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美金刚联合普拉克索治疗帕金森患者临床疗效及对 CysC、Hcy 水平影响 *

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摘要 目的:探究美金刚联合普拉克索在治疗帕金森患者中的临床疗效,并就治疗对患者胱抑素 C(cystatin C, CysC)以及血同型半胱氨酸(homocysteine, Hcy)水平的影响。**方法:**选择 2018 年 1 月至 2020 年 1 月于我院接受治疗的 98 例帕金森患者,随机数字表法均分为两组(每组各 49 例),对照组单纯接受美金刚治疗,研究组在对照组基础上加用普拉克索进行治疗,对比两组治疗有效率,治疗前后 CysC、Hcy 水平,以及治疗前后简易智能精神状态检查量表(mini mental state examination, MMSE)以及帕金森病评定量表 III(parkinson comprehensive rating scale, UPDRS III)评分,最后对两组患者治疗中不良反应发生率进行统计对比。**结果:**(1)研究组患者治疗有效率明显高于对照组患者($P<0.05$);(2)治疗前两组患者 CysC、Hcy 水平对比差异不具有统计学意义($P>0.05$),治疗后研究组患者 CysC、Hcy 水平低于对照组($P<0.05$);(3)治疗前两组患者 MMSE 及 UPDRS III 量表评分对比差异不具有统计学意义($P>0.05$),治疗后研究组患者 MMSE 得分高于对照组,UPDRS III 量表评分低于对照组($P<0.05$);(4)两组治疗不良反应诸如胃肠道反应、嗜睡、体位性低血压等对比无差异($P>0.05$)。**结论:**美金刚联合普拉克索对帕金森具有较好的治疗效果,能够显著改善患者认知及运动功能,降低 CysC、Hcy 水平,同时治疗安全性较高。

关键词:美金刚;普拉克索;帕金森;胱抑素 C(CysC);血同型半胱氨酸(Hcy)

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Effect of Memantine Combined with Pramipexole on the Level of CysC and Hcy in Patients with Parkinson's Disease*

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ABSTRACT Objective: To explore the effect of memantine and pramipexole in the treatment of Parkinson's patients, and the effect of treatment on the levels of cystatin C (CysC) and blood homocysteine (Hcy) in patients. **Methods:** 98 patients with Parkinson's disease who were treated in our hospital from January 2018 to January 2020 were selected as the research subjects. They were divided into experimental group and control group according to the random number table method (49 patients in each group). Patients in the control group received memantine treatment alone. Patients in the experimental group were treated with pramipexole on the basis of patients in the control group. Comparing the treatment efficiency of the two groups of patients, CysC and Hcy levels before and after treatment, and simple intelligent mental state tests before and after treatment. Scores (MMSE) and Parkinson's Disease Rating Scale III (UPDRS III) scores. Finally, the statistical comparison of the incidence of adverse reactions in the treatment of the two groups of patients was performed. **Results:** (1) The comparison showed that the treatment efficiency of the experimental group was significantly higher than Patients in the control group ($P<0.05$). (2) The comparison showed that the differences in CysC and Hcy levels between the two groups of patients before treatment were not statistically significant ($P>0.05$). CysC and Hcy levels in the experimental group were lower than those in the control group after treatment ($P<0.05$). (3) The comparison showed that there was no significant difference in the MMSE and UPDRS III scale scores between the two groups of patients before treatment ($P>0.05$). Higher than the control group, the UPDRS III scale score was lower than the control group ($P<0.05$). (4) There was no significant difference in the incidence of adverse reactions such as gastrointestinal reactions, lethargy, orthostatic hypotension among the two groups ($P>0.05$). **Conclusion:** Memantine combined with Praxor has a better therapeutic effect on Parkinson's, which can significantly improve patients' cognitive and motor functions, reduce CysC and Hcy levels, and at the same time have higher safety in treatment.

Key words: Memantine; Praxo; Parkinson; CysC; Hcy

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前言

帕金森病是一种高发于中老年群体的慢性神经系统退行性疾病,近些年,随着我国社会老龄化的进程,其发病率也呈现递增,数据显示,当前我国 65 岁以上老年人帕金森病的患病率为 1%~2%,85 岁以上老人患病率约为 3%~5%,且发病率随着年龄的增长而上升^[1,2]。帕金森病的病理基础为中脑黑质多巴胺神经元的变性死亡,主要临床表现为不自主震颤、姿势障碍、运动迟缓等,不易控制,会严重降低患者的生活质量,且随着病情的进展,多数患者会出现“开-关”现象、痴呆等,治疗难度进一步升高^[3-5]。当前对帕金森病的治疗多依赖服药干预,但传统的多巴胺治疗方式一方面副作用大,另一方面也难以纠正 PD 进程,治疗效果不佳,因而联合用药治疗成为帕金森症治疗研究热点^[6,7]。美金刚是一种兴奋性氨基酸受体拮抗剂,是临床上常用的中重度阿尔兹海默症治疗药物,普拉克索属抗组胺药,也是临床上帕金森病常用治疗药物之一^[8],二者单独用药治疗在国内外的研究中应用已经十分成熟,但是对于二者的联合应用,临床还存在一定的争议,并且对于二者在帕金森患者认知障碍时期外周血 CysC、Hcy 水平变化研究较少,本文作者通过研究发现,美金刚联合普拉克索对帕金森具有较好的治疗效果,能够显著改善患者认知及运动功能,降低 CysC、Hcy 水平,同时治疗安全性较高。

1 资料与方法

1.1 一般资料

选择 2018 年 1 月~2020 年 1 月于我院治疗的 98 例帕金森患者,随机数字表法均分为研两组(各 49 例)。

纳入标准:均符合国际帕金森病诊断标准^[9];病历资料齐全;原发性帕金森;患者家属对签署知情同意书;获得本院伦理委员会批准。

排除标准:合并精神障碍者;合并周期性肢体运动障碍;近期出现急性脑部感染、脑血管病;合并冠心病、肾衰竭者;合并酒精滥用者;合并严重肝肾功能障碍者。

剔除标准:治疗期间触发其他疾病无法继续施治者;主动要求退出调研者;干预期间自行服用其他药物者;干预期间病情加重无法继续调研者。

1.2 方法

两组患者均在常规治疗的基础上加用药物干预,对照组口服盐酸美金刚片(商品名易倍申,H.Lundbeck A/S,规格 10 mg/片,批准文号:H20120268)进行治疗,应用剂量为第 1 w 5 mg/d,第 2 w 10 mg/d,第 3 w 15 mg/d,第 4 w 20 mg/d 并维持,连续治疗时间为 16 w;研究组在对照组基础上加用普拉克索(德国 Boehringer Ingelheim International GmbH,规格 1.0 mg/片,批准文号:H20140918)进行治疗,使用剂量为 0.375 mg/日,连续治疗时间为 16 w。

1.3 观察指标及评测标准

1.3.1 治疗有效率 根据 Webster 评分^[10]来计算进步率,进而评估治疗有效率,进步率=(治疗前积分-治疗后积分)/治疗前积分×100%,痊愈为进步率 100%,显效为进步率 50%~99%,有效为进步率 10%~49%,无效为进步率 0%~9%。

1.3.2 治疗前后 CysC、Hcy 水平 分别于治疗前后采集两组患者血样,并离心留血清备用,采用酶联免疫吸附法(Enzyme-linked immunosorbent assay,ELISA)对两组患者干预前后的 CysC、Hcy 水平进行检测并实施组间及组内前后对比,操作严格按照说明书实施,每个指标检测 3 次取平均值作为最终结果。

1.3.3 治疗前后 MMSE 及 UPDRS III 量表评分 分别使用 MMSE 及 UPDRS III 量表对两组患者治疗前后的精神及活动情况进行评估,并实施组间及组内对比,MMSE 量表是临床上常用的智力状态及认知功能缺损程度评估量表,能够对受试者 7 个方面进行测试,包括时间定向、地点定向、语言即刻记忆等,满分 30 分,得分 26 分以上为正常;UPDRS III 量表分为言语、面部表情、强直等 14 项,每项区分 0~4 五个选项,得分越高代表患者运动功能越差^[11,12]。

1.3.4 治疗中各类不良反应发生率 治疗过程中胃肠道反应、嗜睡、体位性低血压等的发生率。

1.4 统计学方法

应用 SPSS 19.0,计数资料以(%)表示,计量资料以($\bar{x} \pm s$)表示,分别行卡方检验和 t 检验, $P < 0.05$ 有统计学意义。

2 结果

2.1 一般资料

两组的一般临床资料对比差异不具有统计学意义($P > 0.05$),如表 1 所示。

表 1 两组一般临床资料对比

Table 1 Comparison of general clinical data between two groups

Groups	n	Male / female	Average age (years)	Course of disease(year)
Test group	49	26/23	59.09± 2.01	3.09± 0.21
Control group	49	25/24	59.11± 2.19	3.11± 0.18

2.2 两组治疗有效率对比

研究组患者治疗有效率为 97.96%(48/49),对照组患者治疗有效率为 87.76%(43/49),两组患者治疗有效率对比差异具有统计学意义($P < 0.05$),如表 2 所示。

2.3 两组治疗前后 CysC、Hcy 水平对比

治疗前两组的 CysC、Hcy 水平对比无差异($P > 0.05$),治疗

后两组上述指标水平均较治疗前出现明显下降,前后对比差异具有统计学意义($P < 0.05$),同时组间对比显示研究组患者 CysC、Hcy 水平高于对照组患者($P < 0.05$),如表 3 所示。

2.4 两组治疗前后 MMSE 及 UPDRS III 量表评分对比

治疗前两组患者 MMSE 及 UPDRS III 量表评分对比差异不具有统计学意义($P > 0.05$),治疗后两组患者 MMSE 评分均

较治疗前有下降,UPDRS III 量表评分较治疗前有提高,前后对比差异具有统计学意义($P<0.05$),同时组间对比显示研究组患者 MMSE 评分低于对照组,UPDRS III 量表评分高于对照组($P<0.05$),具体数据如表 4 所示。

表 2 两组治疗有效率对比[例(%)]

Table 2 Comparison of treatment effectiveness between two groups [n(%)]

Groups	n	Marked effect	Effective	Invalid	Efficient
Test group	49	40(81.63)	8(16.33)	1(2.04)	48(97.96)*
Control group	49	35(71.43)	8(16.33)	6(12.24)	43(87.76)

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

表 3 两组治疗前后 CysC、Hcy 水平对比($\bar{x}\pm s$)Table 3 Comparison of CysC and Hcy levels between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	CysC(U/L)		Hcy($\mu\text{mol/L}$)	
		Before treatment	After treatment	Before treatment	After treatment
Test group	49	0.79 $\pm$ 0.12	0.59 $\pm$ 0.02 [#]	14.09 $\pm$ 0.31	11.01 $\pm$ 0.03 [#]
Control group	49	0.81 $\pm$ 0.08	0.65 $\pm$ 0.03 ^{**}	14.11 $\pm$ 0.28	11.27 $\pm$ 0.12 ^{**}

Note: Compared with the control group, * $P<0.05$; compared with before treatment, [#] $P<0.05$.

表 4 两组患者治疗前后 MMSE 及 UPDRS III 量表评分对比($\bar{x}\pm s$)Table 4 Comparison of MMSE and UPDRS III scale scores before and after treatment in the two groups ($\bar{x}\pm s$)

Groups	n	MMSE		UPDRS III	
		Before treatment	After treatment	Before treatment	After treatment
Test group	49	23.98 $\pm$ 0.14	26.01 $\pm$ 1.01 [#]	76.87 $\pm$ 2.88	60.18 $\pm$ 2.89 [#]
Control group	49	23.97 $\pm$ 0.13	25.44 $\pm$ 0.49 ^{**}	76.88 $\pm$ 2.98	67.09 $\pm$ 2.76 ^{**}

2.5 两组不良反应发生率对比

研究组治疗中不良反应发生总率为 10.20%, 对照组治疗

中不良反应发生总率为 8.16%, 两组对比差异无统计学意义($P>0.05$),具体数据如表 5 所示。

表 5 两组患者治疗中各类不良反应发生率对比[例(%)]

Table 5 Comparison of the incidence of various adverse reactions in the treatment of the two groups of patients [n(%)]

Groups	n	Gastrointestinal reaction	Lethargy	Orthostatic hypotension	Total incidence
Test group	49	3(6.12)	1(2.04)	1(2.04)	5(10.20)
Control group	49	2(4.08)	1(2.04)	1(2.04)	4(8.16)

3 讨论

帕金森病是一种持续、缓慢发展的运动障碍疾病,临床研究指出,帕金森病的发病原因主要与患者机体功能减退和修复性减弱有关,治疗困难、病情呈缓慢进展,给患者及社会带来沉重的负担^[13]。帕金森病患者除了临床上运动迟缓和精神障碍等,部分患者还会随病情的发展出现抑郁、睡眠障碍等症状,一般帕金森病患者晚期常并发严重的运动障碍并发症,出现言语障碍、吞咽困难等,甚至可危及患者生命^[14]。流行病学调查资料显示,全球帕金森病患者约占总人口的 0.3%左右,其中以 85 岁以上患者为主^[15],可以预见的是,随着我国社会人群年龄结构的调整变化,帕金森病势必会对我国社会正常发展造成严重影响^[16]。

当前临床上对帕金森病的治疗手段仍主要依赖药物干预,临床实践表明,多巴胺缺失在帕金森病的发生发展中起到重要

作用,因而传统治疗手段多为补充多巴胺,但该给药方式存在如下弊端:(1)多巴胺易被血脑屏障拦截,导致药物利用率低下,加大药量则会直接增加各类副反应强度;(2)长期服用该药物的患者会出现不随意运动或精神症状等,患者多难以耐受,因而目前帕金森病的治疗手段倾向于选择多种药物联合干预^[17,18]。本文作者通过设立不同分组的方式,就美金刚联合普拉克索在治疗帕金森病中的效果以及对患者 CysC、Hcy 水平的影响进行了研究分析,结果显示,相比于单纯应用美金刚进行治疗的对照组患者,加用普拉克索的研究组患者治疗其有效率更高,达到 97.96%,明显高于对照组的 87.76%。有研究指出,美金刚属兴奋性氨基酸受体拮抗剂,是临床上常用的中重度阿尔兹海默症治疗药物,其药理作用为该药物能够保护患者的神经元免受损伤,是一种中度亲和力的 NMDA 受体拮抗剂,对改善阿尔兹海默症患者认知功能效果较好^[19,21]。普拉克索则属于多巴胺受体激动剂的一种,为抗组胺药,治疗帕金森病效果显

著^[22,23]。本文中研究组患者联合应用美金刚和普拉克索后其MMSE及UPDRS III量表评分都较治疗前有明显的改善,分析其原因为美金刚能够缓解神经损伤症状,普拉克索能够兴奋激动多巴胺受体,提高多巴胺摄取利用率,其药物综合作用下明显改善了患者的临床症状。国内外虽然没有报道美金刚联合普拉克索在治疗帕金森病,但是对于普拉克索联合其他药如美多巴、多巴丝肼等有很多,国内学者赵玉燕等^[24]应用美多巴联合普拉克索治疗帕金森患者,疗效显著高于单独应用美多巴组,说明普拉克索在联合其他药物治疗帕金森病有较好的效果。国外学者与本研究不同,多采用经颅磁刺激纠正帕金森病,对于患者的认知障碍效果改善显著^[25]。因此,在后续的临床研究中,也要采用药物联合经颅磁刺激治疗帕金森病,为该病的治疗开辟新的方案和思路。

目前已有较多研究证实CysC、Hcy水平同帕金森患者的临床症状存在相关性,上述因子水平的异常升高会增加帕金森患者病情严重程度^[26]。研究发现,高Hcy会提高机体内 α 突触核蛋白和 β 淀粉样蛋白的生成,进而损伤胆碱能功能,最终导致引起认知障碍^[27]。而CysC则属于内源性组织蛋白酶抑制剂,已被证实与多种神经系统症状相关,帕金森患者多存在多巴胺神经元的损伤现象^[28,29],在该进程中已损伤的神经元细胞会释放出多种炎性因子而加速胶质细胞聚集,同时还会加速机体分泌CysC,而CysC的过量表达又进一步加快胶质细胞的聚集进程,形成了恶性循环^[30,31]。临床研究表明,CysC、Hcy水平与帕金森病存在密切相关性,本文中通过临床干预对比发现,研究组患者治疗后CysC、Hcy水平均较治疗前明显降低,同时也显著低于对照组患者,这说明美金刚联合普拉克索在缓解帕金森患者炎症进程、缓解患者胶质细胞聚集方面效果确切,因而治疗效果也更好^[32,33]。本研究结果还提示,联合治疗其安全性与单纯应用美金刚差异不大,因此其治疗安全性也值得肯定。

综上所述,美金刚联合普拉克索对帕金森具有较好的治疗效果,能够显著改善患者认知及运动功能,降低CysC、Hcy水平,同时治疗安全性较高,值得临床推广应用。本研究也存在一定的不足,样本量少,来源单一,结果可能存在一定的偏倚,没有分析美金刚联合普拉克索在帕金森患者认知障碍不同时期外周血CysC、Hcy水平变化,没有追踪患者的远期疗效,后续需要深入研究。

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