奥氮平联合氟西汀治疗对抑郁症患者血清 NE 水平以及抑郁情绪影响的临床研究 *

李少华 [1]　易筱荣 [2]　张翠芳 [3]　代青湘 [4]　袁德利 [5△]

（1 青海省第三人民医院心理科 青海 西宁 810007；2 青海省人民医院医学检验科 青海 西宁 810000；

3 青海红十字医院心身疾病科 青海 西宁 810007；4 青海大学附属医院老年科 青海 西宁 810000；

5 中国人民解放军北部战区总医院妇产科 辽宁 沈阳 110000）

摘要 目的：研究奥氮平联合氟西汀治疗抑郁症患者的临床疗效，并探讨联合治疗对抑郁症患者血清去甲肾上腺素（Norepinephrine，NE）和抑郁情绪的影响。方法：纳入 2018 年 6 月到 2020 年 5 月在我院接受治疗的抑郁症患者 56 例，随机数表法将其分为对照组和研究组两组。对照组患者接受氟西汀治疗，而研究组患者接受奥氮平联合氟西汀治疗，两组患者均治疗 8 周。比较两组患者年龄、性别、身高、BMI 以及病程等一般资料，并比较两组患者临床治疗疗效、治疗期间不良反应发生率、治疗前后血清 NE 水平。用汉密顿抑郁量表（Hamilton Rating Scale for Depression，HAMD）和抑郁自评量表（Self-Rating Depression Scale，SDS）评估两组患者抑郁情绪。结果：两组患者性别、年龄、身高、BMI、病程以及合并症等一般情况均显示无显著差异（$P>0.05$）。研究组治疗总有效率（92.86%）显著高于对照组（64.29%）总治疗有效率（$P<0.05$），但研究组患者治疗期间不良发生率（32.14%）与对照组（28.57%）比较无显著差异（$P>0.05$）。治疗后，两组患者血清 NE 水平均较治疗前显著升高（$P<0.05$），并且研究组患者治疗后血清 NE 水平均显著高于对照组患者（$P<0.05$）；两组患者血清 HAMD 和 SDS 评分均较治疗前显著降低（$P<0.05$），并且研究组患者治疗后 HAMD 和 SDS 评分均显著低于对照组患者（$P<0.05$）。结论：奥氮平联合氟西汀治疗抑郁症患者安全有效，不良反应发生率较低，可有效升高抑郁症患者血清 NE 水平，而改善患者抑郁情绪。

关键词：奥氮平；氟西汀；抑郁症；去甲肾上腺素

Clinical Study of the Effect of Olanzapine Combined with Fluoxetine Treatment on Serum NE Level and Depression in Patients with Depression*

LI Shao-hua[1], YI Xiao-rong[2], ZHANG Cui-fang[3], DAI Qing-xiang[4], YUAN De-li[5△]

(1 Department of Psychology, Third People's Hospital of Qinghai Province, Xining, Qinghai 810007, China;

2 Department of Laboratory Medicine, Qinghai Provincial People's Hospital, Xining, Qinghai, 810000, China;

3 Department of Psychosomatic Diseases, Qinghai Red Cross Hospital, Xining, Qinghai, 810007, China;

4 Department of Geriatrics, Affiliated Hospital of Qinghai University, Xining, Qinghai, 810000, China; 5 Department of Obstetrics and Gynecology, Northern Theater General Hospital of Chinese People's Liberation Army, Shenyang, Liaoning, 110000, China)

ABSTRACT Objective: To study the clinical efficacy of olanzapine combined with fluoxetine in the treatment of patients with depression, and to explore the effect of combined therapy on serum norepinephrine (NE) and depression in patients with depression. Methods: Fifty-six cases of depression patients who were treated in our hospital from June 2018 to May 2020 were included, and they were divided into two groups: control group and study group by random number table method. Patients in the control group received fluoxetine treatment, while patients in the study group received olanzapine combined with fluoxetine treatment. Patients in both groups were treated for 8 weeks. The two groups of patients were compared with general data such as age, gender, height, BMI, and disease course, and the clinical treatment efficacy, incidence of adverse reactions during treatment, and serum NE levels before and after treatment were compared between the two groups. The Hamilton Rating Scale for Depression (HAMD) and Self-Rating Depression Scale (SDS) were used to evaluate depression in the two groups. Results: There were no significant differences in gender, age, height, BMI, course of disease, and comorbidities between the two groups ($P>0.05$). The total effective rate of treatment in the study group (92.86%) was significantly higher than the total effective rate in the control group (64.29%) ($P<0.05$), but the incidence of adverse events in the study group during treatment (32.14%) was compared with that in the control group (28.57%) There was no significant difference ($P>0.05$). After treatment, the serum NE levels of the two groups of patients were significantly higher than those before treatment ($P<0$.

05), and the serum NE levels of the patients in the study group were significantly higher than those in the control group (*P*<0.05); the serum HAMD and HAMD levels of the two groups were significantly higher after treatment. The SDS scores were significantly lower than those before treatment (*P*<0.05), and the HAMD and SDS scores of patients in the study group were significantly lower than those in the control group after treatment (*P*<0.05). **Conclusion:** Olanzapine combined with fluoxetine is safe and effective in the treatment of patients with depression, and the incidence of adverse reactions is low. It can effectively increase the serum NE level of patients with depression and improve the depression of patients.

Key words: Olanzapine; Fluoxetine; Depression; Norepinephrine

抑郁症是抑郁障碍的一种典型情况,其核心症状是显著持久的情绪低落、兴趣减退等,是一种常见的精神障碍,临床治愈率较高,但极易复发[1,2]。根据世界卫生组织统计数据显示,全球共有大约 3.5 亿人(占全球人口的 5%)遭受着抑郁症的折磨,超过 9500 万中国人一生当中得过抑郁症[3,4]。奥氮平是一种新型的抗抑郁类药物,能与多巴胺受体、5-羟色胺受体和胆碱能受体结合,并具有拮抗作用,同时还可以促进多巴胺和去甲状腺素的释放,临床上常用于治疗抑郁症[5,6]。氟西汀临床广泛应用的选择性 5-羟色胺再摄取抑制剂,可选择性地抑制 5-羟色胺转运体,阻断突触前膜对 5-羟色胺的再摄取,延长和增加 5-羟色胺的作用,从而产生抗抑郁作用[7,8]。奥氮平联合氟西汀是目前临床上用于治疗难治性抑郁症患者推荐治疗方法,然而其临床疗效依然未被认可[9]。部分研究发现,奥氮平联合氟西汀治疗难治性抑郁症患者的临床疗效优于单独使用合氟西汀[10,11];但也有部分研究发现联合治疗临床疗效并不优于氟西汀单独治疗,并且会增加患者治疗期间不良反应的发生率[12]。为进一步明确奥氮平联合氟西汀治疗抑郁症患者的临床疗效及其对抑郁症患者血清 NE 水平的影响,本研究使用奥氮平联合氟西汀对抑郁症患者进行治疗,探讨其临床治疗疗效及对血清 NE 水平的影响。

1 资料与方法

1.1 研究对象

收集 2018 年 6 月到 2020 年 5 月在我院接受治疗的抑郁症患者 56 例,男 23 例,女 33 例,年龄 28-53 岁,平均年龄(38.62±11.53)岁,病程 6-72 个月,平均(43.74±2.12)个月。所有患者根据随机数表法分为对照组(n=28)和研究组(n=28),两组患者一般资料如表 1 所示,具有可比性。此外,本次研究所有纳入研究对象均对本次研究知情,并签订知情同意书。

1.2 治疗方法

对照组患者给予奥氮平(批准文号:H20150142,印度瑞迪博士实验室有限公司)治疗,2.5 mg/d 治疗 4 周,5 mg/d 治疗 4 周,共治疗 8 周。研究组患者给予奥氮平联合氟西汀(批准文号:02907H853,山西仟源医药集团股份有限公司),奥氮平治疗方案同对照组,氟西汀(20 mg/d,治疗 8 周)。

1.3 观察指标

1.3.1 临床疗效评价
治疗前后用汉密顿抑郁量表(Hamilton Rating Scale for Depression,HAMD)对两组抑郁患者抑郁程度进行评分,治疗后 HAMD 评分降低 75%以上评定为痊愈,

50-75%评定为显效,25-50%评定为有效,低于 25%评定为无效。临床治疗总有效率=(痊愈+显效+有效)/总病例数×100%。

1.3.2 血清 NE 水平检测
所有研究对象在治疗前后于清晨采集静脉血 5 mL,血液经离心(室温,3000 rpm,10 分钟)后收集血清。使用北京绿源大德生物科技有限公司生产的去甲肾上腺素(Norepinephrine,NE)检测试剂盒分别检测血清 NE 含量。

1.3.3 抑郁情绪
所有患者均在治疗前后用 HAMD 和抑郁自评量表(Self-rating depression scale,SDS)进行抑郁情绪评估。

1.4 统计学分析

本次研究数据通过 SPSS20.0 (IBM,美国)统计学分析软件进行统计分析,以百分比进行计数,以(均值±标准差)计量资料,计数资料两组间差异选用卡方检验进行分析,计量资料两组间差异选用非配对 t 检验进行分析。P<0.05 表示差异显著具有统计学意义。

2 结果

2.1 两组患者一般资料比较

比较两组患者性别、年龄、升高、BMI、病程以及合并症等一般情况均显示无显著差异(P>0.05),具体如表 1 所示。

2.2 两组患者临床治疗疗效及不良反应比较

治疗后,对照组患者治疗总有效率为 64.29%,显著低于研究组患者 92.86%的临床治疗总有效率,差异显著具有统计学意义(P<0.001),具体如表 2 所示。

治疗过程中,对照组患者治疗期间不良反应发生率为 28.57%,与研究组患者 32.14%不良反应发生率比较无显著差异(P>0.05),具体如表 3 所示。

2.3 两组患者治疗前后血清 NE 水平比较

治疗前,对照组和研究组患者血清 NE 水平比较无显著差异(P>0.05);治疗后,对照组和研究组患者血清 NE 水平均较治疗前降低,差异显著具有统计学意义(P<0.05);并且研究组患者治疗后血清 NE 水平高于对照组患者,差异显著具有统计学意义(P<0.05)。具体如表 4 所示。

2.4 两组患者治疗前后 HAMD 和 SDS 评分比较

治疗前,对照组和研究组患者 HAMD 和 SDS 比较无显著差异(P>0.05);治疗后,对照组和研究组患者 HAMD 和 SDS 均较治疗前降低,差异显著具有统计学意义(P<0.05);并且研究组患者治疗后 HAMD 和 SDS 均低于对照组患者,差异显著具有统计学意义(P<0.05)。具体如表 5 所示。

表 1 一般资料

Table 1 General data

Groups	Control group (n=28)	Research group(n=28)	t/χ^2	P
Gender (female/male)	16/12	17/11	0.074	0.786
age (years)	38.21±11.23	39.02±12.51	1.015	0.328
height (cm)	165.32±5.72	166.78±7.01	0.824	0.692
BMI (kg/m^2)	25.32±8.12	24.92±7.34	0.774	0.699
Disease course(years)	3.62±0.18	3.67±0.23	1.158	0.154
Complications(n)				
hypertension	4	6	0.068	0.815
diabetes	12	10		
Hyperlipidemia	13	14		
Cerebrovascular	12	13		

表 2 比较两组患者临床治疗疗效[(n(%)]

Table 2 Comparison of clinical treatment efficacy between the two groups of patients[n(%)]

Groups	n	Get well	Markedly effective	Effective	Invalid	Total effective rate
Control group	28	4 (14.86)	8 (28.57)	8 (28.57)	10 (35.71)	18 (64.29)
Research group	28	8 (28.57)	10 (35.71)	8 (28.57)	2 (7.43)	26 (92.86)
χ^2						6.788
P						0.009

表 3 比较两组患者治疗期间不良反应(n(%))

Table 3 Comparison of adverse reactions during treatment between the two groups of patients(n(%))

Groups	n	Dizziness	Nausea	Mouth dry	Constipation	Adverse reaction rate(%)
Control group	28	2 (7.14)	2 (7.14)	3 (10.71)	1 (3.57)	8 (28.57)
Research group	28	1 (3.57)	3 (10.71)	2 (7.14)	3 (10.71)	9 (32.14)
χ^2						0.132
P						0.716

Note: Compared with befefore, * $P<0.001$.

表 4 比较两组患者治疗前后血清 NE 水平 (pg/mL)

Table 4 Comparison of serum NE levels before and after treatment in the two groups (pg/mL)

Groups	n	Before treatmen	After treatment
Control group	28	98.23±35.18	115.26±55.74*
Research group	28	99.52±34.18	142.57±53.18*
t		0.857	7.354
P		0.702	<0.001

Note: Compared with befefore, *$P<0.001$.

表 5 比较两组患者治疗前后 HAMD 和 SDS 评分

Table 5 compares the HAMD and SDS scores before and after treatment in the two groups

Groups	n	HAMD		SDS	
		Before treatment	After treatment	Before treatment	After treatment
Control group	28	20.21±3.58	9.23±2.15*	68.15±6.88	54.39±7.17*
Research group	28	20.35±4.01	4.52±3.18*	68.32±7.58	48.39±6.58*
t		0.672	8.139	0.576	9.231
P		0.884	<0.001	0.912	<0.001

3 讨论

抑郁症是抑郁障碍的一种,是一种慢性复发性疾病,其症状包括情绪低落、兴趣减少、思维迟缓、注意力和记忆力减退、自我否定、胃口变差、活动减少等[1,2]。在全世界范围内,抑郁症的患病率呈逐年上升的趋势,目前抑郁症已经成为世界疾病排行榜的第四大疾病;流行病学统计发现,全世界共有 3.5 亿抑郁症患者,有 10-15%的抑郁症患者最终死于自杀[13]。此外,据世界卫生组织统计,抑郁已经成为世界第三大负担疾病,已成为中国成为第二大负担疾病,预计在 2030 年将上升至首位[3, 13]。

目前,抑郁症患者的治疗是一个综合性的治疗方案,明确有效的治疗方案包括抗抑郁药物、心理治疗、电休克治疗和颅脑磁刺激治疗等[14,15]。本研究中使用氟西汀单独治疗和奥氮平联合氟西汀治疗两种治疗方案对抑郁症患者进行治疗,结果发现:在年龄、性别、病程以及合并症等一般资料具有可比性的情况下, 使用奥氮平联合氟西汀治疗方案治疗的研究组患者治疗临床总有效率高于使用氟西汀单独治疗的对照组患者,而两组患者治疗不良反应率无显著差异,这与王彦等人[16]的研究结果一致。王彦等人[16]对比 36 例单独使用奥氮平联合氟西汀治疗的联药组和 32 例使用氟西汀治疗的单药组抑郁症患者治疗后的临床疗效发现, 联药组患者临床治疗总有效率显著高于单药组患者, 并且两组患者治疗期间不良反应发生率对比无显著差异。

奥氮平属于抗精神病类药物,是第二代抗精神病药,也叫新型的抗精神病药,或者叫非典型的抗精神病药,其特点是起效快、作用效果强,目前在临床上广泛地应用于各类精神疾病[17,18]。之前的研究发现,奥氮平不仅可以通过与多巴胺受体、5- 羟色胺受体和胆碱能受体的结合而对这些与情绪中枢神经调控类发挥拮抗作用,而且还可以通过促进多巴胺和去甲肾上腺素的释放而改善抑郁症患者低落的情绪[5,6]。虽然目前抑郁症的发病机制还未被揭示,但一些关于抑郁症发病的学说已经被学界所认可,比如炎症学说、HPA 轴亢进学说、单胺类神经递质紊乱学说等[19-21]。其中,单胺类神经递质紊乱学说是被最早提出,也是目前最被接受的抑郁症发病机制学说。单胺类神经递质包括儿茶酚胺和吲哚胺两大类:儿茶酚胺包括多巴胺、去甲肾上腺素和肾上腺素[22-24]。因此,本研究对两组患者治疗前后血清去甲肾上腺素水平进行比较,以探讨联合用药的研究组临床治疗疗效优于单独用药的对照组的具体机制, 具体结果显示:治疗后两组患者血清去甲肾上腺素均显著上升,而研究组患者升高更多,这 Kuster A 等人[23]的研究结果一致,其研究发现,奥氮平联合氟西汀治疗的抑郁症患者治疗后血清去甲肾上腺素增加和维持时间均显著高于仅使用氟西汀治疗的抑郁症患者,不同的是:Kuster A 等人所纳入的患者为难治性抑郁症患者,而本次研究纳入的抑郁症患者更加广泛,不仅包括难治性抑郁症患者,还包括一般抑郁症患者。

汉密尔顿抑郁量表(Hamilton Depression Scale,HAMD)是目前国内外研究中用于评价患者精神状态变化,是临床上评定抑郁状态时应用得最为普遍的量表 [25-27]。抑郁自评量表(Self-rating depression scale,SDS)是美国教育卫生部推荐用于精神药理学研究的量表之一,其特点是使用简便,并能相当直观地反映抑郁患者的主观感受及其在治疗中的变化,主要适用于具有抑郁症状的成年人,包括门诊及住院患者[28-30]。本次研究还发现:两组患者治疗前 HAMD 和 SDS 评分比较无显著差异,治疗后均降低,但研究组患者 HAMD 和 SDS 评分下降程度显著优于对照组患者。

综上所述,奥氮平联合氟西汀治疗抑郁症临床疗效优于单独使用氟西汀治疗,并且不会增加治疗期间的不良反应,其机制可能与联合用药更有助于促进 NE 的释放有关。但需要指出本研究存在纳入样本量有限的不足。

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