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柴桂温胆定志汤联合舍曲林对抑郁症患者血清单胺类神经递质和外周血单个核细胞 PI3K/Akt 信号通路的影响*

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摘要 目的: 观察柴桂温胆定志汤联合舍曲林对抑郁症患者血清单胺类神经递质和外周血单个核细胞磷脂酰肌醇 3 激酶(PI3K)/蛋白激酶 B(Akt)信号通路的影响。**方法:** 选择 2018 年 10 月~2020 年 6 月期间北京市昌平区中西医结合医院收治的抑郁症患者 128 例,将患者根据信封抽签法分为对照组和实验组,各为 64 例。对照组患者接受舍曲林治疗,实验组患者接受柴桂温胆定志汤联合舍曲林治疗,观察治疗 4 周后两组疗效、各量表评分、血清单胺类神经递质和外周血单个核细胞 PI3K/Akt 信号通路情况,记录两组用药期间不良反应发生情况。**结果:** 实验组的临床总有效率较对照组高($P<0.05$)。治疗后,两组生活质量综合评定问卷(GQOLI-74)评分较治疗前升高,且实验组高于对照组($P<0.05$)。治疗后,两组匹兹堡睡眠质量指数(PSQI)、汉密尔顿抑郁量表(HAMD)评分较治疗前降低,且实验组低于对照组($P<0.05$)。治疗后,两组血清去甲肾上腺素(NE)、5-羟色胺(5-HT)、多巴胺(DA)水平较治疗前升高,且实验组高于对照组($P<0.05$)。治疗后,两组 PI3K 蛋白、Akt 蛋白、白介素-1 β (IL-1 β)、肿瘤坏死因子- α (TNF- α)水平较治疗前降低,且实验组低于对照组($P<0.05$)。两组不良反应发生率对比无统计学差异($P>0.05$)。**结论:** 柴桂温胆定志汤联合舍曲林治疗抑郁症疗效显著,可改善患者睡眠情况,提高生活质量,调节血清单胺类神经递质水平,作用机制可能与调节 PI3K/Akt 信号通路有关。

关键词: 柴桂温胆定志汤;舍曲林;抑郁症;单胺类神经递质;PI3K/Akt 信号通路

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Effects of Chaigui Wendan Dingzhi Decoction Combined with Sertraline on Serum Monoamine Neurotransmitters and PI3K/Akt Signal Pathway of Peripheral Blood Mononuclear Cells in Patients with Depression*

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ABSTRACT Objective: To observe the effects of Chaigui Wendan Dingzhi decoction combined with sertraline on serum monoamine neurotransmitters and phosphatidylinositol 3 kinase (PI3K) / protein kinase B (Akt) signal pathway in peripheral blood mononuclear cells of patients with depression. **Methods:** 128 patients with depression who were treated in Beijing Changping District Hospital of integrated traditional Chinese and Western Medicine from October 2018 to June 2020 were selected, and the patients were divided into control group and experimental group according to the form of envelope lottery, with 64 cases in each group. The patients in the control group were treated with sertraline, and the patients in the experimental group were treated with Chaigui Wendan Dingzhi decoction combined with sertraline. The curative effect, each scale score, serum monoamine neurotransmitters and PI3K/Akt signal pathway of peripheral blood mononuclear cells in the two groups at 4 weeks after treatment were observed, and the adverse reactions during the treatment in the two groups were recorded. **Results:** The total clinical effective rate of the experimental group was higher than that of the control group ($P<0.05$). After treatment, the scores of Generic Quality of Life Inventor-74 (GQOLI-74) of the two groups were higher than those before treatment, and the experimental group was higher than the control group ($P<0.05$). After treatment, the scores of Pittsburgh sleep quality index (PSQI) and Hamilton Depression Scale (HAMD) of the two groups were lower than those before treatment, and the experimental group was lower than the control group ($P<0.05$). After treatment, the serum norepinephrine (NE), serotonin (5-HT), dopamine (DA) levels of the two groups were higher than those before treatment, and the experimental group was higher than the control group ($P<0.05$). After treatment, PI3K protein, Akt protein, interleukin-1 β (IL-1 β), Tumor necrosis factor- α (TNF- α) levels of two groups were lower than those before treatment, and the experimental group was lower than the control group ($P<0.05$). There was no statistical

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difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Chaigui Wendan Dingzhi decoction combined with sertraline is effective in the treatment of depression. It can improve patients' sleep, improve quality of life and regulate the level of serum monoamine neurotransmitters. The mechanism may be related to the regulation of PI3K / Akt signal pathway.

Key words: Chaigui Wendan Dingzhi decoction; Sertraline; Depression; Monoamine neurotransmitters; PI3K/Akt signaling pathway

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前言

抑郁症是指以情绪低落、思维迟缓、主动性下降及兴趣降低等为主要症状的心境障碍综合征,是临床的难治病^[1,2]。目前在治疗方面,临床尚无统一方案。西药治疗如舍曲林可通过改善大脑的 5-羟色胺(5-HT)神经递质的水平来达到改善抑郁情绪的目的^[3],但是此药物不宜长期服用,在一定程度上降低治疗效果。中医学根据抑郁症临床表现,将其归于中医“郁证”范畴,发病诱因以精神情志刺激为主,治疗当以温补心胆阳气、益肝兼助疏泄、养脑涤痰醒神为则^[4]。柴桂温胆定志汤具有疏解肝郁、涤痰开窍、温补心胆阳气等功效,对改善患者抑郁症状有一定效果^[5]。但有关其改善抑郁症的具体机制尚不明确。磷脂酰肌醇 3 激酶(PI3K)/蛋白激酶 B(Akt) 信号通路是介导多种生长因子信号转导的重要通路,在抑郁症的发生发展中发挥重要作用^[6]。本研究观察柴桂温胆定志汤联合舍曲林对抑郁症患者血清单胺类神经递质和外周血单个核细胞 PI3K/Akt 信号通路的影响,旨在为临床治疗提供科学支持。

1 资料与方法

1.1 一般资料

选择 2018 年 10 月~2020 年 6 月期间北京市昌平区中西医结合医院收治的 128 例抑郁症患者,纳入标准:(1)符合《国际疾病分类(第 10 版)》^[7]中的抑郁症相关诊断标准;(2)符合《中医病证诊断疗效标准》^[8]中的相关诊断标准,辨证分型为肝气郁结型,次证:善太息,暖气频作;主证:胸胁作胀,精神抑郁,或脘痞;脉弦,舌苔薄白;(3)自愿受试并能合作的患者。排除标准:(1)产前或产后抑郁症、经前或经后抑郁症、滥用药物后抑郁症、减肥后抑郁症;(2)严重躯体疾病;(3)酒精、阿片类及镇静催眠药物依赖;(4)肝肾功能、脑电图、心电图、心肌酶谱等检查异常;(5)有高度自杀风险;(6)1 个月内参加过其他药物临床试验。将患者根据信封抽签法分为对照组(舍曲林治疗)和实验组(柴桂温胆定志汤联合舍曲林治疗),各为 64 例。两组一般资料对比无差异($P>0.05$),见表 1。研究方案已获得我院伦理学委员会批准进行。

表 1 两组患者一般资料

Table 1 General information of two groups of patients

Groups	Control group(n=64)	Experimental group(n=64)	χ^2/t	P
Male/female(n)	35/29	37/27	0.127	0.722
Age(years)	39.67± 4.28	39.24± 3.91	0.593	0.554
Course of disease(Month)	6.94± 0.83	6.88± 0.76	0.427	0.670
Body mass index(kg/m ²)	25.91± 1.43	26.15± 1.38	-0.996	0.336

1.2 方法

对照组给予盐酸舍曲林胶囊[四川省百草生物药业有限公司,规格:50 mg(按舍曲林计),国药准字 H20070179,生产批号:20180615、20190724、20200315]治疗,50 mg/次,1 次/d,口服。在对照组基础上,实验组加用柴桂温胆定志汤治疗,组方如下:陈皮、黄芩、枳壳、柴胡、桂枝、赤芍、竹茹、半夏、生姜、远志各 10 g,人参 5 g,茯苓 20 g,炙甘草 6 g,菖蒲 6 g,大枣 5 枚。先用 3000 mL 温水浸泡上述药材 30 min,再以大火煮沸,随后小火慢熬,取 300 mL 早晚各服 1 次。两组均治疗 4 周。

1.3 疗效判定依据

治愈:情绪正常,思维迟缓、主动性下降及兴趣降低等临床症状消失。好转:情绪基本正常,临床症状有所好转。无效:未能达到上述标准者。总有效率=治愈率+好转率^[8]。

1.4 观察指标

(1)治疗前、治疗 4 周后(治疗后)采用匹兹堡睡眠质量指数(PSQI)^[9]、汉密尔顿抑郁量表(HAMD)^[10]、生活质量综合评定问卷(GQOLI-74)^[11]评价两组患者睡眠质量、抑郁情况及生活

质量。PSQI 包括入睡时间、睡眠时间、睡眠质量、睡眠障碍、睡眠效率、催眠药物、日间功能障碍 7 项,总分 21 分,分数越高,提示睡眠质量越差。HAMD 包括有罪感、入睡困难、抑郁情绪、自杀、早醒、睡眠不深、迟缓、激越、躯体性焦虑、工作和兴趣、疑病、全身症状、性症状、体重减轻、自制力、精神焦虑、胃肠道症状等项目,总分 100 分,分数越高则患者抑郁越严重。GQOLI-74 包括四个维度,即心理功能、物质生活、躯体功能、社会功能,总分 100 分,分数越高,生活质量越好。(2)治疗前、治疗后分两管抽取两组患者的外周静脉血共 9 mL,其中一管(5 mL)采用德国 SIGMA 公司生产的 3-18KS 离心机,设置离心参数如下:离心半径 9 cm,3600 r/min 离心 13 min,取上清液,保存于低温冰箱中待检测。取血清样本经酶联免疫吸附法检测去甲 5-羟色胺(5-HT)、肾上腺素(NE)、多巴胺(DA)、白介素-1 β (IL-1 β)、肿瘤坏死因子- α (TNF- α)水平,试剂盒均购买于深圳欣博盛生物科技有限公司。另一管(4 mL)以 Ficoll 密度梯度离心法离心、提取外周血单个核细胞。采用 Western Blot 法检测 PI3K、Akt 蛋白含量。(3)观察两组不良反应(包括眩晕、口干、

头痛、厌食、腹泻)的发生率。

1.5 统计学方法

采用 SPSS26.0 对数据进行处理。以率(%)表示计数资料,行 χ^2 检验。以($\bar{x} \pm s$)表示计量资料,行 t 检验。检验水准为 $\alpha=0.05$ 。

2 结果

2.1 总有效率对比

实验组的临床总有效率 92.19%(56/64) 高于对照组 75.00%(48/64),差异有统计学意义($P<0.05$),见表 2。

表 2 总有效率对比 [例(%)]

Table 2 Comparison of total effective rate [n(%)]

Groups	Cure	Become better	Invalid	Total effective rate
Control group(n=64)	18(28.13)	30(46.88)	16(25.00)	48(75.00)
Experimental group(n=64)	23(35.94)	36(56.25)	5(7.81)	59(92.19)
χ^2				6.893
P				0.009

2.2 HAMD、PSQI、GQOLI-74 评分对比

治疗后,两组 GQOLI-74 评分较治疗前升高,且实验组高

于对照组($P<0.05$)。治疗后,两组 HAMD、PSQI 评分较治疗前降低,且实验组低于对照组($P<0.05$)。见表 3。

表 3 PSQI、HAMD、GQOLI-74 评分对比($\bar{x} \pm s$,分)

Table 3 Comparison of PSQI, HAMD and GQOLI-74 scores($\bar{x} \pm s$, scores)

Groups	PSQI	HAMD	GQOLI-74
Control group(n=64)			
Before treatment	14.38 $\pm$ 2.07	22.64 $\pm$ 3.28	64.67 $\pm$ 5.82
After treatment	10.62 $\pm$ 1.83 ^a	17.84 $\pm$ 3.47 ^a	78.95 $\pm$ 6.73 ^a
Experimental group(n=64)			
Before treatment	14.19 $\pm$ 1.98	22.18 $\pm$ 3.05	64.98 $\pm$ 6.06
After treatment	6.74 $\pm$ 1.74 ^{ab}	11.72 $\pm$ 2.96 ^{ab}	89.06 $\pm$ 5.32 ^{ab}

Note: a, b were compared with the same group before treatment and the control group after treatment respectively, and the differences were statistically significant.

2.3 NE、5-HT、DA 水平对比

两组治疗后血清 NE、5-HT、DA 水平较治疗前升高,且实

验组较对照组高($P<0.05$)。见表 4。

表 4 GABA、5-HT、DA 水平对比($\bar{x} \pm s$)

Table 4 Comparison of GABA, 5-HT and DA levels($\bar{x} \pm s$)

Groups	NE(μ g/mL)	5-HT(μ g/mL)	DA(μ g/mL)
Control group(n=64)			
Before treatment	165.63 $\pm$ 20.84	665.82 $\pm$ 83.48	119.47 $\pm$ 18.46
After treatment	247.15 $\pm$ 25.72 ^a	1248.36 $\pm$ 104.27 ^a	164.29 $\pm$ 21.06 ^a
Experimental group(n=64)			
Before treatment	164.67 $\pm$ 23.91	664.17 $\pm$ 79.46	118.36 $\pm$ 19.32
After treatment	288.59 $\pm$ 31.96 ^{ab}	1683.36 $\pm$ 99.51 ^{ab}	193.58 $\pm$ 22.43 ^{ab}

Note: a, b were compared with the same group before treatment and the control group after treatment respectively, and the differences were statistically significant.

2.4 外周血单个核细胞 PI3K/Akt 信号通路相关指标对比

治疗后两组 PI3K 蛋白、IL-1 β 、Akt 蛋白、TNF- α 水平较治疗前降低,且实验组较对照组低($P<0.05$)。见表 5。

2.5 不良反应发生率对比

对照组发生 4 例不良反应事件(口干 1 例、厌食 1 例、腹泻 2 例),实验组发生 6 例(头痛 2 例、口干 2 例、眩晕 1 例、厌食 1 例)。对照组(6.25%)、实验组(9.38%)不良反应发生率对比无统计学差异($\chi^2=0.434$, $P=0.510$)。

表 5 外周血单个核细胞 PI3K/Akt 信号通路相关指标对比($\bar{x} \pm s$)Table 5 Comparison of PI3K / Akt signal pathway related indexes of peripheral blood mononuclear cells($\bar{x} \pm s$)

Groups	PI3K	Akt	IL-1 β (pg/L)	TNF- α (ng/L)
Control group(n=64)				
Before treatment	0.073 $\pm$ 0.006	0.573 $\pm$ 0.009	128.45 $\pm$ 19.46	46.73 $\pm$ 6.92
After treatment	0.059 $\pm$ 0.008 ^a	0.418 $\pm$ 0.008 ^a	87.49 $\pm$ 19.35 ^a	29.46 $\pm$ 4.82 ^a
Experimental group(n=64)				
Before treatment	0.072 $\pm$ 0.009	0.583 $\pm$ 0.007	127.93 $\pm$ 18.74	46.15 $\pm$ 7.38
After treatment	0.042 $\pm$ 0.007 ^{ab}	0.346 $\pm$ 0.005 ^{ab}	61.48 $\pm$ 17.37 ^{ab}	20.81 $\pm$ 4.73 ^{ab}

Note: a, b were compared with the same group before treatment and the control group after treatment respectively, and the differences were statistically significant.

3 讨论

中医认为抑郁症的主要病因为情志内伤,或由于脏腑功能失调,如《灵枢·口问》中记载:"悲哀愁忧则心动,心动则五脏六腑皆摇";《素问·举痛论》亦有云"怒则气上,喜则气缓,悲则气消,恐则气下,寒则气收,惊则气乱,灵则气泄,劳则气耗,思则气结。"明确了情志在抑郁症中发病的重要性^[12,13]。此外,脏腑功能失调导致气机不畅也会造成郁证。《景岳全书·杂证漫·郁证》指出"凡诸郁滞,或表或里或脏或腑,一有滞逆,皆为之郁"^[14]。郁证初期病在气分,病久则气郁不解,由气及血,最终出现痰浊、血瘀、食滞等各种病理变化。故而中医认为对于郁证的治疗,不仅要舒肝解郁、调畅中焦、调理气机、活血化瘀,还要注重调畅情志^[15]。柴桂温胆定志汤由温胆汤、柴胡桂枝汤、四逆散、定志小丸等合方化裁,由柴胡、半夏、黄芩、茯苓、桂枝、枳壳、竹茹、炙甘草、生姜、远志、陈皮、赤白芍、人参、大枣、菖蒲组方而成^[16]。其中柴胡桂枝汤疏达郁结、振奋肝胆脾胃;定志小丸去湿导浊,补心益脑醒神;温胆汤增强涤痰醒神定志之力;四逆散益元气、补五脏、定魂魄、安精神;诸方相合,攻补同施,寒温并用,共奏豁痰开窍、疏解肝郁、温补心阳、养脑醒神之效^[17]。本次研究结果显示,柴桂温胆定志汤联合舍曲林可使患者睡眠质量改善,生活质量提高,抑郁症状减轻,疗效得以提高。盐酸舍曲林胶囊为一种选择性的 5-HT 重摄取抑制剂,通过提高 5-HT 水平,促使自主神经功能恢复,从而达到抗抑郁效果^[18]。而中药治疗更具有针对性,用药后可使患者的情绪、失眠多梦、苔腻等诸多症状得以改善,通过多方面协同作用改善患者情志、脏腑失调,从而达到改善抑郁的治疗目标^[19]。

抑郁症发病机制的单胺类神经递质假说备受认可,其中 NE、5-HT 作为神经递质,其机能减退不仅可致机体情绪障碍,还可通过影响其他递质来诱发抑郁症^[20,21]。DA 是下丘脑多巴胺和脑垂体腺中的一种关键神经递质,可直接影响人类的情绪,其水平增加可促使人兴奋^[22]。本次研究结果显示,柴桂温胆定志汤联合舍曲林可有效调节患者血清单胺类神经递质水平,可能是因为柴胡中成分柴胡皂苷具有调节单胺类神经递质及其代谢产物的作用,从而发挥抗抑郁效果^[23]。定志小丸可宁神除痰,能诱导神经干细胞增殖,保护神经元^[24]。温胆汤可提高伴抑郁行为大鼠内侧前额叶皮层中 DA、NE、5-HT 水平^[25]。此外,以往的研究证实^[26],PI3K/Akt 信号通路也是导致抑郁的免疫学机

制之一。PI3K-AKT 是细胞、个体的各项生命活动中重要的信号通路,人体中外周血单个核细胞 PI3K 和 Akt mRNA 表达增加,启动 PI3K/Akt 信号通路,PI3K、Akt 的蛋白含量升高,促使 IL-1 β 、TNF- α 水平也随之升高,同时影响睡眠进程,最终加重抑郁症状^[27,28]。本次研究中显示,柴桂温胆定志汤联合舍曲林可降低外周血单个核细胞 PI3K 和 Akt 蛋白表达,下调 IL-1 β 、TNF- α 水平。推测柴桂温胆定志汤联合舍曲林是通过 PI3K/AKT 信号通路标志性蛋白发挥抗抑郁的作用。现代药理研究结果显示^[29],柴胡提取物柴胡皂苷 D 可以通过激活 PI3K/AKT/FOXO1 信号通路发挥抗抑郁作用。茯苓中的羧甲基茯苓多糖可经 PI3K/Akt 信号通路发挥抑制细胞凋亡的作用^[30]。另本研究显示两组不良反应发生率对比无统计学差异,提示舍曲林与柴桂温胆定志汤联合治疗安全性较好。

综上所述,柴桂温胆定志汤联合舍曲林可改善抑郁症患者睡眠质量,提高生活质量,减轻抑郁症状,调节血清单胺类神经递质水平,可能通过作用于 PI3K/Akt 信号通路来达到治疗目的,但其具体作用机制有待后续基础研究深入探讨。

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