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舒肝解郁胶囊联合阿戈美拉汀对抑郁症患者血清单胺类神经递质和神经功能相关因子的影响*

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摘要 目的:观察舒肝解郁胶囊联合阿戈美拉汀治疗抑郁症的疗效及对血清单胺类神经递质和神经功能相关因子的影响。**方法:**纳入我院 2017 年 5 月~2020 年 5 月接诊的 120 例抑郁症患者,经双色球随机分组法将患者分为对照组和观察组,各为 60 例。对照组患者予以阿戈美拉汀治疗,观察组患者予以舒肝解郁胶囊联合阿戈美拉汀治疗。比较两组疗效、血清单胺类神经递质、神经功能相关因子、抑郁焦虑评分及不良反应发生率。**结果:**观察组的临床总有效率为 93.33%(56/60),高于对照组的 73.33%(44/60) ($P<0.05$)。两组治疗 6 周后汉密尔顿抑郁量表(HAMD)、汉密尔顿焦虑量表(HAMA)评分较治疗前降低,且观察组较对照组低 ($P<0.05$)。两组治疗 6 周后多巴胺(DA)、去甲肾上腺素(NE)、5-羟色胺(5-HT)水平较治疗前升高,且观察组高于对照组 ($P<0.05$)。两组治疗 6 周后 S100 β 、髓磷脂碱性蛋白(MBP)、神经元特异性烯醇化酶(NSE)水平较治疗前降低,且观察组低于对照组 ($P<0.05$)。两组不良反应发生率对比无差异 ($P>0.05$)。**结论:**舒肝解郁胶囊联合阿戈美拉汀治疗抑郁症,疗效显著,可有效调节血清单胺类神经递质和神经功能,改善抑郁症状,且安全可靠。

关键词:舒肝解郁胶囊;阿戈美拉汀;抑郁症;单胺类神经递质;神经功能

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Effects of Shugan Jieyu Capsule Combined with Agomelatine on Serum Monoamine Neurotransmitters and Nerve Function Related Factors in Patients with Depression*

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ABSTRACT Objective: To observe the efficacy of Shugan Jieyu capsule combined with agomelatine in the treatment of depression and its effect on serum monoamine neurotransmitters and nerve function related factors. **Methods:** 120 patients with depression who were received in our hospital from May 2017 to May 2020 were included. The patients were divided into control group and observation group by two color ball random grouping method, with 60 cases in each group. The patients in the control group were treated with agomelatine, and the patients in the observation group were treated with Shugan Jieyu capsule combined with agomelatine. The efficacy, serum monoamine neurotransmitters, nerve function related factors, depression and anxiety score and the incidence of adverse reactions were compared between the two groups. **Results:** The total clinical effective rate in the observation group was 93.33% (56/60), which was higher than 73.33% (44/60) in the control group ($P<0.05$). 6 weeks after treatment, the scores of Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) in both groups were lower than those before treatment, and the scores of observation group were lower than those of control group ($P<0.05$). 6 weeks after treatment, the levels of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in both groups were higher than those before treatment, and those in observation group were higher than those in control group ($P<0.05$). 6 weeks after treatment, the levels of S100 β , myelin basic protein (MBP) and neuron specific enolase (NSE) in both groups were lower than those before treatment, and those in observation group were lower than those in control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Shugan Jieyu capsule combined with agomelatine is effective in the treatment of depression. It can effectively regulate serum monoamine neurotransmitters and neural function, improve depressive symptoms, and is safe and reliable.

Key words: Shugan Jieyu capsule; Agomelatine; Depression; Monoamine neurotransmitters; Nerve function

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前言

抑郁症是临床常见的情感障碍性疾病,主要特征为兴趣减退、情绪低落、认知功能损害以及思维迟缓等,严重者可出现自杀倾向,给患者及其家庭带来较大的身心压力和经济负担^[1,2]。研究显示抑郁症的全球发病率在3%左右,且随着社会压力增加,抑郁障碍的患病率逐年增加^[3]。阿戈美拉汀为5-羟色胺2C受体拮抗剂,抗抑郁的机制可能与神经元增生、增加海马部位神经元的可塑性有关,是临床常用的抗抑郁药物,具有抗抑郁焦虑及调节生物钟的作用^[4],但抑郁症的治疗难度大且周期长,单类药物长期使用疗效有限,西药引起的不良反应也会对人体造成一定的影响^[5]。舒肝解郁胶囊具有疏肝解郁、健脾安神的作用,是具有良好抗抑郁效果的中成药,临床常用于治疗轻、中度单相抑郁症的药物,用药安全性高、耐受性好^[6]。本研究以抑郁症患者作为研究对象,观察舒肝解郁胶囊联合阿戈美拉汀在此类疾病中的应用价值,以期临床治疗提供参考。

1 资料与方法

1.1 一般资料

纳入我院2017年5月~2020年5月接诊的120例抑郁症患者。纳入标准:(1)符合《国际疾病分类(第10版)》(ICD-10)中抑郁诊断标准^[7]。表现为精神运动性迟滞,兴趣丧失无愉悦感,自我评价自责,精力减退或疲劳感,联想困难或思虑能力下降;(2)入院前2个月未使用任何抗抑郁药;(3)汉密尔顿抑郁量表(HAMD)^[8]评分 ≥ 17 分;(4)患者自愿加入研究并签署知情同意书。排除标准:(1)严重自杀倾向;(2)严重心、肝、肾等重要脏器疾病;(3)因痴呆、失语、昏迷等无法交流者;(4)存在器质性疾病者;(5)怀孕或哺乳期妇女;(6)既往有酒精或药物依赖史者;(7)对本研究药物成分过敏者或禁忌者。研究通过我院伦理学委员会批准进行。经双色球随机分组法将患者分为对照组和观察组,各为60例。对照组患者中男性38例,女性22例;病程范围6~39(21.28 $\pm$ 4.57)月;年龄范围24~67(39.37 $\pm$ 4.82)岁;体质指数范围18~31 kg/m²(23.96 $\pm$ 1.37)kg/m²。观察组患者中男性36例,女性24例;病程范围8~42(21.84 $\pm$ 5.06)月;年龄范围23~68(39.06 $\pm$ 5.31)岁;体质指数范围18~32(23.71 $\pm$ 1.06)kg/m²。两组一般资料比较无差异($P>0.05$),均衡可比。

1.2 治疗方法

对照组接受阿戈美拉汀片(江苏豪森药业集团有限公司,国药准字H20143375,规格:25 mg)治疗,推荐剂量为25 mg,每日1次,睡前口服。2周后若症状没有改善,可增加剂量至50 mg,每日1次,睡前口服。观察组患者在对照组基础上接受舒肝解郁胶囊(四川济生堂药业有限公司,国药准字Z20174037,规格:每粒装0.36 g)治疗,每次2粒,每天2次,早晚各一次,口服。两组疗程均为6周。

1.3 疗效判定依据

心境低落、思维迟缓、精力疲乏核心症状无改善或加重,难以适应现实生活为无效。工作能力未完全恢复,以上症状基本消失或减轻,但能基本适应现实生活为好转。以上症状完全消失,工作能力恢复,能适应现实生活为治愈。总有效率=治愈率+好转率^[9]。

1.4 观察指标

(1)治疗前、治疗6周后采用HAMD^[8]和汉密尔顿焦虑量表(HAMA)^[10]评分评价患者抑郁焦虑情况。其中HAMD、HAMA总评分范围均为0~54分,得分越高表示抑郁、焦虑越严重;(2)于治疗前、治疗6周后的清晨空腹抽取肘静脉血6 mL,室温下静置30 min,经离心半径10 cm,离心转速3600 r/min,离心时间12 min,取得上清液保存待检测。采用酶联免疫吸附法(试剂盒购自南京建成生物工程研究所)血清单胺类神经递质:多巴胺(DA)、去甲肾上腺素(NE)、5-羟色胺(5-HT)和神经功能相关因子:S100 β 、髓磷脂碱性蛋白(MBP)、神经元特异性烯醇化酶(NSE)水平;(3)统计治疗过程中药物相关不良反应情况。

1.5 统计学方法

采用SPSS24.0统计学软件分析数据。计量资料如HAMD评分、DA、NE经检验符合正态分布,以($\bar{x}\pm s$)表示,行组内配对t检验和组间独立样本t检验。计数资料如疗效等以比或率表示,行卡方检验。检验标准设置为 $\alpha=0.05$ (均为双侧检验)。

2 结果

2.1 两组疗效对比

观察组的临床总有效率为93.33%(56/60),高于对照组的73.33%(44/60)($P<0.05$),见表1。

表1 两组疗效对比【例(%)】

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

Groups	Cure	Improve	Invalid	Total effective rate
Control group(n=60)	17(28.33)	27(45.00)	16(26.67)	44(73.33)
Observation group(n=60)	22(36.67)	34(56.67)	4(6.67)	56(93.33)
χ^2				8.647
P				0.003

2.2 两组 HAMD、HAMA 评分对比

两组治疗前HAMD、HAMA评分对比无差异($P>0.05$)。治疗6周后两组HAMD、HAMA评分较治疗前降低,观察组较对照组低($P<0.05$),见表2。

2.3 两组 DA、NE、5-HT 水平对比

两组治疗前DA、NE、5-HT水平对比无差异($P>0.05$)。治疗6周后两组DA、NE、5-HT水平较治疗前升高,观察组较对照组高($P<0.05$),见表3。

表 2 两组 HAMD、HAMA 评分对比($\bar{x}\pm s$, 分)

Table 2 Comparison of HAMD and HAMA scores between the two groups($\bar{x}\pm s$, scores)

Groups	HAMD		HAMA	
	Before treatment	6 weeks after treatment	Before treatment	6 weeks after treatment
Control group(n=60)	23.24±4.49	16.25±2.43a	25.48±4.31	17.46±3.62 ^a
Observation group(n=60)	23.78±3.18	10.78±2.09a	25.09±5.67	11.92±3.97 ^a
t	-0.760	13.219	0.424	7.987
P	0.449	0.000	0.673	0.000

Note: compared with before treatment, ^a $P<0.05$

表 3 两组 DA、NE、5-HT 水平对比($\bar{x}\pm s$)

Table 3 Comparison of DA, NE and 5-HT levels between the two groups($\bar{x}\pm s$)

Groups	DA(pg/mL)		NE(pg/mL)		5-HT(μ mol/L)	
	Before treatment	6 weeks after treatment	Before treatment	6 weeks after treatment	Before treatment	6 weeks after treatment
Control group (n=60)	41.22±5.19	47.67±6.36 ^a	93.22±7.73	126.32±8.41 ^a	2.32±0.31	3.28±0.36 ^a
Observation group (n=60)	41.65±4.26	59.13±5.39 ^a	92.57±7.64	147.58±11.53 ^a	2.37±0.29	4.57±0.32 ^a
t	-0.572	-10.648	0.463	-11.539	-0.912	-20.745
P	0.568	0.000	0.644	0.000	0.363	0.000

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

2.4 两组 S100 β 、MBP、NSE 水平对比

治疗 6 周后两组 S100 β 、MBP、NSE 水平较治疗前降低, 观察组

两组治疗前 S100 β 、MBP、NSE 水平对比无差异($P>0.05$)。

较对照组低($P<0.05$), 见表 4。

表 4 两组 S100 β 、MBP、NSE 水平对比($\bar{x}\pm s$)

Table 4 Comparison of S100 β , MBP and NSE levels between the two groups($\bar{x}\pm s$)

Groups	S100 β (ng/mL)		MBP(ng/mL)		NSE(ng/mL)	
	Before treatment	6 weeks after treatment	Before treatment	6 weeks after treatment	Before treatment	6 weeks after treatment
Control group (n=60)	1.46±0.29	1.17±0.25 ^a	9.98±1.69	6.07±0.83 ^a	9.31±1.12	6.72±0.89 ^a
Observation group (n=60)	1.49±0.31	0.72±0.23 ^a	9.93±1.45	4.26±0.72 ^a	9.24±1.27	4.13±0.71 ^a
t	-0.547	10.261	0.174	12.760	0.320	17.621
P	0.585	0.000	0.862	0.000	0.749	0.000

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

2.5 不良反应

两组不良反应发生率对比无差异($P>0.05$), 见表 5。

表 5 两组不良反应发生率对比[n(%)]

Table 5 Comparison of adverse reaction rates between the two groups[n(%)]

Groups	Dry mouth	Insomnia	Elevated transaminase	Vomit	Total incidence rate
Control group(n=60)	2(3.33)	2(3.33)	1(1.67)	3(5.00)	8(13.33)
Observation group (n=60)	3(5.00)	3(5.00)	1(1.67)	4(6.67)	11(18.33)
χ^2					0.562
P					0.453

3 讨论

抑郁症的诱发因素复杂,目前认可度较高的发病机制有:神经递质及其受体的异常,致使受体敏感性降低;脑源性神经营养因子的改变;下丘脑-垂体-肾上腺轴功能异常;海马的神经病理学改变;炎症细胞因子表达水平升高,导致脑脊液中5-HT水平下降^[11-13]。在抑郁症的治疗方面,临床也一直未能有统一的标准方案,阿戈美拉汀作为首个靶向褪黑素的抗抑郁药物,具有诸多优势,包括耐受性好、对体质量及性功能影响小、撤药反应小等^[14]。2011年美国食品药品监督管理局开始批准阿戈美拉汀作为新型抗抑郁药应用于临床,在2015年中国抑郁障碍防治指南中阿戈美拉汀也被推荐为抗抑郁治疗的一线药物^[15,16]。但抗抑郁药常常引起口干、失眠、便秘、头痛和恶心等不良反应,致使疾病反复发作^[17]。中医认为抑郁症的病因为肝气郁结和情志不舒,治疗主张疏肝解郁。舒肝解郁胶囊由刺五加和贯叶金丝桃组成,有研究证实舒肝解郁胶囊也具有一定的抗抑郁作用^[18]。

本次观察结果表明,与对照组相比,观察组患者的焦虑抑郁改善效果更佳,疗效肯定。阿戈美拉汀的抗抑郁机制主要在于,进入人体后,与5-HT_{2C}受体结合,促进机体DA的分泌和脑部神经的再次生长,从而有效改善人体焦虑、抑郁状态^[19,20]。而舒肝解郁胶囊中的贯叶金丝桃具有抗抑郁的功效,邹卿等人^[21]的药理研究证实其在治疗精神病症状方面效果显著;在国外也有报道证实^[22],贯叶金丝桃用于治疗轻中度抑郁症患者,具有相当的疗效和安全性。刺五加能够祛风湿、补肝肾,从而加强大脑皮层内的抑制过程^[23]。舒肝解郁胶囊为中成药,其药效具有多靶点、多系统的抗抑郁作用,可进一步改善治疗效果。

抑郁症患者体内存在神经分泌、神经递质水平紊乱情况。5-HT主要由色氨酸衍生^[24],NE由脑内肾上腺素能神经末梢和交感节后神经元合成和分泌^[25],二者被认为能影响交感神经兴奋性,与抑郁症的发生、发展关系密切,其水平下降可导致抑郁症患者活动、食欲、心境发生变化。DA是大脑中含量最丰富的儿茶酚胺类神经递质,可有效传递人体兴奋的信息,其水平升高对于焦虑、抑郁的情绪有明显的抑制作用^[26]。此外,当DA、NE、5-HT等神经递质与其受体之间发生失调,会导致神经元活动障碍,引起神经元异常兴奋性。而人体神经功能相关因子与神经元兴奋性相关,诸如S100 β ^[27]、MBP^[28]、NSE^[29]等神经功能相关因子表达异常可加重抑郁病情。本次研究结果显示,舒肝解郁胶囊联合阿戈美拉汀治疗抑郁症患者,可有效调节血清单胺类神经递质和神经功能。现代药理学认为,刺五加提取物能保护DA神经元功能,加速DA、NE、5-HT等神经递质的合成、释放,从而起到抗抑郁作用^[30]。贯叶金丝桃能通过突触前膜和后膜双重作用,升高5-HT水平,故抗抑郁作用显著^[31]。本次研究结果也显示,两组不良反应发生率对比无差异,提示联合治疗未见严重的不良反应发生,安全性好。

综上所述,舒肝解郁胶囊联合阿戈美拉汀治疗抑郁症患者,可有效调节血清单胺类神经递质和神经功能,改善患者抑郁状态,是一个安全可靠的治疗方案。

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