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丹参多酚酸盐对维持性血液透析患者残余肾功能与钙磷代谢的影响*

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摘要 目的:探讨丹参多酚酸盐对维持性血液透析患者残余肾功能与钙磷代谢的影响。**方法:**2014年1月-2019年5月选择在本院肾内科就诊的终末期肾病患者72例,根据随机数字表法分为观察组与对照组各36例。所有患者都给予维持性血液透析治疗,在此基础上观察组给予丹参多酚酸盐治疗,持续3个月,记录残余肾功能与钙磷代谢变化情况。**结果:**治疗后观察组的总有效率为97.2%,高于对照组的83.3% ($P<0.05$)。两组治疗后的24h尿量、肾小球滤过率(glomerular filtration rate, GFR)、血清转化生长因子 $\beta 1$ (Transforming growth factor $\beta 1$, TGF- $\beta 1$)和白介素-6(IL-6)低于治疗前,观察组也低于对照组($P<0.05$)。两组治疗后的血钙值高于治疗前,观察组也高于对照组;两组治疗后的血磷值低于治疗前,观察组也低于对照组($P<0.05$)。**结论:**丹参多酚酸盐在维持性血液透析患者中的应用有利于残余肾功能的恢复,调节钙磷代谢平衡,抑制炎症因子的表达,从而提高治疗效果。

关键词:丹参多酚酸盐;维持性血液透析;残余肾功能;钙磷代谢;肾小球滤过率

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Effects of Salvia Polyphenolate on Residual Renal Function and Calcium and Phosphorus Metabolism in Patients with Maintenance Hemodialysis*

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ABSTRACT Objective: To investigate the effects of salvia polyphenolate on residual renal function and calcium and phosphorus metabolism in patients with maintenance hemodialysis. **Methods:** From January 2014 to May 2019, 72 patients with end-stage renal disease who were treated in the Department of Nephrology of our hospital were selected as the research subjects and were divided into observation group and control group of 36 patients in each groups accorded to random number table method. All patients were treated with maintenance hemodialysis, and the observation group were added given salvia polyphenolate for 3 months, and the residual renal function and calcium and phosphorus metabolism were recorded. **Results:** The total effective rates of the observation group after treatment were 97.2%, which were higher than 83.3% of the control group ($P<0.05$). The 24-hour urine volume, glomerular filtration rate (GFR), serum transforming growth factor $\beta 1$ (TGF- $\beta 1$), and interleukin-6 (IL-6) were lower in the two groups after treatment were lower than in the before treatment, and the observation group were lower than the control group ($P<0.05$). After treatment, the blood calcium value of the two groups were higher than before the treatment, and the observation group were higher than that of the control group ($P<0.05$). **Conclusion:** The application of salvia polyphenolate in maintenance hemodialysis patients is beneficial to the recovery of residual renal function, regulates calcium and phosphorus metabolism balance, and inhibits the expression of inflammatory factors, thereby improving the therapeutic effect.

Key words: Salvia polyphenolate; Maintenance hemodialysis; Residual renal function; Calcium and phosphorus metabolism; Glomerular filtration rate

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前言

慢性肾脏疾病(Chronic kidney disease, CKD)为临床上的常

见疾病,其中部分患者可进展到终末期肾病(End-stage renal disease, ESRD),严重威胁公共健康^[1]。血液透析是终末期肾病患者的主要治疗措施,特别是当前接受维持性血液透析(main-

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tenance hemodialysis, MHD)治疗的终末期肾病患者不断增加^[2-3]。虽然透析能够延长患者的生存时间,但是也可导致机体补体激活,释放过敏毒素,促进炎症因子的大量释放,可能造成钙磷代谢紊乱,造成患者出现淀粉样变、感染、营养不良、动脉粥样硬化等透析相关并发症,不利于患者残余肾功能的改善^[4-6]。当前研究显示维持性血液透析具有经济有效、操作简便等优势,但是长期透析可使得机体出现微炎性反应以及氧化应激状态,导致透析并发症增加,严重情况下可诱导患者死亡^[7,8]。丹参多酚酸盐属于中药制剂,也是一类含有酚羟基的有机酸化合物,能抑制中性粒细胞与内皮细胞的粘附作用,从而发挥对内皮细胞的保护作用^[9,10]。本文具体探讨了丹参多酚酸盐对维持性血液透析患者残余肾功能与钙磷代谢的影响,以明确丹参多酚酸盐的应用效果与机制。

1 资料与方法

1.1 一般资料

2014年1月~2019年5月选择在本院肾内科就诊的终末期肾病患者72例,纳入标准:所有患者均知悉试验内容,均签署了知情同意书;符合终末期肾病的诊断标准;年龄20~70岁;研究得到了医院伦理委员会的批准;透析时间 ≥ 9 月。排除标准:合并有肿瘤、肝炎、结核、活动性风湿性疾病等患者;妊娠与哺乳期妇女;实验期间死亡或转为其他肾脏替代方式治疗者;肾移植患者;恶性肿瘤患者;临床资料缺乏者。

随机数字表法分为观察组与对照组各36例,两组的一般资料对比无差异($P>0.05$),见表1。

表1 两组一般资料对比

Table 1 Comparison of two sets of general information

Groups	n	Age (year)	Gender (men/ women)	Dialysis time (months)	Primary disease (nephritis / hypertensive nephropathy / diabetic nephropathy / other)	Systolic blood pressure(mmHg)	Diastolic blood pressure(mmHg)
Observation group	36	48.53 \pm 5.23	20/16	15.82 \pm 1.23	10/8/6/12	134.11 \pm 5.66	87.27 \pm 2.14
Control group	36	48.56 \pm 4.92	21/15	15.75 \pm 1.89	12/10/4/10	133.89 \pm 3.18	87.76 \pm 1.44

1.2 透析方法

对照组:给予维持性血液透析治疗,透析参数:血流量250 mL/min,透析液流量500 mL/min,透析时间4 h,以肝素抗凝,3次/周,4 h/次。

观察组:在对照组治疗的基础上给予丹参多酚酸盐治疗,在每次透析时加用丹参多酚酸盐(上海绿谷制药有限公司,批号:Z20160249)200 mg,经透析机静脉壶滴入。

两组治疗观察3个月。

1.3 观察指标

(1)疗效标准^[6]:显效:临床症状显著改善,血尿素氮下降 >3.57 mmol/L,血肌酐下降 >44.2 μ mol/L;有效:临床症状有所改善;无效:症状无改善,血肌酐尿素氮无变化甚或上升。(显效+有效)/组内例数 $\times 100.0\%$ =总有效率。(2)在治疗前后记录患者的残余肾功能,包括24 h尿量和肾小球滤过率(glomerular

filtration rate, GFR)。(3)在治疗前后焦虑患者的空腹静脉血2~3 mL,分为两管。第一管不抗凝,静置1 h左右离心分离血清(1500 r/min, 10 min, 4 $^{\circ}$ C),采用酶联免疫法检测血清转化生长因子 $\beta 1$ (TGF- $\beta 1$)、白介素-6(IL-6)含量。第二管进行抗凝,取全血组织,采用色谱法检测血钙、血磷水平。

1.4 统计方法

应用SPSS 21.00分析相关数据,采用($\bar{x} \pm s$)来描述计量数据,通过开展t检验进行数据对比;通过%来描述计数数据,通过开展卡方 χ^2 检验进行数据对比,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 总有效率对比

治疗后观察组的总有效率为97.2%,高于对照组的83.3%,对比差异有统计学意义($P<0.05$),见表2。

表2 两组总有效率对比(例,%)

Table 2 Comparison of the total effective rates of the two groups (n,%)

Groups	n	Marked effect	Effective	Invalid	Total efficiency
Observation group	36	32	3	1	35 (97.2)*
Control group	36	22	8	6	30 (83.3)

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

2.2 残余肾功能对比

两组治疗后的24 h尿量与GFR值低于治疗前,且观察组也低于对照组,对比差异都有统计学意义($P<0.05$),见表3。

2.3 血清TGF- $\beta 1$ 、IL-6对比

两组治疗后的血清TGF- $\beta 1$ 、IL-6低于治疗前,观察组也低

于对照组,对比差异都有统计学意义($P<0.05$),见表4。

2.4 钙磷代谢对比

两组治疗后的血钙值高于治疗前,血磷值低于治疗前,且观察组变化优于对照组($P<0.05$),见表5。

表 3 两组残余肾功能对比($\bar{x} \pm s$)

Table 3 Comparison of residual renal function between the two groups ($\bar{x} \pm s$)

Groups	n	24 hUrine output(mL)		GFR(ml/min)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	36	890.33± 45.33	367.30± 33.78**	8.89± 0.45	6.28± 0.44**
Control group	36	892.87± 24.10	451.98± 22.75*	8.91± 0.41	7.46± 0.34*

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

表 4 两组血清 TGF- β 1、IL-6 值对比(pg/mL, $\bar{x} \pm s$)

Table 4 Comparison of serum TGF- β 1 and IL-6 values between two groups (pg/mL, $\bar{x} \pm s$)

Groups	n	TGF- β 1		IL-6	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	36	325.33± 23.82	139.48± 28.10**	61.39± 5.19	14.58± 2.11**
Control group	36	326.94± 18.93	178.29± 19.30*	62.09± 3.10	26.02± 1.57*

表 5 两组血钙、血磷值变化对比(mmoL/L, $\bar{x} \pm s$)

Table 5 Comparison of changes in blood calcium and blood phosphorus values between the two groups (mmoL/L, $\bar{x} \pm s$)

Groups	n	Blood calcium		Blood Phosphorus	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	36	1.78± 0.11	2.14± 0.10**	2.10± 0.14	1.67± 0.13**
Control group	36	1.79± 0.12	2.00± 0.09*	2.09± 0.13	1.88± 0.14*

3 讨论

维持性血液透析是终末期肾脏疾病的主要治疗方式,能显著延长患者的生存时间。但是透析也在一定程度上引起机体的异常反应,引起一系列的透析相关性急、慢性并发症的发生^{[1][12]}。丹参属于唇形科植物,性微寒、味苦,具有调经止痛、凉血消痈、活血祛瘀、养血安神的功效^[13]。丹参多酚酸盐为丹参的主要成份,是一类含有酚羟基的有机酸化合物,具有比较强的抗氧化作用,可以抑制脂质过氧化,清除氧自由基,对血管内皮细胞损伤具有很好的保护作用^{[14][15]}。本研究显示治疗后观察组的总有效率为 97.2%,高于对照组的 83.3%;两组治疗后的 24 h 尿量与 GFR 值低于治疗前,观察组也低于对照组。目前关于丹参多酚酸盐对维持性血液透析患者的观察只要集中在氧化应激的影响^[16],对于其疗效的研究还缺如。分析其原因为丹参多酚酸盐具有抗血小板聚集、抗血栓形成、抗氧化损伤,清除自由基,改善微循环的作用,从而可减轻脂质过氧化损伤,降低肌酐、尿素氮等毒素调节凝血-纤溶系统,阻遏终末期肾脏疾病的发生发展,提高内生肌酐清除率,从而缓解肾功能衰竭^{[17][18]}。

长期血液透析患者可出现微炎症反应以及氧化应激状态,从而导致透析并发症增加。有研究证实单次和长期血液透析可导致补体激活以及炎症细胞因子表达增高,对脂多糖内毒素等刺激反应增加^{[19][20]}。本研究显示两组治疗后的血清 TGF- β 1、IL-6 低于治疗前,观察组也低于对照组。徐燕^[21]的研究与本研究类似,通过探讨丹参多酚酸盐注射液对糖尿病肾病 DN 的保护作用以及对 TGF- β 1 和单核细胞趋化蛋白-1 (MCP-1) 的影响,发现治疗组血清和尿液中 TGF- β 1、MCP-1 水平均明显下降,但与 Huang YY^[22]等学者的研究不同,该学者发现丹参多酚酸盐透析液对维持性血液透析患者,不能改善单次透析后血清 IL-6、TNF- α 水平,主要是患者的患病的程度和维持性血液透

析的次数不同引起,后续需要进行对比分析。分析其原因为 TGF- β 1、IL-6 是与人体免疫反应关系最为密切的细胞因子,终末期肾脏疾病时机体内毒性物质的堆积可导致肾脏清除细胞因子能力降低,从而使得 TGF- β 1、IL-6 水平升高。并且上述两个因子可作为血液透析膜生物相容性好坏的指标,也可预测透析患者的预后。特别是在高糖透析液刺激后,TGF- β 1 蛋白表达水平升高,血管内皮细胞表现为微绒毛的减少或消失,线粒体的肿胀、内质网的扩张^{[23][24]}。丹参多酚酸盐避免了丹参注射液有效成分易出现沉淀物、易降解等缺点,其质量稳定,浓缩了丹参中的水溶性活性成分^{[25][26]}。该药能抑制脂多糖内毒素诱导的炎症因子的大量分泌,进而改善微循环,有效清除氧自由基,最终达到改善患者微炎症状态的目的^{[27][28]}。

中医理论认为终末期肾脏疾病属于血瘀滞涩、血脉阻塞、燥热伤津,久之导致机体代谢无力、气阴两虚,特别是瘀阻致血行不畅,使得肾损伤更加严重,形成恶性循环。长期血液透析有一定的作用,但是可能不利于钙磷代谢的调节,从而导致机体出现低钙与高磷血症,诱发并发症的发生^{[29][30]}。本研究显示两组治疗后的血钙值高于治疗前,观察组也高于对照组;两组治疗后的血磷值低于治疗前,观察组也低于对照组,王元真^[31]等的研究与本研究类似,发现丹参多酚酸盐治疗慢性肾功能衰竭疗效确切,治疗后患者的血钙升高,血磷降低。从机制上分析,丹参多酚酸盐属于经现代工艺处理提纯的丹参有效浓缩成分,可扩张血管,有效改善机体凝血功能,保防止血栓形成^{[32][33]}。并且该药能抑制炎性介质、从而可调节钙磷代谢紊乱,促进患者的康复^[34]。但由于此次研究样本量较小,且没有进行剂量分析,还有待于更深入的分析进行证实。

总之,丹参多酚酸盐在维持性血液透析患者中的应用有利于残余肾功能的恢复,调节钙磷代谢平衡,抑制炎症因子的表达,从而提高治疗效果。

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