

doi: 10.13241/j.cnki.pmb.2019.14.025

经皮血管腔内成形术联合自体外周血单个核细胞 治疗糖尿病足下肢血管病变的临床研究*

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摘要 目的:探讨经皮血管腔内成形术(PTA)联合自体外周血单个核细胞(PBMNCs)移植治疗糖尿病足下肢血管病变的临床疗效。方法:选取内蒙古医科大学第二附属医院2016年8月至2017年9月期间收治的糖尿病足下肢血管病变患者共120例,按随机数字表法分为3组:对照1组共40例,进行自体PBMNCs移植;对照2组共40例,进行PTA治疗;联合治疗组共40例,在进行PTA治疗的同时于缺血部位注入PBMNCs。观察3组的血管疏通情况,比较治疗前、治疗后1、6、12个月的跛行距离、踝肱指数(ABI),记录3组并发症发生情况。结果:联合治疗组患者的手术成功率为100.00%(40/40),高于对照1组的40.00%(16/40)、对照2组的55.00%(22/40),差异有统计学意义($P<0.05$)。治疗后1、6、12个月联合治疗组的跛行距离、ABI高于对照1组和对照2组($P<0.05$)。联合治疗组并发症总发生率为5.00%(2/40),低于对照1组的37.50%(15/40)和对照2组的25.00%(10/40),差异有统计学意义($P<0.05$)。结论:PTA联合自体PBMNCs移植是一种安全、有效、微创的治疗糖尿病足下肢血管病变的方法,其能够改善患者的血管疏通和病情。

关键词: 糖尿病足;下肢血管病变;经皮血管腔内成形术;外周血单个核细胞;治疗效果

中图分类号: R587.2 **文献标识码:** A **文章编号:** 1673-6273(2019)14-2721-05

Clinical Study of Percutaneous Transluminal Angioplasty Combined with Autologous Peripheral Blood Mononuclear Cell transplantation in the Treatment of Diabetic Foot and Lower Extremity Vascular Disease*

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ABSTRACT Objective: To investigate the clinical effect of percutaneous transluminal angioplasty (PTA) combined with autologous peripheral blood mononuclear cells (PBMNCs) transplantation in the treatment of diabetic foot and lower extremity vascular disease. **Methods:** 120 patients with diabetic foot and lower extremity vascular disease who were treated in the Second Affiliated Hospital of Inner Mongolia Medical University from August 2016 to September 2017 were selected. They were divided into three groups according to the random number table, the control group 1 with 40 cases conducted the PBMNCs transplantation, the control group 2 with 40 cases were treated with PTA, and the combined treatment group with 40 cases was injected with PBMNCs at the site of ischemia while undergoing PTA treatment. The patency of blood vessels in the three groups were observed. The claudication distance and ankle brachial index (ABI) were compared before treatment and 1, 6, 12 months after treatment. The complications of the three groups were recorded. **Results:** The success rate in the combined treatment group was 100.00%(40/40), which was higher than that 40.00% in the control group 1 (16/40) and 55.00% in the control group 2(22/40), and the differences were statistically significant($P<0.05$). The claudication distance and ABI of the combined treatment group at 1,6 and 12 months after treatment were higher than those of the control group 1 and the control group 2 ($P<0.05$). The total response rate of complications in the combined treatment group was 5.00%(2/40), which was lower than 37.50% (15/40) in the control group 1 and 25.00% (10/40) in the control group 2, the differences were statistically significant($P<0.05$). **Conclusion:** PTA combined with autologous PBMNCs transplantation is a safe, effective and minimally invasive method for the treatment of diabetic foot and lower extremity vascular disease, it can improve vascular dredging and condition of patients.

Key words: Diabetic foot; Lower extremity vascular disease; Percutaneous transluminal angioplasty; Peripheral blood mononuclear cells; Treatment effect

* 基金项目:内蒙古自治区自然科学基金项目(2016MS08140)

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(收稿日期:2018-11-30 接受日期:2018-12-23)

Chinese Library Classification(CLC): R587.2 Document code: A

Article ID: 1673-6273(2019)14-2721-05

前言

糖尿病足可分为神经病变足、缺血病变足或两者共存的病变足,该病为糖尿病的一种慢性并发症,是血管神经病变、局部缺血与感染、创伤反复作用的结果,糖尿病足严重者甚至需要被截肢^[1]。神经病变足患者较为少见且一般很少截肢,但缺血病变足较为常见,其中以糖尿病足下肢血管病变最为常见且多半存在截肢的可能性。为了避免截肢,减少患者的痛苦,糖尿病足患者治疗的关键是血运重建^[2-4]。经皮血管腔内成形术(Percutaneous transluminal angioplasty, PTA)是血运重建治疗糖尿病足的有效方法,该方法是经皮肤穿刺或将皮肤切开,于透视控制状态下进行动脉插管,进而使血管扩张,以达到解除血管腔狭窄或闭塞的目的^[5-7]。外周血单个核细胞(Peripheral blood mononuclear cells, PBMNCs)是指一群具有可分化为血管内皮祖细胞潜能的细胞,而血管内皮祖细胞最终可分化为血管内皮细胞,并分泌多种血管生成因子,将 PBMNCs 用于移植可促进血管再生,改善侧支循环,从而达到治疗糖尿病足下肢血管病变的目的^[8-10]。如果将 PBMNCs 移植与 PTA 治疗技术联合应用,将可能在解除糖尿病足患者下肢血管狭窄或闭塞的基础上,同时促进患者的下肢小血管的再生,从根本上改善患者的下肢侧支循环,进一步提高糖尿病足下肢血管病变的疗效^[11]。因此,本研究通过将 PTA 和自体 PBMNCs 移植用于治疗糖尿病足下肢血管病变,并对其疗效进行评价,旨在为临床治疗糖尿病足下肢血管病变提供参考依据,现报道如下。

1 资料与方法

1.1 临床资料

选取内蒙古医科大学第二附属医院 2016 年 8 月至 2017 年 9 月期间收治的糖尿病足下肢血管病变患者 120 例,纳入标准:(1)空腹血糖 ≥ 7.0 mmol/L,或服糖后血糖 ≥ 11.1 mmol/L;(2)下肢动脉(包括足部动脉、股、胫后或腓)搏动消失或减弱;(3)局部组织缺血改变,表现为疼痛(静息痛)、麻木或伴有足部坏疽或溃疡;(4)多普勒超声检测显示下肢动脉狭窄或闭塞且踝/肱比值 <0.7 ,磁共振血管成像(Magnetic resonance angiography, MRA)显示下肢动脉狭窄或闭塞。排除标准:(1)患有严重的心脑血管疾病者;(2)骨科疾病不耐行走者;(3)恶性肿瘤患者;(4)患有精神疾病无法配合研究者。120 例患者按随机数字表法分为 3 组:对照 1 组共 40 例,其中男性 20 例,女性 20 例;年龄 29-67 岁,平均 (47.23 ± 10.36) 岁,病程 3-10 年,平均 (7.29 ± 2.13) 年。对照 2 组共 40 例,其中男性 21 例,女性 19 例;年龄 30-65 岁,平均 (48.26 ± 11.45) 岁,病程 3-11 年,平均 (8.07 ± 2.06) 年。联合治疗组共 40 例,其中男性 22 例,女性 18 例;年龄 30-68 岁,平均 (49.18 ± 10.76) 岁,病程 4-10 年,平均 (7.89 ± 1.93) 年。3 组患者临床资料比较差异无统计学意义($P>0.05$),具有可比性。所有患者签署了知情同意书,且本研究方案经内蒙古医科大学第二附属医院伦理委员会批准。

1.2 方法

对照 1 组进行自体 PBMNCs 移植,对照 2 组进行 PTA 治疗,联合治疗组在进行 PTA 治疗的同时于缺血部位注入 PBMNCs。对照 1 组和联合治疗组患者均符合进行 PBMNCs 移植的条件,给予患者肌注粒细胞集落刺激因子(金磊赛强,长春金磊药业)300 μ g,2 次/d,连续注射 5d,进行 PBMNCs 的动员,监测外周血白细胞的数量,观察患者动员期间是否有不良反应,使用 Fresenius AS104 血细胞分离机(费森尤斯,德国)分离和采集 PBMNCs,并配制 50 mL 的细胞混悬液供移植用。PBMNCs 采集后常温保存即可,并于 4 h 内进行移植。PTA 手术前 5 d,对照 2 组和联合治疗组患者均需每晚口服硫酸氢氯吡格雷片(乐普药业股份有限公司,规格:75 mg/片,批号:国药准字:H20123116)75 mg,手术开始时采用 AmphirionDeep 球囊(英泰克,意大利)在导管室中对患者因病变出现的血管狭窄或闭塞进行扩张的操作。将研究中分离纯化的 PBMNCs 注入到患者发生血管闭塞或狭窄的部位,若扩张失败,则将 PBMNCs 注入到患者发生血管闭塞或狭窄的部位近端,扩张成功后,患者均需每晚服用硫酸氢氯吡格雷片 75 mg,直至手术结束。

1.3 观察指标

采用多普勒彩超检测及 MRA 检查治疗后的血管疏通情况,手术成功率即为血管疏通患者所占比例。所有患者门诊复查 12 个月,记录治疗前及治疗后 1、6、12 个月 3 组患者的跛行距离及踝肱指数(Ankle brachial index, ABI)。记录 3 组并发症发生情况。

1.4 统计学方法

采用 SPSS 22.0 进行统计学分析,采用 $(\bar{x} \pm s)$ 表示计量资料,实施 t 检验,多组间比较采用单因素方差分析,采用[n(%)]表示计数资料,实施 χ^2 检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 3 组血管疏通情况及手术成功率比较

多普勒彩超检查及 MRA 检查结果显示:联合治疗组手术成功 40 例,患者病足经治疗后下肢血管疏通、侧支数量显著增加,患者的胫前、胫后或腓动脉狭窄、闭塞或病变症状均得到了不同程度的改善;其中疏通血管 1 支有 14 例,疏通血管 7 支有 15 例,疏通血管 9 支有 11 例;联合治疗组患者的下肢肢温和疼痛不适感均得到了较大的改善,其中足背部和胫后动脉可检测到搏动的患者共有 18 例。对照 1 组手术成功 16 例,其中疏通血管 1 支有 10 例,疏通血管 7 支有 3 例,疏通血管 9 支有 3 例;足背部和胫后动脉可检测到搏动的患者共有 2 例。对照 2 组手术成功 22 例,其中疏通血管 1 支有 15 例,疏通血管 7 支有 3 例,疏通血管 9 支有 4 例;足背部和胫后动脉可检测到搏动的患者共有 4 例。联合治疗组患者的手术成功率为 100.00% (40/40),高于对照 1 组的 40.00% (16/40)、对照 2 组的 55.00% (22/40),差异有统计学意义($\chi^2=34.286, 23.226, P=0.000, 0.000$)。

2.2 3 组治疗前后跛行距离比较

治疗前 3 组跛行距离比较差异无统计学意义($P>0.05$)。与

治疗前比较,3组患者治疗后1、6、12个月的跛行距离均显著增加($P<0.05$)。与对照1组和对照2组患者比较,治疗后1、6、12个月联合治疗组的跛行距离显著增加,且对照2组的跛行距离大于对照1组($P<0.05$)。见表1。

表1 3组治疗前及治疗后1、6、12个月的跛行距离比较($\bar{x} \pm s$)Table 1 Comparison of claudication distance before treatment and 1,6,12 months after treatment in the three groups($\bar{x} \pm s$)

Groups	Before treatment	1 month after treatment	6 months after treatment	12 months after treatment
Control group 1(n=40)	23.89± 4.33	57.31± 8.22*	100.31± 15.17*	120.34± 23.36*
Control group 2(n=40)	23.08± 4.32	120.11± 12.24**	250.61± 6.33**	379.75± 51.22**
Combined treatment group (n=40)	22.99± 4.53	139.13± 19.33**▲	406.10± 56.61**▲	642.21± 64.66**▲
F	1.271	6.723	7.333	7.314
P	0.059	0.000	0.000	0.000

Note: compared with before treatment, * $P<0.05$; compared with control group 1, $P<0.05$; compared with control group 2, ▲ $P<0.05$.

2.3 3组治疗前后ABI比较

治疗前3组ABI比较差异无统计学意义($P>0.05$)。与治疗1组和对照2组患者比较,联合治疗组治疗后1、6、12个月的ABI均显著增加($P<0.05$),但对照1组和对照2组治疗后1、6、12个月的ABI比较差异无统计学意义($P>0.05$)。见表2。

表2 3组治疗前及治疗后1、6、12个月ABI比较($\bar{x} \pm s$)Table 2 Comparison of ABI before treatment and 1,6,12 months after treatment in the three groups($\bar{x} \pm s$)

Groups	Before treatment	1 month after treatment	6 months after treatment	12 months after treatment
Control group 1(n=40)	0.61± 0.03	0.63± 0.04*	0.73± 0.06*	0.74± 0.11*
Control group 2(n=40)	0.62± 0.04	0.65± 0.05*	0.71± 0.08*	0.76± 0.09*
Combined treatment group(n=40)	0.59± 0.02	0.72± 0.03**▲	0.78± 0.05**▲	0.84± 0.08**▲
F	2.271	7.776	10.312	8.305
P	0.074	0.000	0.000	0.000

Note: compared with before treatment, * $P<0.05$; compared with control group 1, $P<0.05$; compared with control group 2, ▲ $P<0.05$.

2.4 3组并发症发生情况比较

联合治疗组并发症总发生率为5.00%(2/40),低于对照1组的37.50%(15/40)和对照2组的25.00%(10/40),差异有统计学意义($P<0.05$)。见表3。

表3 3组并发症发生情况比较[n(%)]

Table 3 Comparison of complications in the three groups [n(%)]

Groups	Ulcer	Skin and soft tissue gangrene	Foot gangrene	Nausea and vomiting	Dizzy	Total response rate of complications
Control group 1(n=40)	6(15.00)	2(5.00)	2(5.00)	3(7.50)	2(5.00)	15(37.50)*
Control group 2(n=40)	5(12.50)	1(2.50)	1(2.50)	2(5.00)	1(2.50)	10(25.00)*
Combined treatment group(n=40)	1(2.50)	0(0.00)	0(0.00)	1(2.50)	0(0.00)	2(5.00)
χ^2						6.419
P						0.031

Note: compared with combined treatment group, * $P<0.05$.

3 讨论

近年来,糖尿病足下肢血管病变患者明显增加,其早期症状表现为肢体乏力和间歇性跛行,并伴有肢体皮肤干燥暗淡且弹性变差、易发冷、手足麻木、有刺痛或灼痛感、休息痛、下肢动脉的搏动减弱甚至消失等。而疾病的后期症状则表现为难愈合的慢性溃疡、足趾冰冷、皮色发绀、肢端溃烂或坏死^[12-14]。糖尿病足下肢血管病变采用常规的药物、手术搭桥或PTA等治疗方

法并不能彻底治愈,随着患者病情的不断恶化,严重时甚至可导致肢体坏疽、截肢,严重影响患者的身心健康^[15-17]。目前关于糖尿病足下肢血管病变患者的临床治疗效果评价,除了常用的影像学检查手段用于检查治疗后的血管疏通情况、治疗后随访检查患者的溃疡与坏疽等情况,还有以下指标可用于评价疗效:跛行距离是指患者从刚开始行走直到患者出现疼痛时所走过的总行程,可间接体现出下肢血管缺血或病变的程度。ABI则是指踝动脉和肱动脉的压强的比值,也可体现出下肢血管病变

的程度^[18,19]。但 ABI 体现出的血液灌注部位仅为下肢主干动脉,并不能体现出侧支循环部分,所以不能完全反映外周循环的改善程度^[20-22]。本研究采用粒细胞集落刺激因子刺激的方式,动员和采集 PBMNCs,并联合 PTA 治疗,在扩张血管的同时,移植 PBMNCs 到病变血管,促进血管再生,以缓解患者的各种临床症状。

本研究结果显示,通过 PTA 联合自体 PBMNCs 移植的方法进行治疗,40 例糖尿病足下肢血管病变患者的手术成功率达 100%,患者症状均得到了极大的改善,治疗后跛行距离和 ABI 均显著增加,并发症发生率显著降低;且与单独行 PBMNCs 移植或单独行 PTA 治疗进行比较,联合治疗组的疗效更优。人内皮祖细胞(Endothelial progenitor cells,EPCs)主要分布在骨髓中,少量分布于外周血中,是参与人胚胎和出生后的血管生成的重要细胞,但骨髓采集 EPCs 的采髓量大且需要全身麻醉,严格限制了 EPCs 在糖尿病足下肢血管病变患者移植治疗中的应用,而 PBMNCs 中也存在 EPCs,通过粒细胞集落刺激因子的刺激可将骨髓中的 EPCs 动员到外周血循环系统中^[23-25]。因此本研究中采用粒细胞集落刺激因子动员骨髓中的 EPCs 到外周血中,同时本研究采用 Fresenius AS104 血细胞分离机便可安全有效的分离采集到大量的 PBMNCs。已有研究显示骨髓干细胞移植后可促进入血管内皮细胞生长因子(Vascular endothelial growth factor,VEGF)和碱性成纤维细胞生长因子等血管生长因子的分泌,促进血管生成,使细胞移植的疗效更好^[26-28]。而与骨髓源性的 EPCs 一致,非骨髓源性的 PBMNCs 中的内皮细胞也可分泌 VEGF 等促血管生成的细胞生长因子^[29,30],因此本研究中采用自体 PBMNCs 移植联合 PTA 技术治疗糖尿病足下肢缺血性的方法是可行的,而 PTA 技术是通过将发生病变的狭窄闭塞的动脉管腔通过球囊扩张或支架膨胀,使血管内径恢复,病变肢体血运重建而达到治疗糖尿病足下肢血管病变目的的一种技术,具有微创、安全、有效的特点。目前 PTA 治疗糖尿病足的成功率较高,而结合 PBMNCs 移植可使新生血管避免再发生狭窄、闭塞或病变。

综上所述,PTA 联合自体 PBMNCs 移植治疗糖尿病足下肢血管病变的临床治疗效果显著,是一种安全、有效、微创的治疗方法。

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