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普拉克索联合补肾活血通络胶囊治疗老年帕金森病的临床疗效及对血清5-HT、BDNF、S-100β水平的影响*

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摘要 目的：分析普拉克索联合补肾活血通络胶囊治疗老年帕金森病的临床效果及对血清5-羟色胺(5-HT)、脑源性神经营养因子(BDNF)、S-100β水平的影响。**方法：**选择我院2014年12月~2016年12月收治的96例老年帕金森病患者，按随机数字表法分为对照组和研究组，每组48例。对照组采用普拉克索治疗，研究组基于对照组加以补肾活血通络胶囊治疗。观察并比较两组临床疗效指标统一帕金森病评分量表Ⅰ（unified parkinson's disease rating scale，UPDRS）Ⅰ、UPDRS Ⅱ、UPDRS Ⅲ、UPDRS Ⅳ、总UPDRS，血清5-HT、BDNF、S-100β水平的变化及不良反应的发生情况。**结果：**治疗后，研究组总有效率为87.50%，显著高于对照组(64.58%，*P*<0.05)。两组治疗后的UPDRSⅠ、UPDRSⅡ、UPDRSⅢ、UPDRSⅣ、总UPDRS、血清S-100β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。两组治疗后的血清5-HT、BDNF水平均较治疗前明显上升，且研究组以上指标均明显高于对照组(*P*<0.05)。研究组不良反应发生率显著低于对照组(*P*<0.05)。**结论：**普拉克索联合补肾活血通络胶囊治疗治疗老年帕金森病的临床效果优于单用普拉克索，可能与其显著提高血清5-HT及BDNF表达并降低S-100β水平有关。

关键词：老年帕金森病；普拉克索；补肾活血通络胶囊；临床研究；5-羟色胺；脑源性神经营养因子；S-100β蛋白

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Clinical Efficacy of Pramipexole Combined with Bushen Huoxue Tongluo Capsule in the Treatment of Senile Parkinson's Disease and Its Effect on the Serum Levels of 5-HT, BDNF, S-100β*

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ABSTRACT Objective: To research the clinical efficacy of pramipexole combined with bushen huoxue tongluo capsule in the treatment of senile Parkinson's disease and analyze its effect on the serum levels of 5-hydroxytryptamine (5-HT), brain derived neurotrophic factor (BDNF), S-100. **Methods:** 96 cases of Parkinson's disease admitted from December 2014 to December 2016 were divided into the control group and the research group according to random number table method, with 48 cases in each group. The control group was treated with pramipexole, and the research group was treated with Bushen Huoxue Tongluo Capsule based on the control group. The clinical curative effect, changes of unified parkinson's disease rating scale (UPDRS) I, UPDRS II, UPDRS III, UPDRSI V, total UPDRS, serum levels of 5-HT, BDNF, S-100β, and adverse reactions occur between two groups was observed and compared. **Results:** After treatment, the total effective rate of study group was 87.50%, which was significantly higher than that of the control group (64.58%, *P*<0.05). the levels of UPDRS Ⅰ, UPDRS Ⅱ, UPDRSⅢ, UPDRSⅣ, total UPDRS, and serum S-100β in both groups after treatment were significantly lower than those before treatment. The above indexes in the research group are obviously lower than those in the control group. The levels of serum 5-HT and BDNF after treatment in both groups were significantly higher than those before treatment, and the above indexes in the research group were significantly higher than those in the control group (*P*<0.05). The adverse reaction rate in the research group was significantly lower than that in the control group (*P*<0.05). **Conclusion:** Pramipexole combined with Bushen Huoxue Tongluo capsule is superior to pramipexole alone in the treatment of senile Parkinson's disease, which may be related to significantly increasing the expression of serum level of 5-HT and BDNF and decreasing the level of S-100β.

Key words: Elderly Parkinson's disease; Bushen Huoxue Tongluo capsule; Pramipexole; 5-hydroxytryptamine; Brain-derived neurotrophic factor; S-100β protein

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前言

帕金森病为神经系统常见变性疾病，多发于老年人群，能够引起多种临床症状，明显影响患者身心健康[1,2]。年龄老化为帕金森病的主要诱因，国外研究发现随着年龄的不断增加，可引起钙、铜、铁发生聚集，并降低多巴胺脱羧酶及酪氨酸羟化酶的活性，升高发病率。同时，遗传、环节毒物、感染等因素和发病也有着良好的相关性[3,4]。近年来有研究报道[5,6]帕金森病发展和蛋白异常表达有着紧密联系，5- 羟色胺(5-HT)属神经递质，可调控体温、睡眠、痛觉等生理功能；脑源性神经营养因子(BDNF) 能够参与神经细胞的分化、发生，利于神经细胞的修复；S-100β 蛋白可调控神经病变，并诱导机体多种级联反应，其水平变化可提示疾病的进展程度。

目前，老年帕金森病无特效疗法，普拉克索为其常用药物，对受体存在选择性及高亲和力，但其远期疗效并不理想，不良反应较为显著[7,8]。中医药存在减毒增效、安全等优势，现已受到临床广泛重视，补肾活血通络胶囊可通络止血，活血祛瘀，临床关于其应用于老年帕金森病的报道并不全面。本研究主要探讨了普拉克索联合补肾活血通络胶囊治疗治疗老年帕金森病的临床效果及对血清 5-HT、BDNF、S-100β 水平的影响。

1 资料与方法

1.1 一般资料

96 例老年帕金森患者入选标准：均与帕金森病诊断标准相符[9]；属中医肾虚血瘀型颤证：表情呆滞、面色晦暗、肢体震颤、形体偏瘦、活动受限、言语不利、步态慌张、腰膝酸软、苔薄白、脉涩；帕金森病 H-Y 分级低于 3 级；近期无催眠镇静药物使用史；内部脏器未见明显病变。排除标准：痴呆、抑郁或认知功能障碍；存在影响睡眠的其他因素；过敏体质。对照组 22 例女，26 例男；年龄 52~71 岁，平均(62.40± 1.85)岁；H-Y 分级：8 例Ⅰ级，12 例Ⅱ级，28 例Ⅲ级。研究组 25 例女，23 例男；年龄 51~72 岁，平均(62.99± 1.92)岁；H-Y 分级：9 例Ⅰ级，13 例Ⅱ级，26 例Ⅲ级。两组基础资料比较差异均无统计学意义 P>0.05)，存在互比性。

1.2 方法

对照组接受普拉克索治疗，第 1 周普拉克索(四川沱牌药业有限公司，0.25 g/ 片，140913) 每日剂量 <0.375 mg，tid；第 2 周每日总剂量维持在 0.375~0.75 mg；第 3 周药物剂量增加至每日 1.5 mg。研究组基于对照组加以补肾活血通络胶囊治疗，包含何首乌 12 g、地黄 20 g、枸杞子 15 g、钩藤 30 g、白芍 20 g、龟甲 12 g、桃仁 9 g、当归 9 g、丹参 12 g、僵蚕 9 g、全蝎 6 g 等，均统一制作为中药胶囊，每次 10 粒，bid，口服，两组均持续治疗 3 个月。于用药结束时评估患者疗效，记录不良反应的发生情况。

1.3 观察指标

1.3.1 临床疗效 治疗后，总 UPDRS 减少≥ 50%即治愈，减少在 20%~49%即显效，减少在 1%~19%即好转，减少在 1%以下即无效[10]。

1.3.2 统一帕金森病评分量表(UPDRS)观察 总 UPDRS 评估患者总病情程度，分数和病情程度呈正相关；UPDRSⅠ、UPDRSⅡ分别反映行为及精神情感，日常生活活动能力，UPDRSⅢ及 UPDRSⅣ反映运动功能[11]。

1.3.3 血清指标测定 于用药前及结束时抽取患者 2 mL 晨起静脉血，将其进行常规分离后保存待用。5-HT、BDNF、S-100β 按酶联免疫法进行，试剂盒均来自通蔚试剂(上海)有限公司。

1.3.4 不良反应的发生情况 包括疲劳、精神症状、开关现象、恶心、呕吐。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包，计量资料以($\bar{x}\pm s$)表示，组间比较选用 t 检验，计数资料用[(例)%]表示，组间比较采用 x^2 检验比较，以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后，研究组总有效率为 87.50%，显著高于对照组(64.58%，P<0.05)。

表 1 两组临床疗效比较[例(%)]

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

Groups	n	Cure	Significant effect	Better	Invalid	Total effective rate
Control group	48	5(10.42)	12(25.00)	14(29.17)	17(35.41)	31(64.58)
Research group	48	11(22.92)	23(47.91)	8(16.67)	6(2.50)	42(87.50)#

Note: Compared with control group #P<0.05.

2.2 两组治疗前后各项 UPDRS 评分的比较

治疗前，两组各项 UPDRS 评分比较差异无统计学意义(P>0.05)；治疗后，两组各项 UPDRS 评分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(P>0.05)，见表 2。

表 2 两组治疗前后各项 UPDRS 评分的比较($\bar{x}\pm s$)

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

Groups	n	Time	UPDRSⅠ	UPDRSⅡ	UPDRSⅢ	UPDRSⅣ	Total UPDRS
Control group	48	Before treatment	4.76± 0.59	22.95± 2.86	27.49± 3.39	2.64± 0.33	56.20± 7.02
		After treatment	3.42± 0.81△	17.68± 2.20△	23.15± 2.92△	1.93± 0.20△	42.17± 5.21△
Research group	48	Before treatment	4.69± 0.63	23.20± 2.69	27.20± 3.29	2.59± 0.35	56.87± 7.85
		After treatment	2.11± 0.26△#	13.41± 1.65△#	19.57± 2.33△#	1.24± 0.15△#	36.19± 4.51△#

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

2.3 两组治疗前后血清 5-HT、BDNF、S-100β 水平的比较

治疗前，两组血清 5-HT、BDNF、S-100β 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 5-HT、BDNF 水平均较治疗前显著上升，而血清 S-100β 水平较治疗前下降，研究组以上指标的变化较对照组更明显(P<0.05)，见表 3。

表 3 两组治疗前后血清 5-HT、BDNF、S-100β 水平的比较($\bar{x}\pm s$)

Table 3 Comparison of serum levels of 5-HT, BDNF, S-100β between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	5-HT(μg/L)	BDNF(μg/L)	S-100β(μg/L)
Control group	48	Before treatment	170.25± 21.25	12.59± 1.56	4.29± 0.52
		After treatment	230.86± 28.77$^{\triangle}$	18.62± 2.20$^{\triangle}$	2.60± 0.33$^{\triangle}$
Research group	48	Before treatment	171.19± 20.65	12.90± 1.73	4.14± 0.56
		After treatment	306.39± 38.28$^{\triangle\#}$	21.23± 2.62$^{\triangle\#}$	1.48± 0.18$^{\triangle\#}$

Note: Compared with control group $^{\#}P$<0.05; Compared with before treatment $^{\triangle}$ P<0.05.

2.4 两组不良反应发生情况的比较

如表 4 所示，研究组不良反应发生率低于对照组(P<0.05)，见表 4。

表 4 两组不良反应发生情况的比较[(例)%]

Table 4 Comparison the incidence of adverse reactions between two groups [n(%)]

Groups	n	Weak	Mental symptoms	Switching phenomenon	Feel sick and vomit	Adverse reaction rate
Control group	48	5(10.42)	3(6.25)	6(12.50)	4(8.33)	18(37.50)
Research group	48	3(6.25)	2(4.17)	2(4.17)	1(2.08)	8(16.67)

3 讨论

老年帕金森病的起病相对隐匿，呈缓慢进展，并可引起一系列临床表现[12,13]。参照其病理变化特征，临床多选择增加多巴胺浓度，从而减轻其临床表现，发挥疾病的治疗作用[14]。但老年帕金森病患者多伴程度不一的基础疾病，增加临床治疗难度，脑深部刺激术、丘脑毁损术等手术治疗老年帕金森病的远期疗效并不理想[15-17]，药物已成为为老年帕金森病的重要治疗手段。

左旋多巴胺为老年帕金森治疗的代表药物，有研究显示[18,19]左旋多巴胺存在一定程度的神经毒性作用。多巴胺受体激动剂的有效性及安全性已得到临床研究证实[20]。普拉克索能够使患者运动症状显著改善，同时可缓解患者的抑郁状态[21,22]。但 Olanow CW 等[23]研究表示，单用西医治疗难以彻底根治，总有效率较低，存在一定局限性，本研究也证实此观点。

帕金森病属祖国医学＂震颤、颤证＂等范畴，脑为主要病位，并和脾肾等有着密切联系，肝肾亏虚致阴血不足，水难涵木，使肝风内动，难以濡养筋脉，致肌肉强直，肢体震颤，加之肾精不足，津亏阴虚，脉络瘀滞，痰淤互结，引脑脉失养，使病程迁延难愈[24]。此病风瘫淤阻为标，肝肾亏虚为本，属虚实夹杂、本虚标实之证，治疗应以活血通络补肾为主[25]。补肾活血通络胶囊中何首乌、地黄可培元固本、养血滋阴、益精补肾，枸杞子、钩藤、白芍、龟甲可熄风定颤、柔肝养血，桃仁、当归及丹参可通络祛瘀、活血养血，僵蚕、全蝎可搜风通络、涤痰祛瘀，诸药共起熄风通络、活血定颤、柔肝养血、益精补肾之功效。Wang C 等[26]研究发现老年帕金森病患者应用补肾活血通络胶囊的临床效果确切。本研究显示普拉克索联合补肾活血通络胶囊治疗的总有效率高于单用普拉克索组，且 UPDRS 评分改善更为明显，证实其可行性高，但具体作用机制并不明确。

5-HT 为脑内的一种神经递质，于帕金森发病中发挥关键作用。机体正常状态下，5-HT 能够抑制多巴胺的生成，但随着多巴胺能神经元的丢失及变性，可减少 5-HT 的释放[27,28]。BDNF 为神经营养因子，能够于内分泌系统、周围神经系统、中枢神经系统中分布，但以中枢神经系统中含量最为丰富，能够利于神经元的修复、再生，诱导多巴胺神经元的分化及存活，提高神经系统的学习及记忆能力，避免神经元受到缺氧缺血等伤害。神经细胞坏死或者凋亡后可增加脑脊液及血清中 S-100β 蛋白浓度[29,30]。近年来，老年帕金森病患者通过抗精神病药物可使神经突触处相应的递质降解产生抑制，从而使神经递质的起效时间延长，导致负反馈产生抑制，增强正反馈，利于神经末梢处的相应神经递质的生成。本研究显示两组治疗后血清 5-HT、BDNF 水平明显下降，S-100β 水平相应上升，但普拉克索联合补肾活血通络胶囊组改善更为明显，说明二者联合治疗更能有效调节机体内环境状态，从而调控细胞因子的表达，起到治疗作用。且本研究显示普拉克索联合补肾活血通络胶囊组不良反应更少，提示补肾活血通络胶囊能够提高治疗安全性。

综上所述，普拉克索联合补肾活血通络胶囊治疗治疗老年帕金森病的临床效果优于单用普拉克索，可能与其显著提高血清 5-HT 及 BDNF 表达并降低 S-100β 水平有关。

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