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舒血宁注射液联合多巴丝肼治疗帕金森病的临床疗效及对脑区血流量与血清炎性因子的影响

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摘要 目的：探讨舒血宁注射液联合多巴丝肼治疗帕金森病的疗效及对脑区血流量与血清炎性因子的影响。**方法：**选择我院 2014 年 9 月~2017 年 9 月收治的 94 例帕金森病患者，按随机数表法分为对照组和研究组，每组 47 例。对照组予以多巴丝肼治疗，研究组在对照组基础上加以舒血宁注射液治疗。比较两组临床疗效，治疗前后 UPDRSⅡ评分、UPDRSⅢ评分、UPDRS 评分、脑区血流量、血清白细胞介素 -1β(IL-1β)、白细胞介素 -6(IL-6)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子 -α(TNF-α)水平的变化和不良反应的发生情况。**结果：**治疗后，研究组总有效率显著高于对照组(P<0.05)。两组治疗后 UPDRSⅡ评分、UPDRSⅢ评分、UPDRS 评分、血清 IL-1β、IL-6、hs-CRP 和 TNF-α 水平均较治疗前显著下降，且研究组以上指标均明显低于对照组(P<0.05)。两组治疗后脑区血流量均较治疗前显著增加，且研究组明显高于对照组(P<0.05)。两组均有恶心、头晕、失眠及呕吐发生，组间不良反应的发生率比较差异无统计学意义(P>0.05)。**结论：**舒血宁注射液联合多巴丝肼治疗帕金森病的临床疗效明显优于单用多巴丝肼，其能够促进脑部血流循环，调节脑区血流量，降低炎性因子的水平。

关键词：帕金森病；舒血宁注射液；多巴丝肼；脑区血流量；炎性因子

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Clinical Efficacy of Shuxuening Injection Combined with Dopamine Hydrazine in the Treatment of Parkinson's Disease and Its Effect on the Cerebral Blood Flow and Serum Inflammatory Factors

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ABSTRACT Objective: To explore the clinical Efficacy of shuxuening injection combined with dopamine hydrazine in the treatment of Parkinson's disease and its effect on the blood flow and serum inflammatory factors. **Methods:** 94 patients with Parkinson's disease who were treated from September 2014 to September 2017 in our hospital were selectd and divided into the control group and the research group according to the random number table method, with 47 cases in each group. The control group was treated with dopamine hydrazine, and the research group was treated with shuxuening injection based on the control group. Then the clinical curative effect, change of UP- DRS Ⅱ score, UPDRS Ⅲ score, UPDRS score, cerebral blood flow, the serum Interleukin-1β(IL-1β), interleukin 6 (IL-6), hypersensitive c-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) levels before and after treatment, and the incidence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate of research group was higher than that of the control group (P<0.05), the UPDRS Ⅱ score, UPDRS Ⅲscore, UPDRS score, serum levels of IL-1β, IL-6, hs-CRP and TNF-α of both group were significantly decreased than those before treatment, and the above indicators of research group were significantly lower than those of the control group(P<0.05). The blood flow in the brain area of both groups were significantly higher than those before treatment, which was more obviously in the research group than that in the control group (P<0.05). Nausea, dizziness, insomnia and vomiting were found in both groups, but significant difference was found between two groups (P>0.05). **Conclusion:** Shuxuening injection combined with dopamine hydrazine is more effective in the treatment of Parkinson's disease than dodohydrazine alone, it can promote the brain blood circula- tion, regulate the brain blood flow, reduce the levels of inflammatory factors.

Key words: Parkinson's disease; Shuxuening injection; Dopamine hydrazine; Cerebral blood flow; Inflammatory cytokines

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前言

帕金森病为慢性进展性神经系统病变，多发于老年人群，主要临床表现为静止性震颤、肌强直、运动迟缓、姿势步态障碍，同时可伴睡眠障碍、抑郁等非运动症状，患者生活质量明显降低[1,2]。药物为帕金森病的首选治疗方式，但目前仍缺乏特效药物，多巴丝肼较为常用，但长期使用存在剂末效应，且不良反

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应明显,可进一步影响疗效[3,4]。

舒血宁注射液作为一种中药提取剂,可促进氧自由基的清除、改善微循环、提高细胞免疫活性等,其在心脑血管疾病中的效果已得到临床肯定,但较少关于其在帕金森病中的应用报道[5,6]。研究表明[7]帕金森病患者脑部血流灌注异常参与了其脑部病变的发生发展[8],炎症反应在帕金森病中也发挥了重要作用,患者血清多种炎性因子水平明显增加,并与病情程度显著相关。本研究主要探讨了舒血宁注射液联合多巴丝肼治疗帕金森病的临床疗效及对患者脑区血流量与血清炎性因子水平的影响,以期为帕金森病的临床治疗提供参考依据。

1 资料与方法

1.1 一般资料

选择我院 2014 年 9 月 ~2017 年 9 月收治的 94 例帕金森病患者。入选标准:与帕金森病诊断标准[9]相符:(符合① 项且满足② 项中任 3 项,并排除③ 项中任意 1 项):① 运动迟缓;② 单侧起病、病情呈进行性发展、伴静止性震颤等;③ 明确脑炎史、反复脑损伤或者脑卒中史、椎体束征呈阳性、小脑征等;近期未服用非甾体类抗炎或者激素药; 无相关抗帕金森药物治疗史。排除标准:帕金森叠加综合征;特发性震颤;肝肾功能明显不全;严重认知功能障碍或者精神障碍;额颞叶痴呆、血管性痴呆、阿尔茨海默病等其他类型痴呆;造血系统或者免疫系统病变;Hoehn-Yahr 分级超过Ⅲ级。

按随机数表法将所有患者随机分为对照组和研究组,每组 47 例。对照组中, 女 20 例, 男 27 例; 年龄 48~71 岁, 平均(62.19± 7.75)岁;平均病程(2.24± 0.63)年;H-Y 分级:Ⅰ级 24 例、Ⅱ级 18 例、Ⅲ级 5 例。研究组中,女 22 例,男 25 例;年龄 47~70 岁,平均(61.85± 8.42)岁;平均病程(2.17± 0.76)年;H-Y 分级:Ⅰ级 27 例、Ⅱ级 17 例、Ⅲ级 3 例。两组基础资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组予以多巴丝肼(规格:0.25g / 片,批号:150625,生产厂家:上海罗氏制药有限公司)治疗,第 1 周口服 125 mg/ 次,每 12 h 1 次;第 2 周口服 125 mg/ 次,每 8h1 次;第 3 周口服 125 mg/ 次,每 6 h 1 次,并以此剂量维持治疗,持续治疗 12 周。研究组在对照组基础上加以舒血宁注射液 (规格:2 mL× 10 支 / 盒,批号:150419,生产厂家:朗致集团万荣药业有限公司)治疗, 将 20 mL 舒血宁注射液与 250 mL 0.9%氯化钠溶液混合,予以患者静脉滴注,每天 1 次,持续治疗 3 周。于治疗第 33 周结束时评估疗效,并观察治疗期间不良反应的发生情况。

1.3 观察指标

1.3.1 临床疗效评估 治疗后 UPDRS 减少超过 30%即显效,在 5%~30%即好转,低于 5%即无效[9]。

1.3.2 指标测定 于治疗前及第 12 周结束时采用帕金森统一评分量表(UPDRS)评估患者总病情程度,分数越高提示病情程度越重;采用 UPDRSⅡ评估患者日常生活能力,UPDRSⅢ评估患者运动障碍[10]。同期选择 GE8 排螺旋 CT 机(河南兆龙电子技术有限公司)分别测量双侧基底节区、颞叶、顶叶及额叶血流量,并进行定量分析。于治疗前及治疗第 3 周结束时采集患者 2 mL 空腹静脉血,予以 GF105 型血液分离机(广州富一液体分离技术有限公司)按 3000 转 / 分钟分离 10 分钟,保留上清液于 -20℃ 低温箱中待检。以酶联免疫法测定白细胞介素 -1β(IL-1β)、白细胞介素 -6(IL-6)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子 -α(TNF-α)水平,试剂盒均由通蔚试剂(上海)有限公司提供,均由同组工作人员严格参照说明书进行。

1.4 统计学分析

数据处理选用 SPSS18.0 进行, 数据均符合正态分布,用($\bar{x}$± s)表示计量资料,比较选用独立样本 t 检验进行,用[(例)%]表示计数资料,比较用 x^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后, 研究组总有效率显著高于对照组 (85.11% vs. 63.83%),比较差异有统计学意义(P<0.05),见表 1。

表 1 两组临床疗效比较[例(%)]

Table 1 Comparison the clinical efficacy between two groups[n(%)]

Group	n	Effectiveness	Effective	Ineffective	Total effective rate
Control group	47	10(21.28)	20(42.55)	17(36.17)	30(63.83)
Research group	47	18(32.30)	22(46.81)	7(14.89)	40(85.11)#

Note: Compared with the control group, #P<0.05.

2.2 两组治疗前后 UPDRSⅡ评分、UPDRSⅢ评分、UPDRS 评分比较

治疗前,两组 UPDRSⅡ评分、UPDRSⅢ评分、UPDRS 评分比较差异无统计学意义(P>0.05);治疗后,两组 UPDRSⅡ评分、UPDRSⅢ评分、UPDRS 评分均较治疗前显著下降,且研究组以上指标明显低于对照组,比较差异有统计学意义(P<0.05),见表2。

2.3 两组治疗前后脑区血流量比较

治疗前,两组脑区血流量比较差异无统计学意义(P>0.05);治疗后,两组脑区血流量均较治疗前显著增加,且研究组明显高于对照组,比较差异有统计学意义(P<0.05),见表 3。

2.4 两组治疗前后血清炎性因子水平比较

治疗前, 两组血清炎性因子水平比较差异无统计学意义(P>0.05);治疗后,两组血清炎性因子(IL-1β、IL-6、hs-CRP 和 TNF-α)水平均较治疗前显著下降,且研究组以上指标均显著低于对照组,比较差异有统计学意义(P<0.05),见表 4。

2.5 两组不良反应发生情况的比较

两组均有恶心、头晕、失眠及呕吐发生,组间不良反应发生率比较差异无统计学意义(P>0.05),见表 5。

表 2 两组治疗前后 UPDRSⅡ评分、UPDRSⅢ评分、UPDRS 评分比较($\bar{x}\pm s$)

Table 2 Comparison of the UPDRSII score, UPDRSIII score, UPDRS score before treatment and after treatment between two groups($\bar{x}\pm s$)

Groups	n	Time	UPDRSⅡscore(point)	UPDRSⅢscore(point)	UPDRSscore(point)
Control group	47	Before treatment	16.90± 2.65	35.49± 4.39	49.65± 6.84
		After treatment	14.65± 1.76►	27.88± 3.90►	30.21± 4.19►
Research group	47	Before treatment	17.42± 2.19	34.62± 4.80	48.42± 7.65
		After treatment	12.11± 1.20#►	25.41± 3.12#►	25.10± 3.61#►

Note: Compared with control group #P<0.05; Compared with before treatment ►P<0.05.

表 3 两组治疗前后脑区血流量比较($\bar{x}\pm s$,100 mL/min)

Table 3 Comparison of the brain blood flow before treatment and after treatment between two groups ($\bar{x}\pm s$,100 mL/min)

Groups	n	Time	Right lobe	Left lobe	Right parietal lobe	Left parietal lobe	Right frontal lobe	Left frontal lobe	Right basal ganglia	Left basal ganglia
Control group	47	Before treatment	45.79± 6.88	47.60± 5.42	46.11± 5.43	40.58± 5.93	43.20± 6.88	41.88± 4.86	46.88± 5.15	45.79± 6.13
		After treatment	50.20± 7.52►	56.53± 8.77►	49.17± 7.42►	47.31± 6.51►	47.13± 6.14►	46.52± 6.13►	50.75± 7.70►	51.64± 7.84►
Research group	47	Before treatment	46.21± 5.74	48.52± 6.55	45.70± 6.53	41.79± 5.12	42.86± 5.70	40.96± 5.41	47.40± 4.72	46.25± 5.49
		After treatment	56.98± 9.70#►	61.18± 9.90#►	55.26± 9.60#►	53.66± 7.63#►	50.87± 7.43#►	0.84± 7.80#►	56.28± 9.76#►	55.93± 9.62#►

Note: Compared with control group #P<0.05; Compared with before treatment ►P<0.05.

表 4 两组治疗前后血清炎性因子水平比较($\bar{x}\pm s$)

Table 4 Comparison of the serum inflammatory factors levels before treatment and after treatment between two groups($\bar{x}\pm s$)

Groups	n	Time	IL-1β(pg/mL)	IL-6(ng/L)	hs-CRP(mg/L)	TNF-α(ng/L)
Control group	47	Before treatment	268.15± 39.86	25.08± 3.79	13.79± 2.43	24.79± 3.86
			30.65± 4.50►	13.65± 2.01►	8.60± 1.36►	12.17± 1.85►
Research group	47	Before treatment	280.90± 35.16	24.77± 2.80	14.10± 2.00	25.30± 3.42
			26.88± 3.21#►	10.15± 1.75#►	6.52± 0.87#►	9.64± 1.39#►

Note: Compared with control group #P<0.05; Compared with before treatment ►P<0.05.

表 5 两组不良反应发生情况的比较[例(%)]

Table 5 Comparison the incidence of adverse reactions between two groups[n(%)]

Groups	n	Nausea	Dizziness	Insomnia	Vomiting	Total adverse reaction rate
Control group	47	3(6.38)	3(6.38)	2(4.26)	2(4.26)	9(19.15)
Research group	47	2(4.26)	1(2.13)	1(2.13)	3(6.38)	7(14.89)

3 讨论

帕金森病临床多通过增加多巴胺浓度以减轻其临床表现。尽管脑深部刺激术、丘脑毁损术等手术治疗帕金森病的近期效果较佳,但远期疗效并不理想,且容易出现明显的并发症[11,12]。基因治疗尚在初始研究阶段,缺乏可靠的研究结果,干细胞移植虽于动物实验中已得到不错的效果,但临床应用仍存在较多问题[13,14]。目前,临床多采用药物控制病情,左旋多巴胺为帕金森治疗的代表药物,其能够经主动转运增加脑内多巴胺浓度,起到替代治疗目的,恢复正常的运动行为。但有研究报道[15,16]左旋多巴胺存在一定程度的神经毒性作用,且疗效可随着治疗时间的增加不断下降,同时存在较显著的副反应。多巴丝肼为卡丝肼和左旋多巴的复合物,其中卡丝肼能够于机体内生成去甲肾上腺素及苯丙胺,改善运动迟缓及肌强直[17]。相关研究证实[18,19]早期少量多巴丝肼能够起到不错的效果,但随着病情进展其用量需不断增加,容易出现呕吐、恶心等不适,且长时间服用能够降低黑质细胞对多巴胺的控制能力,最终影响效果。

舒血宁注射液为银杏叶提取剂,主要物质为萜烯和黄酮,能够避免细胞膜发生脂质过氧反应,清除多种自由基,缓解其对神经细胞的毒性反应,改善脑组织水肿及缺血[20]。有研究结果显示[21,22]舒血宁注射液也可保护多巴胺神经元,且可提高患者认知及学习能力,促进损伤神经的修复,利于神经递质的更新。动物研究实验报道[23]银杏叶能够清除自由基,降低丙二醇水平,增加黑质区多巴胺神经元数目。本研究结果显示舒血宁

注射液联合多巴丝肼组总有效率高于单用多巴丝肼组,且治疗后UPDRS 各量表评分改善更明显，说明二者联合治疗能够提高疗效,可能与其能够起到协同作用有关,但具体作用机制仍有待进一步研究以明确。

多数帕金森病患者存在一定程度的脑血流改变,从而引起脑功能及脑内代谢相应变化[24,25]。本研究结果显示舒血宁注射液联合多巴丝肼治疗的患者脑区血流量上升更明显,提示二者联合治疗能够促进脑部血流的改善,利于脑部代谢,可能与舒血宁注射液中银杏能够扩张血管,改善微循环有关。目前,临床缺乏对帕金森病作用机制的深入及系统研究,既往研究显示[26,27]炎性反应是其发生的主要机制，帕金森病患者血清 IL-1β、IL-6、hs-CRP 及 TNF-α 水平明显上升，可激活小胶质细胞,导致多巴胺能神经细胞受损，且可结合多巴胺能神经元受体,诱导细胞变性及凋亡。本结果显示舒血宁注射液联合多巴丝肼组治疗的患者血清 IL-1β、IL-6、hs-CRP 及 TNF-α 水平较单用多巴丝肼组治疗的患者更低,提示二者共同作用更能有效缓解机体炎性反应,下调炎性因子的表达,减缓临床症状[30]。同时,本结果显示两组不良反应相似,说明舒血宁注射液并未增加患者痛苦。但本研究并不是大样本的临床研究,且观察时间较短,其远期疗效和安全性尚有待于进一步研究证实。

综上所述,舒血宁注射液联合多巴丝肼治疗帕金森病的临床疗效明显优于单用多巴丝肼，其能够促进脑部血流循环,调节脑区血流量,降低炎性因子的水平。

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