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自体骨髓衍生单核细胞植入治疗血管生成对硬皮病严重肢体缺血的影响*

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摘要 目的:探讨自体骨髓单个核细胞(bone marrow mononuclear cells, BM-MNC)植入治疗血管生成对硬皮病严重肢体缺血的影响。**方法:**收集我院 2018 年 6 月-2021 年 1 月收治的腔隙性脑梗死(cerebral lacunar infarction, CLI)伴系统性硬皮病患者(systemic sclerosis, SSc)患者 60 例,根据患者治疗意愿区分为研究组(接受 BM-MNC 治疗, 30 例)与对照组(接受常规保守治疗, 30 例),对比两组患者干预后疼痛度、跛行距离、踝肱指数(ankle brachial index, ABI)、经皮氧分压以及不良反应的发生情况。**结果:**治疗前两组患者的 VAS 评分、跛行距离组间差异无统计学意义($P>0.05$),治疗 1 个月时两组患者的 VAS 评分均较治疗前均降低,跛行距离均延长,组间差异明显($P<0.05$),治疗 6 个月时比较显示研究组 VAS 评分明显低于对照组,跛行距离明显高于对照组($P<0.05$)。治疗前两组患者的 ABI、经皮氧分压差异无统计学意义($P>0.05$),治疗 1 个月时两组患者的 ABI、经皮氧分压均较治疗前升高($P<0.05$),组间差异明显($P<0.05$),治疗 6 个月时比较显示研究组 ABI 和经皮氧分压明显高于对照组($P<0.05$)。研究组治疗 6 个月期间出现中风 1 例,肝肾功异常 2 例,不良反应总发生率为 6.00%,对照组治疗 6 个月期间出现非致命性心肌梗死 1 例,中风 1 例,肝肾功能异常 3 例,不良反应总发生率 10.00%,两组间不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**对 CLI 伴发 SSc 患者实施自体骨髓衍生单核细胞植入治疗可行性较好,能够显著改善患者的肢体功能及患肢血运,同时治疗安全性较高,值得临床推广应用。

关键词:自体骨髓衍生单核细胞;硬皮病;严重肢体缺血

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The Effect of Autologous Bone Marrow-derived Monocyte Implantation for Therapeutic Angiogenesis on Severe Limb Ischemia in Scleroderma*

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ABSTRACT Objective: To investigate the effect of autologous bone marrow-derived monocytes implantation on severe limb ischemia in patients with scleroderma. **Methods:** 60 cases of CLI patients with SSc in our hospital from June 2018 to January 2021 were collected and divided into study group (30 cases received BM-MNC treatment) and control group (30 cases received conventional conservative treatment) according to the treatment willingness of patients. The pain degree, claudication distance, ankle brachial index (ABI), transcutaneous oxygen partial pressure and adverse reactions of the two groups after intervention were compared. **Results:** Before treatment, there was no significant difference in the VAS score and claudication distance between the two groups of patients ($P>0.05$). At 1 month of treatment, the VAS scores of the two groups were lower than before treatment, and the claudication distance was prolonged. There was a difference between the groups ($P<0.05$), the comparison after 6 months of treatment showed that the VAS score of the study group was significantly lower than that of the control group, and the claudication distance was significantly higher than that of the control group ($P<0.05$). Before treatment, there was no significant difference in ABI and transcutaneous oxygen partial pressure between the two groups of patients ($P>0.05$). After 1 month of treatment, the ABI and transcutaneous oxygen partial pressure of the two groups were both higher than before treatment ($P<0.05$), the difference between the groups was significant ($P<0.05$). The comparison at 6 months of treatment showed that the ABI and transcutaneous oxygen partial pressure in the study group were significantly higher than those in the control group ($P<0.05$). During 6 months of treatment in the study group, there was 1 case of stroke and 2 cases of abnormal liver and kidney function. The total incidence of adverse reactions was 6.00%. During the 6 months of treatment in the control group, 1 case of non-fatal myocardial infarction, 1 case of stroke, liver and kidney 3 cases of abnormal work, the total incidence of adverse reactions was 10.00%, there was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** The feasibility of autologous bone marrow-derived monocytes implantation in patients with CLI associated with SSc is good, which can significantly im-

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prove the limb function and blood supply of patients, and has high safety, which is worthy of clinical application.

Key words: Autologous bone marrow-derived monocytes; Scleroderma; Severe limb ischemia

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前言

危重肢体缺血(Critical limb ischemia, CLI)是由慢性动脉阻塞引起的,主要由动脉硬化闭塞症(arteriosclerosis obliterans, ASO)、血栓闭塞性脉管炎(thromboangiitis obliterans, TAO)和胶原疾病(Crohn's disease, CD)引起,当传统的血管重建方法,如旁路手术或血管内治疗(endovascular treatment, EVT)失败或无指示时,CLI患者往往需要截肢治疗^[1-3]。CD患者尤其是系统性硬化症(scleroderma, SSc),出现雷诺现象或溃疡(duodenal ulcer, DU),可伸缩的缺血性溃疡对患者的生活质量(quality of life, QOL)产生负面影响,并可能导致截肢^[4,5]。临床治疗一般通过药物治疗为主,比如静脉注射伊洛前列素,磷酸二酯酶5(PDE5)抑制剂等,但长期治疗可能使患者对药物产生一定耐药性^[6,7]。此外,CLI患者在EVT或手术旁路术后的长期结局较差,目前有研究发现CLI脊髓性硬化患者需要建立促进外周循环的新策略^[8,9]。据报道,促进外周循环的细胞治疗方法之一是使用骨髓来源的单核细胞(BM-MNC)治疗血管生成^[10]。本文通过收集我院近三年收治的硬皮病严重肢体缺血患者,分析自体骨髓衍生单核细胞植入治疗效果。

1 资料与方法

1.1 一般资料

收集我院2018年6月-2021年1月收治的CLI伴SSc患者60例,根据患者治疗意愿区分为研究组(接受BM-MNC治疗,30例)与对照组(接受常规保守治疗,30例),研究组:男7例,女23例,年龄30~70岁,平均(56.7±12.1)岁,体质量指数(body mass index, BMI)平均(21.3±4.0)kg/m²,其中高血压12例(40.0%),高血脂5例(16.7%),高血糖4例(13.3%),吸烟患者12例(40.0%)。对照组:男8例,女22例,年龄30~65岁,平均(52.4±16.1)岁, BMI平均(21.9±3.8)kg/m²,其中高血压13例(43.3%),高血脂5例(16.7%)、高血糖3例(10.0%),吸烟患者3例(10.0%)。两组基础资料间差异无统计学意义($P>0.05$),具有可比性。

纳入标准:(1)临床病历资料齐全完备;(2)均符合CLI伴SSc诊断标准^[11];(3)CLI患者均由SSc引起;(4)患者意识清晰能够配合开展调研;(5)研究符合伦理道德,患者均知情同意;(6)均为下肢CLI患者。

排除标准:(1)不适合进行CLI手术或非手术血运重建治疗;(2)冠状动脉疾病或脑血管疾病;(3)慢性或急性炎症的临床或实验室症状、以前(过去5年)或当前肿瘤病史;(4)视网膜病变的糖尿病;(5)年龄超过80岁;(6)神经系统疾病或意识障碍性疾病者;(7)妊娠或哺乳期者。

1.2 研究方法

对照组患者接受常规CLI伴发SSc保守治疗;研究组患者则接受BM-MNC治疗,具体措施如下:(1)术前骨髓动员,通过

注射粒细胞集落刺激因子(G-CSF)连续动员3天;(2)术前骨髓评估,术前开展血常规和外周血白细胞总数检测(确定白细胞升高至 $45\times 10^9/L$ 左右);(3)骨髓干细胞获得,于患者双侧髂后上棘部穿刺抽取骨髓,总共抽取约300~400 mL骨髓,放入无菌玻璃瓶中摇匀,使用人问充值干细胞分离液处理后离心提取约50~100 mL的骨髓单个核细胞;(4)干细胞移植,确定患者患肢缺血部位后标记穿刺点,每个穿刺点约注射1~2 mL的骨髓单个核细胞,对溃疡部位可适当增加注射点,消毒后包扎。

1.3 观察指标及评测标准

重点观测如下几个指标:(1)治疗前、治疗1个月、治疗6个月两组患者的视觉模拟量表评分(visual analog scale, VAS)、跛行距离,其中VAS量表^[12]是利用0~10 cm的直线作为评估工具,0代表无痛,10代表剧痛,由受试者根据自身情况选择某一刻度代表自身疼痛度的评估方式,跛行距离则是指受试者以正常速度(60~70 m/min)步行的最长无痛距离^[13];(2)治疗前、治疗1个月、治疗6个月两组患者的踝肱指数(ABI)、经皮氧分压,其中ABI的检测采用美国心脏学会推荐标准,对患者患肢动脉输出道阻塞程度进行评估,经皮氧分压则选择日本Colin公司生产的VP1000型动脉硬化检测仪进行检测;(3)不良心血管事件(非致命性心肌梗死、失代偿性心力衰竭、中风等)发生率。

1.4 统计学方法

选择SPSS22.0统计软件对研究采集数据开展分析,其中计量资料采用(均数±标准差)的方式表示,开展正态分布以及方差齐性检验,对满足正态分布或方差齐性的数据组间差异使用t检验,方差不齐数据应用近似t检验,多组间的差异性比较采用F检验,对组间的计数资料差异性使用卡方检验,取 $P<0.05$ 为差异具有统计学意义^[14]。

2 结果

2.1 两组患者不同时间点疼痛度及跛行距离比较

治疗前两组患者的VAS评分、跛行距离组间差异无统计学意义($P>0.05$),治疗1个月时两组患者的VAS评分均较治疗前均降低,跛行距离均延长,组间差异明显($P<0.05$),治疗6个月时比较显示研究组VAS评分明显低于对照组,跛行距离明显高于对照组($P<0.05$),具体数据如表1所示。

2.2 两组患者不同时间点ABI与经皮氧分压比较

治疗前两组患者的ABI、经皮氧分压差异无统计学意义($P>0.05$),治疗1个月时两组患者的ABI、经皮氧分压均较治疗前均升高($P<0.05$),组间差异明显($P<0.05$),治疗6个月时比较显示研究组ABI和经皮氧分压明显高于对照组($P<0.05$),具体数据如表2所示。

2.3 两组患者治疗不良反应发生率比较

研究组治疗6个月期间出现中风1例,肝肾功异常2例,不良反应总发生率为6.00%,对照组治疗6个月期间出现非致

命性心肌梗死 1 例, 中风 1 例, 肝肾功能异常 3 例, 不良反应总发生率 10.00%, 两组间不良反应发生率比较差异无统计学意义 ($P>0.05$), 具体数据如表 3 所示。

表 1 两组患者不同时间点疼痛度及跛行距离比较($\bar{x} \pm s$)

Table 1 Comparison of pain degree and claudication distance between the two groups at different time points($\bar{x} \pm s$)

Groups	n	VAS			Limp distance(km)		
		Before intervention	The intervention lasted for one month	The intervention lasted for 6 months	Before intervention	The intervention lasted for one month	The intervention lasted for 6 months
Research group	50	5.49 $\pm$ 0.32	2.43 $\pm$ 0.21 ^{*&}	1.32 $\pm$ 0.11 ^{*&}	0.28 $\pm$ 0.03	0.41 $\pm$ 0.03 ^{*&}	0.51 $\pm$ 0.02 ^{*&}
Control group	50	5.51 $\pm$ 0.24	2.82 $\pm$ 0.19 [*]	1.59 $\pm$ 0.09 ^{*#}	0.29 $\pm$ 0.04	0.34 $\pm$ 0.03 [*]	0.44 $\pm$ 0.03 ^{*#}

Note: compared with before intervention, ^{*} $P<0.05$, compared with one month after intervention, [#] $P<0.05$, compared with control group, [&] $P<0.05$.

表 2 两组患者不同时间点 ABI 与经皮氧分压比较($\bar{x} \pm s$)

Table 2 Comparison of ABI and percutaneous oxygen partial pressure at different time points between the two groups($\bar{x} \pm s$)

Groups	n	ABI			Transcutaneous oxygen partial pressure(mmHg)		
		Before intervention	The intervention lasted for one month	The intervention lasted for 6 months	Before intervention	The intervention lasted for one month	The intervention lasted for 6 months
Research group	50	0.40 $\pm$ 0.11	0.48 $\pm$ 0.12 ^{*&}	0.56 $\pm$ 0.12 ^{*&}	27.98 $\pm$ 2.32	31.22 $\pm$ 1.32 ^{*&}	33.87 $\pm$ 2.01 ^{*&}
Control group	50	0.39 $\pm$ 0.09	0.43 $\pm$ 0.11 [*]	0.49 $\pm$ 0.09 ^{*#}	28.11 $\pm$ 1.23	29.98 $\pm$ 1.22 [*]	31.89 $\pm$ 1.98 ^{*#}

Note: compared with before intervention, ^{*} $P<0.05$, compared with one month after intervention, [#] $P<0.05$, compared with control group, [&] $P<0.05$.

表 3 两组患者治疗不良反应发生率比较[例(%)]

Table 3 Comparison of the incidence of adverse reactions between the two groups[n(%)]

Groups	n	Non fatal myocardial infarction	Decompensated psychological failure	apoplexy	Abnormal liver and kidney function	Total incidence
Research group	50	0(0.00)	0(0.00)	1(2.00)	2(4.00)	3(6.00)
Control group	50	1(2.00)	0(0.00)	1(2.00)	3(6.00)	5(10.00)

3 讨论

自体骨髓衍生单核细胞又名骨髓基质干细胞,是在哺乳动物骨髓基质中发现的一类具有高度分化潜能和自我更新能力的干细胞,是具有分化为骨、软骨、脂肪、神经和成肌细胞等细胞亚群的干细胞^[15,16]。自体骨髓衍生单核细胞广泛存在于结缔组织和器官间质内,但主要分布于骨髓组织中,此类细胞不仅能够对造血干细胞产生机械支持作用,同时还能够分泌多种生长因子来支持机体造血功能^[17]。近些年关于自体骨髓衍生单核细胞的研究较多,已有的研究指出,将干细胞植入关节软骨损伤兔模型中,可以加快兔膝关节软骨修复进程,促进其关节功能恢复^[18]。还有研究指出,自体骨髓干细胞原位移植在治疗急性心肌梗死中效果较好,能够显著降低心肌梗死面积,改善患者心功能^[19]。肢体缺血性疾病在国内发病率呈现升高趋势,尽管血管搭桥和血管腔内介入治疗对部分患者能够取得较好的近期疗效,但往往随访显示远期效果并不理想,多数患者仍然会出现截肢结局^[20]。2002 年学者 Tataishi-Yuyama E 等首次报道了应用患者自体骨髓干细胞移植治疗缺血性下肢血管病,临床疗效值得肯定,从而为肢体缺血性疾病开创了新思路,近些

年也有较多的研究指出自体骨髓干细胞对肢体缺血性疾病患者干预效果较好,患者截肢率出现降低。

本研究通过设立对照分组的方式,探究了应用自体骨髓衍生单核细胞植入治疗 CLI 伴 SSc 患者的临床有效性,结果显示,相比于开展常规保守治疗的对照组患者,应用自体骨髓衍生单核细胞进行治疗的研究组患者在干预 1 个月和 6 个月时肢体疼痛度出现显著降低,其跛行距离出现明显升高。Huang R^[21]等学者的研究通过建造家兔下肢缺血模型并使用自体骨髓单核细胞进行干预发现,该方式能够显著促进缺血部位新生血管的形成以及侧支血管的再生,对改善缺血区域的供血和功能具有积极意义。还有学者通过对下肢缺血糖尿病及非糖尿病鼠模型进行骨髓干细胞移植发现,骨髓移植能够诱导血管生成,在糖尿病并发下肢缺血患者中安全性值得肯定^[22]。本文作者分析认为,出现上述临床现象的机制可能有如下几点:(1)自体骨髓衍生单核细胞能够促进缺血部位的新生血管以及侧支血管的再生,从而起到改善缺血区域供血的功能;(2)自体骨髓衍生单核细胞移植可以促进多种细胞生长因子的分泌,如血管内皮生长因子,从而加快组织细胞的再生进程;(3)自体骨髓衍生单核细胞移植能够减轻缺血部位细胞凋亡进程,从而相对改善缺

血缺氧状态^[23-25]。

文中还进一步就两组患者接受干预后 ABI 以及经皮氧分压的变化进行了分析,结果显示研究组患者接受干预后 ABI 以及经皮氧分压较干预前出现了明显的升高,同时组间比较显示研究组优于对照组。有学者的研究结果指出,自体骨髓衍生单核细胞移植可以改善局部部位的缺血缺氧症状,其机制可能与自体骨髓衍生单核细胞移植能够促进细胞因子分泌,从而加速组织功能修复有关^[26-29]。与叶丹^[30]等学者的研究类似,该学者探究了自体骨髓干细胞移植治疗下肢缺血性患者的疗效,结果显示实验组在治疗 6 个月时疼痛感,冰凉感和跛行距离评分均低于治疗前;实验组 ABI 在治疗 6 个月时高于治疗前,经皮氧分压在治疗 1 个月及 6 个月时均高于治疗前,实验组治疗 6 个月疼痛感,冰凉感和跛行距离评分均低于对照组,实验组 ABI 和经皮氧分压均高于对照组。本文作者分析认为,自体骨髓衍生单核细胞移植在分化过程中会分泌诸如成纤维细胞生长因子、胰岛素样生长因子、转化生长因子 $\beta 1$ 等物质,这些都能够促使细胞出现分裂增殖、增生、转移,进而增加血管的通透性,促进心血管生成,而新生血管的出现又会改善局部组织的缺血缺氧症状,进而对其 ABI 和经皮氧分压产生影响。最后文中关于不良反应发生率的比较,说明自体骨髓衍生单核细胞移植具有较好的安全性,并不会出现明显的不良反应,因而临床推广性较好。这也在以往的其他疾病的研究中得到了证实,如同焕杰^[31]等学者的研究发现行自体骨髓干细胞移植治疗患者术中未出现严重不良反应,说明自体骨髓干细胞移植治疗有良好的安全性。本研究创新性的将自体骨髓衍生单核细胞植入应用于 CLI 伴发 SSc 患者,得到了显著的治疗效果,为后续 CLI 伴发 SSc 患者的治疗提供了新的思路和方法。但是由于时间原因,本研究治疗后没有进行随访,将在后续继续研究。

综上所述,对 CLI 伴发 SSc 患者实施自体骨髓衍生单核细胞植入治疗可行性较好,能够显著改善患者的肢体功能及患肢血运,同时治疗安全性较高,值得临床推广应用。

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747-809

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