

doi: 10.13241/j.cnki.pmb.2020.15.029

盐酸美金刚联合银杏叶提取物对阿尔茨海默病患者血清 BDNF、NGF、DA 水平和认知功能的影响 *

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摘要 目的:探讨盐酸美金刚联合银杏叶提取物对阿尔茨海默病患者血清脑源性神经营养因子(BDNF)、神经营养因子(NGF)浓度、多巴胺(DA)水平和认知功能的影响。**方法:**将我院 2017 年 6 月至 2018 年 7 月收治的 92 例阿尔茨海默病患者按随机数字表法分为对照组 49 例和研究组 43 例,对照组采用盐酸美金刚治疗,研究组在对照组基础上联合银杏叶提取物治疗。比较两组临床疗效,治疗前后血清 BDNF、NGF、DA 水平、认知功能、简易精神状态检查量表(MMSE)、日常生活能力(ADL)评分的变化和不良反应的发生情况。**结果:**治疗后,研究组总有效率为 90.70%,显著高于对照组(69.39%, $P<0.05$)。治疗前,两组血清 BDNF、NGF、DA 水平、MMSE 和 ADL 评分比较差异无统计学意义($P>0.05$);治疗后,两组以上指标均较治疗前显著上升,且研究组以上指标明显高于对照组($P<0.05$)。两组不良反应总发生率比较差异无统计学意义($P>0.05$)。**结论:**盐酸美金刚联合银杏叶提取物可提高阿尔茨海默病的疗效,改善患者认知功能,可能与增加 BDNF、NGF、DA 的表达有关。

关键词:阿尔茨海默病;盐酸美金刚;银杏叶提取物;脑源性神经营养因子

中图分类号:R749.1 **文献标识码:**A **文章编号:**1673-6273(2020)15-2944-04

Effects of Memantine Hydrochloride Combined with Ginkgo Biloba Extract on the Serum Levels of BDNF, NGF, DA and Cognitive Function of Alzheimer's Disease Patients*

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ABSTRACT Objective: To investigate the effects of memantine hydrochloride combined with ginkgo biloba extract on the serum brain-derived neurotrophic factor (BDNF), neurotrophic factor (NGF) concentration, dopamine (DA) levels and cognitive function of alzheimer's disease patients. **Methods:** A total of 92 patients with alzheimer's disease admitted to our hospital from June 2017 to July 2018 were randomly divided into 49 patients in the control group and 43 patients in the research group. The control group was treated with memantine hydrochloride, and the research group was treated with ginkgo biloba extract on the basis of the control group. The clinical efficacy, changes of serum BDNF, NGF, DA levels, cognitive function, MMSE, ADL scores before and after treatment and incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of research group was 90.70%, which was significantly higher than that of the control group (69.39%, $P<0.05$). Before treatment, there was no significant difference in the serum levels of BDNF, NGF, DA, MMSE and ADL between the two groups ($P>0.05$). After treatment, the indexes in both groups were significantly higher than those before treatment, which were significantly higher in the research group than those in the control group ($P<0.05$). There was no significant difference in the total incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Memantine hydrochloride combined with ginkgo biloba extract can improve the efficacy and the cognitive function of Alzheimer's disease patients, which may be related to the increased serum levels of BDNF, NGF and DA.

Key words: Alzheimer's disease; Memantine hydrochloride; Ginkgo biloba extract; Brain-derived neurotrophic factor

Chinese Library Classification(CLC): R749.1 **Document code:** A

Article ID: 1673-6273(2020)15-2944-04

* 基金项目:海南省自然科学基金面上项目(818MS129)

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(收稿日期:2020-03-06 接受日期:2020-03-29)

前言

阿尔茨海默病为神经系统的常见退行性疾病,临床上以日常生活能力下降、认知功能衰退和行为及精神异常为主要症状,具有发病缓慢、隐匿,致残率高等特点^[1,2]。目前,阿尔茨海默病缺乏特效药物治疗,有关研究显示尽早在对症、支持的综合性疗法上进行病因干预可一定程度延缓疾病进展^[3]。近年来研究表明兴奋性谷氨酸毒性在阿尔茨海默病发病中有重要作用,多种细胞因子过度兴奋可导致神经元受损,促进神经元内钙离子超载,从而诱导神经退行性病变^[4]。Paonessa F 等研究认为神经兴奋性毒性主要由谷氨酸的 N-甲基-D-门冬氨酸(N-Methyl-D-Aspartic Acid, NMDA)受体介导,调控此神经元的突触活性可能有利于阿尔茨海默病的治疗^[5]。

盐酸美金刚作为一种 NMDA 受体拮抗剂,能够选择性阻断 NMDA 受体,调节脑部谷氨酸浓度,延缓疾病进展^[6]。银杏叶提取物是神经系统疾病的常用植物药物之一,相关研究报道^[7]银杏在提升感知功能及记忆力方面有明显优势,临床研究表明银杏叶提取物也可一定程度的改善脑部神经兴奋毒性,且盐酸美金刚、银杏叶提取物均可改善患者日常生活能力和认知功能^[8,9],但目前临床缺乏二者联合应用的报道。本研究旨在探讨盐酸美金刚联合银杏叶提取物对阿尔茨海默病患者血清脑源性神经营养因子(Brain-derived neurotrophic factor, BDNF)、神经营养因子(neurotrophic factor, NGF)浓度,用酶联免疫法测定多巴胺(dopamine, DA)水平和认知功能的影响。

1 资料与方法

1.1 一般资料

选择我院 2017 年 6 月到 2018 年 7 月收治的 92 例阿尔茨海默病患者,入选标准:符合阿尔茨海默病诊断标准^[10];心肝肾等器官无明显异常;近 2 周内未接受促智药物治疗;年龄 63~77 岁。排除标准:突然发病,早期出现癫痫发作、步态障碍及行为变化;视野缺损、感觉缺失、轻偏瘫等局灶性神经症状或早期锥体外系症状;其他可能影响记忆及相关症状的内科疾病;药物、酒精滥用史;本研究药物禁忌证。92 例患者按随机数字表法分为 49 例对照组和 43 例研究组,对照组男 20 例,女

29 例;年龄(67.91 ± 7.53)岁;文化程度:大学及以上 6 例,中学 28 例,小学及以下 15 例。研究组男 17 例,女 26 例;年龄(68.64 ± 7.02)岁;文化程度:大学及以上 4 例,中学 25 例,小学及以下 14 例。两组一般资料比较无统计学差异($P > 0.05$)。

1.2 治疗方法

对照组予以盐酸美金刚(厂家:灵北制药(天津)有限公司,规格:10 mg/片,批号:20170102)治疗,第 1 周晨起口服 5 mg,第 2 周早晚各服用 5 mg,第 3 周口服 15 mg(晨起 10 mg、晚上 5 mg),第 4 周早晚各服用 10 mg,并以此剂量进行维持治疗。研究组在对照组基础上联合银杏叶提取物(厂家:Dr. Willmar Schwabe GmbH & Co.KG,规格:40 mg/片,批号:20161014)治疗,口服 0.8 mg,每天 3 次。所有患者均治疗 6 个月,于治疗结束时评价疗效,观察不良反应的发生情况。

1.3 观察指标

1.3.1 临床疗效评价 显效:症状基本好转,智能损伤显著改善,反应较为灵敏,生活能够自理,回答问题较为正确,可进行一般的日常生活活动;有效:症状有所改善,生活基本可自理,反应较为迟钝,人格、智力仍有部分异常;无效:未达到以上标准。显效及有效均为总有效^[11]。

1.3.2 血液指标 于治疗前及治疗结束时收集患者外周空腹静脉血 4 mL,用放射免疫法测定血清 BDNF、NGF 浓度,用酶联免疫法测定 DA 浓度。

1.3.3 认知功能评价 于治疗前后进行简易精神状态检查量表(MMSE)评价,总分 30 分,分数与患者认知功能状态呈正比^[12]。日常生活能力(ADL)评分^[13]:总共 10 个项目,总分为 0~100 分,分数和日常生活能力呈正比。

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,计数资料以[(例)%]表示,组间比较采用 χ^2 检验,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 90.70%,显著高于对照组的(69.39%, $P < 0.05$),见表 1。

表 1 两组临床疗效的比较[例(%)]

Table 1 Comparison of curative effect between two groups [n(%)]

Groups	n	Effective	Effective	Invalid	Total effective rate
Control group	49	22(44.90)	12(24.49)	15(30.61)	34(69.39)
Research group	43	29(67.44)	10(23.26)	4(9.30)	39(90.70) [#]

Note: Compared with control group, [#] $P < 0.05$.

2.2 两组治疗前后血清 BDNF、NGF、DA 水平分析

治疗前,两组血清 BDNF、NGF、DA 水平比较差异无统计学意义($P > 0.05$);治疗后,两组血清 BDNF、NGF、DA 水平均较治疗前显著上升,且研究组以上指标显著高于对照组,比较差异有统计学意义($P < 0.05$),见表 2。

2.3 两组治疗前后 MMSE、ADL 评分的比较

治疗前,两组 MMSE、ADL 评分比较差异无统计学意义

($P > 0.05$);治疗后,两组 MMSE、ADL 评分均较治疗前显著升高,且研究组以上指标明显高于对照组($P < 0.05$),见表 3。

2.4 两组不良反应的发生情况

治疗过程中,两组总不良反应发生率比较无统计学差异($P > 0.05$),见表 4。

3 讨论

表 2 两组治疗前后血清 BDNF、NGF、DA 水平分析($\bar{x} \pm s$)Table 2 Analysis of serum levels of BDNF, NGF and DA in the two groups before and after treatment ($\bar{x} \pm s$)

Groups	n	Time	BDNF($\mu\text{g/L}$)	NGF(ng/L)	DA(ng/mL)
Control group	49	Before treatment	28.71 $\pm$ 3.85	13.29 $\pm$ 1.48	92.09 $\pm$ 11.08
		After treatment	39.81 $\pm$ 5.31 ^a	18.93 $\pm$ 2.74	119.42 $\pm$ 14.27 ^a
Research group	43	Before treatment	29.65 $\pm$ 3.21	14.10 $\pm$ 1.24	94.18 $\pm$ 13.28
		After treatment	53.10 $\pm$ 8.40 ^{a, #}	26.75 $\pm$ 3.96 ^{a, #}	145.20 $\pm$ 20.09 ^{a, #}

Note: VS control group, [#] $P < 0.05$; VS before treatment, ^a $P < 0.05$.

表 3 两组治疗前后 MMSE、ADL 评分的比较($\bar{x} \pm s$)Table 3 Comparison of the MMSE and ADL scores between two groups before and after treatment ($\bar{x} \pm s$)

Groups	n	Time	MMSE(points)	ADL(points)
Control group	49	Before treatment	15.87 $\pm$ 2.33	48.98 $\pm$ 5.52
		After treatment	21.05 $\pm$ 3.01	61.25 $\pm$ 8.04
Research group	43	Before treatment	15.13 $\pm$ 2.85	50.73 $\pm$ 4.75
		After treatment	24.69 $\pm$ 3.49 [#]	67.02 $\pm$ 9.27 [#]

Note: Compared with control group, [#] $P < 0.05$; Compared with before treatment, ^a $P < 0.05$.

表 4 两组不良反应的发生情况比较[例(%)]

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

Groups	n	Dizziness	Headache	Lethargy	Incidence rate of Adverse Reactions
Control group	49	3(6.12)	3(6.12)	2(4.08)	8(16.33)
Research group	43	2(4.65)	2(4.65)	2(4.65)	6(13.95)

阿尔茨海默病为老年人群的常见疾病之一,随着目前人口老龄化的加剧,其发生率明显升高。阿尔茨海默病的病情多样,临床治疗难度较大,现已成为严重威胁患者生活质量及精神健康的疾病。阿尔茨海默病的病因目前尚未完全明确,研究显示此类患者的痴呆表现可能和 NMDA 受体参与的兴奋性氨基酸毒性作用有关^[14]。NMDA 受体可参与大脑记忆形成、突出传递等功能,脑内谷氨酸浓度大量增加可引起兴奋性毒性作用,导致 NMDA 受体为持续性激活状态,促进钙离子超载及细胞凋亡,使患者记忆 - 长时程效应出现缺失,影响认知功能^[15,16]。

盐酸美金刚为快速动力性、强电压依赖性的 NMDA 受体拮抗剂,具有无竞争性、亲和力和低等特点,能够选择性调控 NMDA 受体,抑制钙离子内流,保护神经功能,抑制兴奋性毒性的生成,避免神经元死亡或损伤^[17,18]。相关研究报道盐酸美金刚阻断谷氨酸兴奋性毒性的同时对谷氨酸参与正常记忆、学习等生理作用无影响^[19]。Cromberg LE 等研究表明盐酸美金刚通过提高 NMDA 受体活性可促进海马突触传递,进一步起到提高记忆力及神经保护作用,延缓阿尔茨海默病的进展^[20]。但也有研究显示^[21]盐酸美金刚对部分阿尔茨海默病的疗效欠佳,仍有待提高。

银杏叶提取物富含黄酮、有机酸等物质,具有多种药理作用,现已开展于神经系统、心脑血管等疾病的预防及治疗中^[22]。临床研究表明脑组织的氧化代谢率高,抗氧化能力较弱,容易产生氧化损伤,银杏胶质细胞和神经元功能,增加阿尔茨海默病的发生风险。银杏叶提取物中的活性成分能够有效清除氧自由

基,避免细胞老化^[23]。国外研究显示 β 淀粉样蛋白(A β)分泌过度可在脑组织内异常沉积,从而对神经元突触产生毒性作用,引起神经细胞坏死^[24]。银杏叶提取物能够阻止 A β 原纤维形成,避免 A β 在脑内大量沉积,减弱其神经毒性,还可保护脑部屏障结构及功能。另有研究报道银杏叶提取物能够增加脑部血液供应,改善缺血性损伤,从而减少谷氨酸毒性,保护脑组织功能^[25]。以上研究表明银杏叶提取物在阿尔茨海默病治疗上有一定优势。本研究结果显示盐酸美金刚联合银杏叶提取物组总有效率较盐酸美金刚高,表明二者联合能够起到良好的效果,但具有机制有待进一步探讨。

研究表明阿尔茨海默病发生和部分细胞因子的表达缺失有关^[26,27]。BDNF 为神经营养因子,能够分布于内分泌系统、周围神经系统、中枢神经系统,以中枢神经系统中含量最为丰富,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。NGF 为神经细胞生长及调节的主要因子之一,可参与神经细胞的生长发育、增殖再生,还可预防突触损伤、衰老所致神经细胞变性^[28]。DA 为机体重要的神经递质,阿尔茨海默病患者机体 DA 水平相对较低,其浓度改变是评价药物疗效的可靠依据^[29,30]。本研究结果显示盐酸美金刚联合银杏叶提取物治疗后患者以上指标均上升,且较单用盐酸美金刚改善更明显,提示二者联合能够促进 BDNF、NGF 和 DA 的表达,从而保护神经功能,减轻患者痴呆症状。

阿尔茨海默病作为一种神经系统退行性疾病,可引起认知

行为改变。MMSE 的内容简单,测定时间短,易于患者接受,是目前临床测定阿尔茨海默病智能损伤程度的最常見量表^[31]。ADL 量表能够客观评价患者日常生活功能损伤程度,信效度高^[32]。本研究结果显示联合银杏内酯注射液组治疗后 MMSE 及 ADL 评分显著较治疗前显著上升,且较单用盐酸美金刚改善更明显,说明其可有效保护患者大脑的认知功能,提高患者记忆能力,从而改善患者日常生活能力,减轻患者痴呆症状。两组治疗期间均有少数患者发生轻微的不良反 应,但未影响后续治疗,提示银杏叶提取物未增加不良反 应。

综上所述,盐酸美金刚联合银杏叶提取物可提高阿尔茨海默病的疗效,改善患者认知功能,可能与增加 BDNF、NGF、DA 的表达有关。

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