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石杉碱甲联合注射用鼠神经生长因子对老年痴呆MMSE评分及日常生活能力的影响*

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摘要 目的：研究石杉碱甲联合注射用鼠神经生长因子对老年痴呆简易智力状态检查量表(MMSE)及日常生活能力量表(ADL)评分的影响。**方法：**选择2015年6月～2018年6月我院收治的98例老年痴呆患者，随机分为两组。对照组口服石杉碱甲，起始给药剂量为每次100 μg，每天2次，第2周给药剂量调整为每次150 μg，每天2次，维持用量。观察组联合静脉滴注鼠神经生长因子，每次20 μg，每天1次。比较两组治疗前后ADL和MMSE评分、血清白细胞介素(IL)-1β、C-反应蛋白(CRP)、IL-6、肿瘤坏死因子-α(TNF-α)水平的变化。**结果：**治疗后，观察组的总有效率为87.75%(43/49)，明显高于对照组[69.39%(34/49)](P<0.05)；两组治疗后的ADL和MMSE评分及血清IL-1β、CRP、IL-6和TNF-α水平均较治疗前明显降低(P<0.05)，且观察组以上指标均明显低于对照组(P<0.05)。**结论：**与单用石杉碱甲相比，注射用鼠神经生长因子联合石杉碱甲可更有效改善其日常生活能力和认知功能，且能显著降低血清炎症因子水平。

关键词：石杉碱甲；鼠神经生长因子；老年痴呆；日常生活能力

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Effect of Huperzine A Combined with Mouse Nerve Growth Factor for Injection on the MMSE Score and Activity of Daily Life of Senile Patients with Dementia*

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ABSTRACT Objective: To investigate the effect of Huperzine A combined with mouse nerve growth factor for injection on the MMSE score and activity of daily life of cenile patients with dementi. **Methods:** 98 cases of senile patients withdementia who were treated in our hospital from June 2015 to June 2018 were selected and randomly divided into two groups. The control group was given Huperzine A orally. The initial dosage was 100 μg each time, twice a day. The dosage of Huperzine A was adjusted to 150 μg each time at the 2nd week, twice a day, and the dosage was maintained. The observation group was given intravenous drip of mouse nerve growth factor, 20 g each time, 1 times a day on the basis of control group. The changes of ADL and MMSE scores, serum levels of interleukin (IL)-1beta, C-reactive protein (CRP), IL-6 and tumor necrosis factor-alpha (TNF-alpha) were compared between the two groups before and after treatment. **Results:** After treatment, the total effective rate of observation group was 87.75%(43/49), which was significantly higher than that of the control group [69.39%(34/49)](P<0.05). After treatment, the ADL and MMSE scores, serum IL-1β, CRP, IL-6 and TNF-α levels in both groups were significantly lower than those before treatment (P<0.05), and the above indexes in the observation group were significantly lower than those in the control group (P<0.05). **Conclusion:** Compared with Huperzine A alone, Huperzine A combined with mouse nerve growth factor can more effectively improve the daily living ability, cognitive function of mice and reduce the level of serum inflammatory factors.

Key words: Huperzine A; Mouse nerve growth factor; Senile dementia; Daily living ability

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前言

老年痴呆是一种以认知障碍、记忆减退以及人格改变为临床特征的神经系统退行性疾病，目前已成为继心血管疾病、恶性肿瘤以及脑血管疾病之后导致老年人死亡的第四位病因[1]。老年痴呆患者的病理学改变主要包括老年斑、脑萎缩、神经元

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内神经纤维缠结、突触丢失、神经元丢失以及胶质增生等[2,3]。目前，一般采用脑循环改善剂、脑保护剂以及脑代谢复活剂等常规药物治疗老年痴呆，但尚无绝对有效的治疗药物，寻找具有确切疗效的药物仍是临床上重要的研究课题。

石杉碱甲不仅可以高效且可逆地抑制胆碱酯酶，从而对机体的神经功能发挥保护作用，还可以减轻蛋白激酶 C 以及抗过氧化氢抑制药等所诱导的神经细胞凋亡作用[4,5]。鼠神经生长因子不仅可以对正常神经细胞发挥营养因子功效，还可以修复以及保护受到损伤的神经细胞，因此被广泛应用于临床治疗神经系统疾病的研究中[6,7]。本研究主要分析了注射用鼠神经生长因子联合石杉碱甲对老年痴呆患者日常生活能力和认知功能的效果，现将结果报道如下。

1 资料与方法

1.1 一般资料

选择 2015 年 6 月～2018 年 6 月我院收治的 98 例老年痴呆患者，排除对石杉碱甲以及鼠神经生长因子过敏患者，合并肿瘤患者，意识不清患者，由于严重内科疾病、各种神经疾病和头部外伤史等原因造成影响认知功能以及脑功能的患者。用抽签法将所有患者随机分为两组。观察组 49 例，男 27 例，女 22 例；年龄 62~90 岁，平均(72.53± 6.42) 岁；病程 5 个月 ~10 年，平均 (3.41± 0.59) 年。对照组 49 例，男 26 例，女 23 例；年龄 63~91 岁，平均 (73.82± 5.69) 岁；病程 5 个月 ~10 年，平均 (3.62± 0.57) 年。两组的基线资料比较差异均无统计学意义 (P>0.05)，具有可比性。

1.2 治疗方法

对照组：口服石杉碱甲(批号：国药准字 H10960133，生产厂家：上海复旦复华药业有限公司，规格：50 μg)治疗，起始给药剂量为每次 100 μg，每天 2 次，分别于早饭及晚饭时口服，第 2 w 给药剂量调整为每次 150 μg，每天 2 次，维持用量。观察组：联合静脉滴注鼠神经生长因子(批号：国药试字 S20020116，生产厂家：厦门北大之路生物工程有限公司，规格：2000 AU (4 μg)/ 支)治疗，每次 20 μg，每天 1 次。两组均治疗 1 个月。

1.3 观察指标

采用 ADL 量表评估患者的日常生活能力，评分越高表明生活质量越好。采用 MMSE 评估患者的认知功能状态，MMSE 量表主要包括记忆力、定向力、注意力、语言能力和回忆力者五个方面，满分值是 30 分，评分值越高则说明患者的认知功能越佳。

比较两组的疗效：① 显效：经过治疗后，患者的 MMSE 量表评分值与满分即 39 分接近；② 有效：经过治疗后，患者的 MMSE 量表评分值与治疗前相比升高 15 %~ 40 %；③ 无效：经过治疗后，患者的 MMSE 量表评分值与治疗前相比无显著的差异。

于治疗前后采集 3 mL 静脉血，采用 ELISA 法检测血清 IL-1β、CRP、IL-6、TNF-α 水平，试剂盒均购自海博生物技术有限公司。

1.4 统计学分析

采用 SPSS21.0 软件进行统计学分析，计量资料以 $\bar{x}\pm s$ 表示，组间和组内对比用方差分析和 t 检验，组间率的比较用 x^2 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效对比

治疗后，观察组的总有效率为 87.75%，明显高于对照组 (69.39%，P<0.05)，见表 1。

表 1 两组临床疗效的比较

Table 1 Comparison of the clinical effect between two groups

Groups	n	Effective	Valid	Invalid	Total effect rate(%)
Observation group	49	19	24	6	87.75*
Control group	49	14	20	15	69.39

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

2.2 两组治疗前后 ADL 和 MMSE 评分对比

两组治疗后的 ADL 和 MMSE 评分均脚治疗前明显降低 (P<0.05)，且观察组以上指标均明显低于对照组(P<0.05)，见表 2。

表 2 两组治疗前后 ADL 和 MMSE 评分对比($\bar{x}\pm s$, 分)

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

Groups	n		ADL	MMSE
Observation group	49	Before treatment	43.65± 11.78	15.32± 2.49
		After treatment	68.32± 15.67*#	26.34± 4.25*#
Control group	49	Before treatment	42.78± 10.41	15.67± 2.53
		After treatment	59.33± 13.42#	20.89± 3.62#

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

2.3 两组治疗前后血清 IL-1β、CRP、IL-6、TNF-α 水平对比

两组治疗后的血清 IL-1β、CRP、IL-6、TNF-α 水平均较治疗前明显降低(P<0.05)，且观察组以上指标均明显低于对照组 (P<0.05)，见表 3。

表 3 两组治疗前后血清 IL-1β、CRP、IL-6、TNF-α 水平对比 ($\bar{x}\pm s$, ng/L)

Table 3 Comparison of the serum IL-1β, CRP, IL-6 and TNF-α levels between two groups before and after treatment($\bar{x}\pm s$, ng/L)

Groups	n		IL-1β	CRP	IL-6	TNF-α
Observation group	49	Before treatment	23.41± 3.72	7.38± 1.24	26.34± 3.25	44.62± 5.73
		After treatment	20.61± 1.73*#	6.25± 1.14*#	21.62± 2.39*#	40.82± 4.93*#
Control group	49	Before treatment	23.69± 3.48	7.35± 1.19	25.93± 3.47	45.13± 5.24
		After treatment	18.24± 1.29#	5.37± 1.26#	18.62± 2.45#	36.57± 4.29#

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

2.4 两组不良反应发生情况比较

两组治疗过程中血压、体温以及心率等生命体征及血尿常规和肝肾功能等检查指标均未出现明显异常的改变。

3 讨论

老年痴呆是一种较常见的脑退行性疾病，起病时不易察觉，较为隐匿。随着全球人口老龄化趋势的日益加重，老年痴呆患者的数量也逐年增多，预计到 2020 年我国的老年痴呆症患者例数可能会高达 2100 万，给社会以及患者家庭带来极大的负担[8,9]。目前，关于老年痴呆发病机制的假说主要包括：中枢胆碱能受损学说、β 淀粉样蛋白级联学说、Tau 蛋白学说和兴奋性氨基酸毒性学说[10-13]。Winblad B 等[14]研究认为老年痴呆的发生可能是由于机体的神经系统发生变性或者异常的改变，出现胆碱能神经功能障碍，造成胆碱能递质水平明显降低，引发记忆、语言、视空间以及执行等多种认知功能障碍[15,16]。其治疗手段包括手术治疗、康复治疗和药物治疗，药物治疗方案中主要包括谷氨酸受体拮抗剂以及胆碱酯酶抑制剂，虽然可缓解患者的痴呆症状，但是无法阻止病变的进一步发展[17]。

石杉碱甲可以使乙酰胆碱的水解受到抑制而减少，还能激活突触前膜上的 M 受体或者 N 受体，拮抗突触后膜上的 M 受体，显著增强胆碱能的活性和功能；并且通过使乙酰胆碱前体得到补充，促进胆碱能神经元的兴奋以及乙酰胆碱的合成，进而达到改善认知功能，增强记忆和学习能力的效果[18-22]。有多项研究显示鼠神经生长因子具有营养与保护胶质细胞以及神经元，促进损伤神恢复等作用，因此被广泛应用于治疗中毒性脑炎、外周神经损伤和麻痹性认知障碍等疾病，但其治疗老年痴呆患者的研究较为少见[23-26]。

本研究结果显示注射用鼠神经生长因子联合石杉碱甲对老年痴呆的治疗效果明显优于单用石杉碱甲治疗。分析其原因为鼠神经生长因子具有促突起生长以及神经元营养双重生物学功能，对中枢及周围神经元的分化、发育、生长、再生以及功能特性的表达均发挥着重要的生物调控功能[27,28]。注射用鼠神经生长因子联合石杉碱甲可更明显改善老年痴呆的日常生活能力和认知功能。鼠神经生长因子由于富含生物活性蛋白，可以使神经细胞的分化和生长发育速度加快，并有效促进神经元轴突发生再生，抑制神经元萎缩或死亡，保护感觉神经元和交感神经元，降低中枢神经系统受损的程度[29,30]。此外，两组患者治疗后的血清 IL-1β、CRP、IL-6、TNF-α 水平均明显降低，注射用鼠神经生长因子联合石杉碱治疗的患者以上指标更低，表明降低血清细胞因子水平可能是鼠神经生长因子发挥治疗老年痴呆作用的机制之一。

综上所述，与单用石杉碱甲相比，注射用鼠神经生长因子联合石杉碱甲可更有效改善其日常生活能力和认知功能，且能显著降低血清炎症因子水平。

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