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谷红联合尼莫地平在小血管病性认知障碍与大动脉粥样硬化性 认知障碍中的疗效分析*

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摘要 目的:谷红联合尼莫地平对小血管病性认知障碍与大动脉粥样硬化性认知障碍进行治疗,考察对两种类型血管性认知障碍的疗效。**方法:**以2017年-2019年12月就诊于我院血管性认知功能障碍(vascular cognitive impairment, VCI)患者为研究对象,大动脉粥样硬化型(large artery atherosclerotic, LAA)204例,为LAA组,小血管性(small vessel disease, SVD)226例,为SVD组,所有患者均给予基础治疗,在此基础上,LAA组和SVD组均进行谷红注射液和尼莫地平联合治疗,以临床疗效、认知功能评分以及不良反应情况为考察指标,考察谷红联合尼莫地平对两种类型血管性认知障碍的治疗效果。**结果:**经过谷红注射液联合尼莫地平的治疗,LAA组和SVD组均取得了较好的疗效,LAA组总有效率为90.20%,SVD组总有效率为88.05%,两组总有效率比较,无显著差异($P>0.05$);治疗前两组患者的蒙特利尔认知量表(Montreal Cognitive Assessment, MoCA)评分和简易精神状态量表(Mini-Mental State Exam, MMSE)评分均无统计学差异($P>0.05$);治疗后,LAA组和SVD组患者的MOCA评分和MMSE评分均显著的改善($P<0.05$),其中LAA组MOCA评分由 19.31 ± 5.45 提升至 22.31 ± 6.21 ,MMSE评分由 21.45 ± 5.91 提升至 25.23 ± 3.21 ,SVD组MOCA评分由 19.28 ± 4.01 提升至 22.88 ± 5.73 ,MMSE评分由 21.30 ± 7.76 提升至 25.08 ± 6.19 ,但两组间各项评分无显著差异($P>0.05$);治疗期间LAA组和SVD组均未出现严重不良反应,共有7例患者出现轻度头部胀痛、面部潮红等,其中LAA组3(1.47%)例,SVD组4(1.96%)例,两组间比较无显著差异($P>0.05$)。**结论:**谷红注射液联合尼莫地平治疗小血管病性认知障碍与大动脉粥样硬化性认知障碍,均能显著缓解患者认知功能障碍症状,临床疗效显著,无严重不良反应,有一定的推广价值。

关键词:谷红注射液;尼莫地平;小血管病性;大动脉粥样硬化性;认知障碍

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Analysis of the Curative Effect of Guhong Combined with Nimodipine in the Cognitive Impairment of Small Vessel Disease and the Cognitive Impairment of Large Atherosclerosis*

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ABSTRACT Objective: To investigate the effect of Guhong injection combined with nimodipine on small blood vessel disease cognitive impairment and large artery atherosclerotic cognitive impairment. **Methods:** Taking VCI patients who were treated in our hospital from 2017 to December 2019 as the research object, 204 cases of LAA type were in the LAA group, and 226 cases of SVD type were in the SVD group. All patients were given basic treatment. On this basis, the LAA group and the SVD group were treated with Guhong injection and nimodipine. The clinical efficacy, cognitive function scores and adverse reactions were used as indicators to investigate the therapeutic effect of Guhong combined with nimodipine on two types of vascular cognitive impairment. **Results:** After the treatment of Guhong injection combined with nimodipine, the LAA group and the SVD group achieved good results. The total effective rate in the LAA group was 90.20%, and the total effective rate in the SVD group was 88.05%. There was no significant difference in total effective rate between the two groups ($P>0.05$). There was no statistical difference between the MOCA score and MMSE score of the two groups before treatment ($P>0.05$). After treatment, the MOCA score and MMSE score of the patients in the LAA group and the SVD group were significantly improved ($P<0.05$). The MOCA score in the LAA group increased from 19.31 ± 5.45 to 22.31 ± 6.21 , and the MMSE score increased from 21.45 ± 5.91 to 25.23 ± 3.21 , the MOCA score of the SVD group increased from 19.28 ± 4.01 to 22.88 ± 5.73 , and the MMSE score increased from 21.30 ± 7.76 to 25.08 ± 6.19 , but there was no significant difference in the scores between the two groups ($P>0.05$). During the treatment period, neither the LAA group nor the SVD group had serious adverse reactions. A total of 7 patients had

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mild head pain and facial flushing, among which 3 (1.47 %) cases in the LAA group and 4(1.96 %) cases in the SVD group There was no significant difference between the groups ($P>0.05$). **Conclusion:** Guhong injection combined with nimodipine in the treatment of small blood vessel cognitive impairment and large artery atherosclerotic cognitive impairment can significantly alleviate the symptoms of cognitive dysfunction in patients. The clinical effect is remarkable, there is no serious adverse reaction, and it has certain promotion value.

Key words: Guhong injection; nimodipine; Small vessel disease; Large atherosclerosis; Cognitive impairment

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前言

脑血管疾病是老年人群的常见病,由脑血管疾病引起的认知障碍已经成为痴呆的第二大病因。脑血管疾病常也会引起认知功能障碍,由此引起从轻度认知障碍到的痴呆的综合征被称为血管性认知障碍(vascular cognitive impairment, VCI),随着脑血管病率不断增多,VCI 患病也呈逐年递增趋势^[1,2]。但 VCI 与其他型认知障碍相比,通过有效的干预和治疗措施,可以阻止延缓患者认知功能进一步衰退^[3]。小血管病 (small vessel disease, SVD)和大动脉粥样硬化(large artery atherosclerosis, LAA)是 VCI 的两大最重要的病因^[4,5]。SVD 是指由各种原因影响脑内小动脉、微动脉、小静脉等所导致的一类中枢神经系统常见疾病,在中老年群体的发病率较高,血管性认知功能障碍患者中有大约 60 %的患者合并脑小血管病,阿尔茨海默患者中由约 33 %合并脑小血管病^[6]。LAA 是缺血性脑卒的一个主要的 TOAST 分型^[7],指由颅内、外大中供血动脉(颈动脉、大脑中动脉)的显著狭窄闭塞,进而引起脑组织缺血等一系列改变的一类疾病^[8],有研究表明 LAA 神经功能缺损程度和认知障碍程度显著相关,神经功能缺损程度越重,认知障碍越重^[9]。早期对脑血管病的干预和治疗能有效延缓和阻止认知损伤的进展^[10]。脑部血

流灌注的改善、受损神经元的修复是治疗的关键。

尼莫地平为一种神经元保护剂,有扩张血管作用,内阻滞神经元细胞钙离子内流,预防神经元细胞的凋亡和坏死,从而发挥神经元保护作用,对 VCI 患者起到治疗作用^[11,12]。谷红注射液为一种中西药联合制剂,由中药红花提取物和乙酰谷酰胺制成的无菌水溶液,二者具有协同作用,能扩张血管,改善微血管循环和血流动力学,从而发挥改善神经的代谢功能、维持神经系统应激能力的作用,可用于 VCI 的临床治疗^[13-16]。

因此本研究谷红联合尼莫地平,对小血管病性认知障碍与大动脉粥样硬化性认知障碍进行治疗,考察对两种类型血管性认知障碍的疗效,具体报道如下。

1 材料与方法

1.1 基本信息

以 2017 年~2019 年 12 月就诊于我院 VCI 患者为研究对象,LAA 型 204 例,为 LAA 组,SVD 型 226 例,为 SVD 组,两组患者基本信息如性别构成比、年龄、病程、受教育程度、基础疾病等经分析无统计学意义($P>0.05$),见表 1,具有可比性。患者家属签署知情同意书,获得医院伦理委员会的准许。

表 1 LAA 组和 SVD 组基本资料比较

Table 1 Comparison of basic data between LAA group and SVD group

Groups	Age(years)		Gender		Course of disease (years)		Education level (year)	Hypertension	Hyperlipidemia
	Age range	Average age	Male	Female	Range	Average Course			
Group LAA (n=204)	41~75	65.3± 7.8	112	92	1.0~5.3	3.4± 1.4	8.92± 4.41	126	103
Group SVD (n=226)	42~78	67.1± 6.6	114	112	1.2~5.6	3.1± 1.7	8.38± 3.02	131	115

1.2 诊断标准

目前对于 VCI 尚无统一的诊断标准。依据 NINDS-AIREN 诊断标准^[17]并结专家共识制定本研究诊断标准,如下:(1)患者存在认知功能障碍,MoCa 评分 ≥ 26 分;(2)存在 LAA 和 SVD 型血管损害因素,有影像学诊断依据;(3)有客观依据证实患者认知功能障碍与血管损伤存在因果关系。

1.3 纳入与排除标准

纳入标准:(1)符合 VCI 诊断标准,且病程大于 3 个月;(2)所有患者年龄 >40 岁,均接受 CT 或 MRI 检查;(3)具有一定的书写和阅读能力;(4)患者意识清醒,自愿参加本研究,依从性较好;(5)未使用相关改善认知功能药物。

排除标准:(1)阿尔茨海默病或其他痴呆类型者;(2)患有失语者;(3)中枢神经系统损伤、外伤等所导致的卒中者;(4)长

期服用镇静催眠药、中枢兴奋剂者;(5)严重躯体疾病或精神障碍者。

1.4 治疗方法

所有患者均给予基础治疗,对合并有血管危险因素、高血压、高血脂、糖尿病等基础性疾病进行血压控制,抗血小板凝聚和降血糖治疗,且进行运动功能康复训练和认知功能训练,但不能使用其他具有扩张血管、调节神经递质和抗精神病类药物。

LAA 组和 SVD 组均进行谷红注射液和尼莫地平联合治疗。尼莫地平每次服用剂量为 30.0 mg,每天 3 次,疗程均为 3 个月。在尼莫地平的基础上接受谷红注射液治疗,20 mL 谷红注射液,稀释后静脉滴注,每天 1 次,连续 20 d,停止十天后进行下一疗程,共 3 个疗程。两组患者在接受治疗期间需暂停使用钙离子拮抗剂和其他会影响临床疗效的药物。

1.5 观察指标

1.5.1 疗效判断标准 显效:患者疗效指数 $\geq 20\%$;有效: $12\% \leq$ 患者疗效指数 $<20\%$;无效:患者疗效指数 $<12\%$;计算总有效率^[18]。

1.5.2 认知功能评分 记录患者的 MOCA^[19]和 MMSE^[20]评分。MOCA 量表总分为 30 分,评分越高认知情况越好,MMSE 量表评分范围为 0~30 分,评分越高认知情况越好。

1.5.3 不良反应情况 记录治疗过程中的不良反应,如症状、体征等情况并分析可能因素。

1.6 数据处理

应用 SPSS 19.0,计量资料以 $\bar{x} \pm s$ 表示,使用 t 检验,计数资料采用率(%)表示,使用 χ^2 检验, $P < 0.05$ 有统计学意义。

2 结果

2.1 临床疗效

经过谷红注射液联合尼莫地平的治疗,LAA 组合 SVD 组均取得了较好的疗效,LAA 组总有效率为 90.20%,SVD 组总有效率为 88.05%,两组总有效率比较,无显著差异($P > 0.05$),见表 2。

表 2 LAA 组和 SVD 组(例,%)

Table 2 LAA group and SVD group (n,%)

Groups	Significant effective	Effective	Invalid	Total effective
Group LAA (n=204)	83(40.69)	101(49.51)	20 (9.80)	184(90.20)
Group SVD (n=226)	94(41.59)	105(46.46)	27(11.95)	199(88.05)

2.2 认知功能评分

治疗后,LAA 组和 SVD 组患者的 MOCA 评分和 MMSE 评分均显著的改善 ($P < 0.05$),其中 LAA 组 MOCA 评分由 19.31 ± 5.45 提升至 22.31 ± 6.21 ,MMSE 评分由 21.45 ± 5.91 提

升至 25.23 ± 3.21 ,SVD 组 MOCA 评分由 19.28 ± 4.01 提升至 22.88 ± 5.73 ,MMSE 评分由 21.30 ± 7.76 提升至 25.08 ± 6.19 ,但两组间各项评分无显著差异($P > 0.05$),见表 3。

表 3 治疗前后认知功能评分

Table 3 Cognitive function score before and after treatment

Groups	MOCA Score		MMSE Score	
	Before treatment	After treatment	Before treatment	After treatment
Group LAA (n=204)	19.31 ± 5.45	$22.31 \pm 6.21^*$	21.45 ± 5.91	$25.23 \pm 3.21^*$
Group SVD (n=226)	19.28 ± 4.01	$22.88 \pm 5.73^*$	21.30 ± 7.76	$25.08 \pm 6.19^*$

Note: $*P < 0.05$, compared with before treatment.

2.3 不良反应情况

治疗期间 LAA 组和 SVD 组均未出现严重不良反应,共有 7 例患者出现轻度头部胀痛、面部潮红等,其中 LAA 组 3(1.47%)例,SVD 组 4(1.96%)例,两组间比较无显著差异($P > 0.05$),两组持续使用一段时间后不良反应自行消失。

3 讨论

老龄化进程的加剧,血管性痴呆已经成为第二痴呆因素,能够通过有效的干预治疗阻碍疾病进展,早期给与患者有效的治疗具有重要意义^[21]。因此积极探寻血管性认知障碍的有效治疗手段至关重要的,常见的危险因素主要包括脑卒中、脑小血管疾病和脑白质损伤等^[22,23]。

脑小血管病包括终末小动脉和微小动脉的病变,常表现为卒中、认知障碍和总体功能下降。脑小血管病变会降低脑血流量调节功能,虽然对患者的记忆力和执行力等多个区域均有损害,但病情发展缓慢,早期往往使得患者和医生忽视,但病情的发展给患者、社会带来了严重负担。脑小血管病会导致脑白质损害,诱发脑小血管病认知功能障碍,其机制为单一小动脉阻塞引起腔隙性梗死,使皮层下白质受损^[25,26]。认知功能是由整个大脑协同控制的一个非常复杂的过程^[27]。大动脉粥样硬化型患

者其脑血管狭窄程度均大于 50%,侧支循环较差,脑梗死面积大,较大的脑梗死面积常会引起大脑皮层或皮层下大范围的损害,导致与认知功能有关部位的缺血、坏死,进而引起较严重的认知功能损害。LAA 型脑卒中可进一步引起多发性脑梗死,多位置的梗死严重损伤了皮层 - 皮层下环路中联系通路,超越了大脑的代偿能力,因此 LAA 型引起的认知障碍会涉及多个领域,损害程度也更重。

尼莫地平属于二氢吡啶类,为一种钙离子通道阻断剂,脂溶性高,易通过血 - 脑屏障,可以选择性作用于脑血管,抑制细胞内钙从钙库释放的同时,也能抑制异常的钙离子内流,缓解胞内钙离子超载,从而发挥对缺血性神经损伤的保护作用,也可以降低脑血管周围组织纤维变性以及脂质沉积,能有效改善血管性、退行性以及混合性等痴呆患者的认知功能^[28]。

谷红注射液由中药红花提取物和乙酰谷酰胺混合制成。红花具有活血化瘀、通络止痛的功效,红花提取物主要含有红花苷类和红花黄色素 A 等成分^[29],能够增加脑供血,减轻再灌注损伤,有助于脑血管疾病的修复。红花提取液也具有降脂作用,降低丙氨酸氨基转移酶水平,保护肝功能等作用,还可改善心肌缺血状态,其对心血管疾病的作用久已被临床证实^[30]。乙酰谷酰胺为一种神经肽,可通过星形胶质细胞代谢生成 γ - 氨基丁

酸和谷氨酸,谷氨酸在星形胶质细胞代谢产生还原性谷胱甘肽, γ -氨基丁酸和还原性谷胱甘肽对中枢神经细胞有重要的保护效果,有降血脂、改善神经细胞代谢等作用,可对 VCI 患者已受损神经细胞进行修复^[3]。乙酰谷酰胺和红花提取物协同发挥对血管性认知障碍的治疗作用。

本研究显示经过谷红注射液联合尼莫地平的治疗,LAA 组和 SVD 组均取得了较好的疗效;治疗后,LAA 组和 SVD 组患者的 MOCA 评分和 MMSE 评分均显著改善,治疗期间 LAA 组和 SVD 组均未出现严重不良反应,本研究共有 7 例患者出现轻度头部胀痛、面部潮红等,其中 LAA 组 3(1.47%)例,SVD 组 4(1.96%)例,两组持续使用一段时间后其不良反应自行消失,可能与尼莫地平的扩张血管作用有关。于怀成^[32]等学者研究叶酸、甲钴胺与尼莫地平合用对脑小血管病所致认知功能障碍,发现治疗组认知功能的改善总有效率明显高于对照组。董永娥^[33]等采用奥拉西坦与吡拉西坦治疗动脉粥样硬化性脑梗死急性期认知功能障碍,发现治疗后,联合组 MMSE、MoCA 评分高于吡拉西坦治疗组。本研究结果显示谷红注射液联合尼莫地平治疗小血管病性认知障碍与大动脉粥样硬化性认知障碍,均能显著缓解患者认知功能障碍症状,分期其原因主要是谷红注射液联合尼莫地平联合应用,发挥其协同作用,通过增加脑供血,减轻再灌注损伤,修复脑血管,同时也能保护中枢神经细胞,改善神经细胞代谢,从而改善认知障碍。国内外目前对于谷红注射液联合尼莫地平治疗认知障碍的研究相对较少,以望在本研究的基础上进行用药研究。本研究也存在一定的不足,样本来源单一,结果可能存在一定的偏倚,后续需要联合当地的多家医院进行深入探究,分析谷红注射液联合尼莫地平治疗小血管病性认知障碍与大动脉粥样硬化性认知障碍的作用机制。

综上所述,谷红注射液联合尼莫地平治疗小血管病性认知障碍与大动脉粥样硬化性认知障碍,均能显著缓解患者认知功能障碍症状,临床疗效显著,无严重不良反应,具有一定的推广价值。

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