniCel DxH 800 Coulter血液分析仪(Beckman coulter)分析测定患者血红蛋白(Hb)和红细胞比容(Hct)。

1.2.3 营养状况检测 选取前白蛋白(PA)和转铁蛋白(TRF)作为评价患者营养状况的指标。采用日立7180型全自动生化分析仪,采用免疫比浊法测定前白蛋白和转铁蛋白浓度,所有操作均严格按照相关试剂盒的操作说明进行。

1.2.4 T细胞分类检测和免疫球蛋白检测 取患者静脉血,肝素抗凝后,采用FACSCalibur流式细胞仪(BD Biosciences)对T细胞进行分类计数,检测CD4⁺、CD8⁺和CD4⁺/CD8⁺的T细胞数量,CD4⁺和CD8⁺的荧光抗体由法国Immunotech公司生产。采用日立7180型全自动生化仪,使用免疫比浊法检测免疫球蛋白IgA、IgM和IgG浓度,所有操作均遵照相关试剂盒操作说明进行。

1.3 观察指标

比较两组患者用药前和用药12周后血红蛋白、红细胞比容、营养状况、免疫功能(包括T细胞分类和免疫球蛋白)的变化情况。

1.4 统计学分析

采用SPSS 19.0软件进行数据录入及分析。计量资料采用均数±方差的形式表示,组内采用配对t检验进行比较分析,组间采用独立样本t检验进行分析;计数资料采用频数(百分比)表示,组间采用卡方检验进行比较。以 $P<0.05$ 为差异存在统计学意义。

2 结果

2.1 两组患者治疗前后Hb和Hct值比较

两组患者治疗前Hb和Hct值比较没有显著差异($P>0.05$)。接受相应12周治疗后,两组患者的Hb和Hct均有显著升高($P<0.05$),且观察组患者的Hb和Hct值均明显高于对照组($P<0.05$)。详见表1。

表1 两组患者治疗前后Hb和Hct比较

Table 1 Comparison of the Hb and Hct pre- and post- treatment between two groups

Groups	Cases	Time point	Hb (g/L)	Hct (%)
Control group	65	Pre-treatment	67.3± 10.4	21.4± 2.9
		Post-treatment	74.5± 11.2 ^a	25.7± 3.0 ^a
Observation group	74	Pre-treatment	66.9± 9.7	21.8± 3.1
		Post-treatment	93.4± 12.3 ^{ab}	29.3± 2.7 ^{ab}

Notes: a: significant difference when compared to pre-treatment, $P<0.05$; b: significant difference when compared to the control group, $P<0.05$.

2.2 两组患者治疗前后营养状况比较

治疗前,两组患者 PA 和 TRF 水平比较差异没有统计学意义($P>0.05$)。治疗后,两组患者的 PA 值均较治疗前有显著提高

($P<0.05$), 对照组治疗后的 TRF 值与治疗前无明显差异($P>0.05$), 而观察组治疗后的 PA 和 TRF 均明显升高($P<0.05$)。详见表 2。

表 2 两组患者治疗前后营养状况比较

Table 2 Comparison of the nutrition pre- and post-treatment between two groups

Groups	Cases	Time point	PA (mg/L)	TRF (g/L)
Control group	65	Pre-treatment	220.36± 41.65	1.94± 0.24
		Post-treatment	279.54± 48.34 ^a	2.59± 0.51 ^a
Observation group	74	Pre-treatment	222.14± 43.51	1.89± 0.26
		Post-treatment	330.74± 56.78 ^{ab}	3.22± 0.63 ^{ab}

Notes: a: significant difference when compared to pre-treatment, $P<0.05$; b: significant difference when compared to the control group, $P<0.05$.

2.3 两组患者治疗前后免疫功能比较

两组患者治疗前 $CD4^+$ 细胞百分比、 $CD8^+$ 细胞百分比、 $CD4^+/CD8^+$ 细胞百分比、IgA、IgM 和 IgG 等免疫功能指标比较均没有显著统计学差异($P>0.05$)。治疗后,对照组患者 $CD4^+$ 细胞比例、IgA 和 IgM 的值均明显升高($P<0.05$), 而观察组患者治

疗后的 $CD4^+$ 细胞比例、 $CD4^+/CD8^+$ 细胞比例以及 IgA、IgM 和 IgG 三类免疫球蛋白均有明显升高($P<0.05$), 而 $CD8^+$ 细胞比例显著降低($P<0.05$)。治疗后,观察组患者上述六项免疫功能指标与对照组相比均有明显差异($P<0.05$)。详见表 3。

表 3 两组患者治疗前后免疫功能比较

Table 3 Comparison of the immunity pre- and post- treatment between two groups

Groups	Cases	Time point	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$ (%)	IgA(g/L)	IgM(g/L)	IgG(g/L)
Control group	65	Pre-treatment	38.13± 6.54	36.47± 5.98	1.047± 0.123	1.177± 0.245	1.597± 0.287	10.57± 2.13
		Post-treatment	40.13± 7.16 ^a	36.01± 4.69	1.071± 0.121	1.321± 0.231 ^a	1.691± 0.304 ^a	11.06± 2.21
Observation group	74	Pre-treatment	38.26± 6.49	36.92± 5.87	1.052± 0.131	1.182± 0.239	1.582± 0.291	10.49± 2.10
		Post-treatment	45.02± 8.13 ^{ab}	30.46± 4.12 ^{ab}	1.696± 0.12 ^{ab}	1.616± 0.456 ^{ab}	1.976± 0.342 ^{ab}	16.49± 3.48 ^{ab}

Notes: a: significant difference when compared to pre-treatment, $P<0.05$; b: significant difference when compared to the control group, $P<0.05$.

3 讨论

多数慢性肾功能不全维持性血液透析患者都有贫血的临床表现,这主要与促红细胞生成素不足或者活性下降,以及红细胞寿命缩短等有关。因此,对于这一类的患者,临床上常规予以铁剂、维生素 B12 等补充,但对于贫血的治疗效果十分有限^[10]。促红细胞生成素(Erythropoietin,EPO)是主要由肾脏和肝脏分泌的一种肽类激素,可以作用于骨髓红系造血干细胞,促进干细胞分裂、分化、生成红细胞^[11]。慢性肾功能不全患者由于肾脏功能收缩,体内 EPO 的含量显著降低,同时患者血清中存在一些抑制骨髓干细胞分化的毒性物质以及与 EPO 受体竞争结合的毒素,导致红细胞的生成明显减少^[12,13]。重组人促红细胞生成素(Recombinant human erythropoietin,rhuEPO)是利用基因工程技术人工合成的一种促红细胞生成素,对于因 EPO 缺少导致的贫血有较好的治疗效果^[14]。本研究结果显示相比常规输血治疗,rhuEPO 可以进一步提高血液透析患者的血红蛋白量以及红细胞压积,说明 rhuEPO 对血液透析患者的贫血有很好的治疗效果。除了纠正贫血,有研究报告 rhuEPO 对肾衰竭患者改善心血管事件有很大的帮助,这可能贫血纠正后,左心室肥厚等心血管代偿得到一定的改善,进而减少了心血管事件的发生^[15,16]。

我们的研究还显示除了纠正贫血,rhuEPO 对血液透析患者的营养状况也有明显的改善,患者的血清前白蛋白和转铁蛋白量都有显著升高,这与国内外的一些报道相一致。这可能与

患者在贫血纠正后,食欲也有所改善,进而摄入了更多的营养物质,同时 rhuEPO 也有纠正氨基酸代谢异常的作用,两者相结合能够有效改善血液透析患者的营养状况^[17]。另外,EPO 还具有提高免疫功能、抑制炎症因子的释放和减少炎性细胞浸润的作用^[18]。我们的研究结果也证实 rhuEPO 能够有效提高患者 $CD4^+$ 细胞以及 $CD4^+/CD8^+$ 细胞的比例,同时提高 IgA、IgM 和 IgG 免疫球蛋白的浓度,这说明 rhuEPO 能够提高患者的免疫功能。

值得注意的是,rhuEPO 在使用时可能会造成高血压、血栓形成等不良反应,因此在血液透析患者的使用中需加强对相关症状及指标的监测和随访^[19]。在部分患者中,rhuEPO 的治疗效果不佳,主要与铁缺乏有关。因此,在 rhuEPO 使用的同时,加强铁剂的补充也十分重要。除了铁缺乏,有些药物如血管紧张素转换酶抑制剂(ACEI)、血管紧张素受体拮抗剂(ARB)等以及甲状旁腺激素(PTH)水平较高等,都可能降低 rhuEPO 治疗的反应性,在临床工作中需要特别留意^[20]。

综上所述,重组人促红细胞生成素可以有效纠正血液透析患者的贫血情况,改善营养状况,提高免疫功能。

参考文献(References)

- [1] Prasad N, Jha V. Hemodialysis in Asia[J]. Kidney Dis (Basel), 2015, 1 (3): 165-177
- [2] Beiraghdar F, Panahi Y, Einollahi B, et al. Evaluation of a biosimilar recombinant alpha epoetin in the management of anemia in hemodial-

- ysis patients[J]. Saudi Pharm J, 2015, 23(5): 544-548
- [3] KDIGO Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease [J]. Kidney inter, 2012, 2(Suppl): 297-335
- [4] Ghanta M, Jim B. Renal Transplantation in advanced chronic kidney disease patients[J]. Med Clin North Am, 2016,100(3): 465-476
- [5] Qamar A, Bhatt DL. Stroke prevention in atrial fibrillation in patients with chronic kidney disease [J]. Circulation, 2016, 133 (15): 1512-1515
- [6] Roxo RS, Xavier VB, Miorin LA, et al. Impact of neuromuscular electrical stimulation on functional capacity of patients with chronic kidney disease on hemodialysis[J]. J Bras Nefrol, 2016, 38(3): 344-350
- [7] Elsheikh N, Sherif N, Zeid SA, et al. The link between bone disease and cardiovascular complication in hemodialysis patients[J]. Electron Physician, 2016, 8(6): 2483-2488
- [8] Kawahito K, Aizawa K, Oki S, et al. Heart valve surgery in hemodialysis-dependent patients: nutrition status impact on surgical outcome[J]. J Artif Organs, 2016, 19(2): 134-140
- [9] Michels WM, Jaar BG, Ephraim PL, et al. Intravenous iron administration strategies and anemia management in hemodialysis patients[J]. Nephrol Dial Transplant, 2016, 6 [Epub ahead of print]
- [10] Fishbane S. Balance of benefit and risk in intravenous iron treatment in chronic kidney disease[J]. Semin Nephrol, 2016, 36(2): 124-129
- [11] Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and diseases [J]. Br J Haematol, 2016, 174(5): 661-673
- [12] Zhang H, Li X, Kan Y, et al. Analysis of the correlation between serum resistin and the variability of erythropoietin responsiveness in patients with chronic kidney disease [J]. Exp Ther Med, 2015, 10(5): 1925-1930
- [13] Hertzberg-Bigelman E, Barashi R, Levy R, et al. Down-regulation of cardiac erythropoietin receptor and its downstream activated signal transducer phospho-STAT-5 in a rat model of chronic kidney disease[J]. Isr Med Assoc J, 2016, 18(6): 326-330
- [14] Sanchez-Gonzalez LR, Castro-Melendez SE, Angeles-Torres AC, et al. Efficacy and safety of adjuvant recombinant human erythropoietin and ferrous sulfate as treatment for iron deficiency anemia during the third trimester of pregnancy [J]. Eur J Obstet Gynecol Reprod Biol, 2016, 205: 32-36
- [15] Briet M, Barhoumi T, Mian MO, et al. Effects of recombinant human erythropoietin on resistance artery endothelial function in stage 4 chronic kidney disease[J]. J Am Heart Assoc, 2013, 2(2): e000128
- [16] Teixeira M, Rodrigues-Santos P, Garrido P, et al. Cardiac antiapoptotic and proliferative effect of recombinant human erythropoietin in a moderate stage of chronic renal failure in the rat [J]. J Pharm Bioallied Sci, 2012, 4(1): 76-83
- [17] Honda H, Kimata N, Wakai K, et al. Associations among epoetin therapy, inflammation, nutritional status, and mortality in patients on hemodialysis[J]. J Ren Nutr, 2014, 24(5): 322-329
- [18] Jasiulewicz A, Lisowska KA, Debska-Slizien A, et al. Phenotype, proliferation and apoptosis of B lymphocytes in hemodialysis patients treated with recombinant human erythropoietin [J]. Int Immunol, 2016,8 [Epub ahead of print]
- [19] Ribeiro S, Garrido P, Fernandes J, et al. Renal risk-benefit determinants of recombinant human erythropoietin therapy in the remnant kidney rat model - hypertension, anaemia, inflammation and drug dose[J]. Clin Exp Pharmacol Physiol, 2016, 43(3): 3443-3454
- [20] Hu JP, Cheng X, Xu XF, et al. Reactivity of patients with maintenance hemodialysis to erythropoietin in the treatment of renal anemia [J]. J Biol Regul Homeost Agents, 2016, 30(2): 535-540

(上接第 2919 页)

- [15] Henning T R, Butler K, Hanson D, et al. Increased susceptibility to vaginal simian/human immunodeficiency virus transmission in pig-tailed macaques coinfectd with Chlamydia trachomatis and Trichomonas vaginalis [J]. Journal of Infectious Diseases, 2014, 210(8): 1239-1247
- [16] Seña A C, Bachmann L H, Hobbs M M. Persistent and recurrent Trichomonas vaginalis infections: epidemiology, treatment and management considerations[J]. Expert review of anti-infective therapy, 2014, 12(6): 673-685
- [17] Valadkhani Z. Role of pH on Adhesion of Trichomonas Vaginalis Isolated from Symptomatic & Asymptomatic Women to Vaginal Epithelial Cells in Vitro [J]. Iranian Journal of Medical Sciences, 2015, 29(3): 134-139
- [18] Han C, Wu W, Fan A, et al. Diagnostic and therapeutic advancements for aerobic vaginitis [J]. Archives of gynecology and obstetrics, 2015, 291(2): 251-257
- [19] Miranda A E, Pinto V M, Gaydos C A. Trichomonas vaginalis infection among young pregnant women in Brazil [J]. Brazilian Journal of Infectious Diseases, 2014, 18(6): 669-671
- [20] Arbabi M, Fakhrieh Z, Delavari M, et al. Prevalence of Trichomonas vaginalis infection in Kashan city, Iran (2012-2013)[J]. International Journal of Reproductive BioMedicine, 2014, 12(7): 507-512