

· 临床研究 ·

复方二氯醋酸二异丙胺联合门冬氨酸鸟氨酸治疗老年性非酒精性脂肪性肝炎的效果研究

冯曲波^{1*}, 颜婷², 伍国林³

(¹ 四川省林业中心医院药剂科, 成都 610081; ² 四川省医学科学院·四川省人民医院药学部, 成都 610072; ³ 四川省妇幼保健院药学部, 成都 610045)

【摘要】 目的 探讨复方二氯醋酸二异丙胺联合门冬氨酸鸟氨酸治疗老年性非酒精性脂肪性肝炎(NASH)的效果。**方法** 选取2019年1月至2019年12月于四川省林业中心医院治疗住院的老年性NASH患者95例,根据随机数表法分为对照组与观察组,每组各46例。对照组给予阿托伐他汀治疗,观察组在对照组的基础上给予复方二氯醋酸二异丙胺联合门冬氨酸鸟氨酸进行治疗。比较2组患者的肝功能指标、血脂指标、超声影像学评分、非酒精性脂肪性肝病活动度积分(NAS)、炎症因子及不良反应发生情况。采用SPSS 26.0统计学软件进行数据分析。根据数据类型,组间比较采用独立样本 t 检验或 χ^2 检验。**结果** 与对照组相比,治疗后观察组肝功能指标丙氨酸氨基转移酶[(53.29±6.84)和(65.73±7.25)U/L]、天门冬氨酸氨基转移酶[(34.61±4.27)和(45.73±5.12)U/L]及 γ -谷氨酰转移酶[(41.25±3.59)和(64.74±5.52)U/L]显著降低(均 $P<0.05$),血脂指标总胆固醇[(4.12±0.64)和(4.87±0.66)mmol/L]、甘油三酯[(1.42±0.31)和(1.63±0.42)mmol/L]及低密度脂蛋白胆固醇[(2.27±0.61)和(3.04±0.59)mmol/L]显著降低(均 $P<0.05$),超声影像学评分[(6.18±1.34)和(7.25±1.46)分]及NAS积分[(3.27±0.54)和(3.85±0.73)分]显著降低(均 $P<0.05$),血清中白细胞介素-6[(109.43±11.87)和(129.75±10.96) μ g/L]、肿瘤坏死因子- α [(51.26±6.05)和(63.18±6.72) μ g/L]及转化生长因子- β [(6.03±1.92)和(8.45±2.21) μ g/L]显著降低(均 $P<0.05$)。2组患者不良反应发生率比较,差异无统计学意义($P>0.05$)。**结论** 复方二氯醋酸二异丙胺联合门冬氨酸鸟氨酸辅助治疗老年性NASH的效果显著,具有一定的临床应用价值。

【关键词】 非酒精性脂肪性肝炎;复方二氯醋酸二异丙胺;门冬氨酸鸟氨酸;阿托伐他汀

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Efficacy of compound diisopropylamine dichloroacetate combined with ornithine aspartate in treatment of non-alcoholic steatohepatitis in the elderly

FENG Qu-Bo^{1*}, YAN Ting², WU Guo-Lin³

(¹Department of Pharmacy, Sichuan Provincial Forestry Central Hospital, Chengdu 610081, China; ²Department of Pharmacy, Sichuan Academy of Medical Sciences·Sichuan Provincial People's Hospital, Chengdu 610072, China; ³Department of Pharmacy, Sichuan Provincial Maternity and Child Health Care Hospital, Chengdu 610045, China)

【Abstract】 Objective To investigate the effect of compound diisopropylamine dichloroacetate combined with ornithine aspartate in the treatment of non-alcoholic steatohepatitis (NASH) in the elderly. **Methods** A total of 95 elderly patients with NASH hospitalized in Sichuan Forestry Central Hospital from January 2019 to December 2019 were prospectively recruited and then randomly divided into control group and observation group, with 46 cases in each group. The control group was treated with atorvastatin, and the observation group was treated with compound diisopropylamine dichloroacetate combined with ornithine aspartate on the basis of atorvastatin. The indicators of liver function, blood lipid, ultrasonic imaging score, NASH activity score (NAS), inflammatory factors and adverse reactions were compared between the 2 groups. SPSS statistics 26.0 was used for data analysis. According to the data types, independent sample t test or χ^2 -square test was employed for intergroup comparison. **Results** After treatment, the observation group had significantly lower indicators in liver function, including alanine aminotransferase [(53.29±6.84) vs (65.73±7.25) U/L], aspartate aminotransferase [(34.61±4.27) vs (45.73±5.12) U/L] and γ -glutamyltransferase [(41.25±3.59) vs (64.74±5.52) U/L] (all $P<0.05$), decreased blood lipid indicators, such as total cholesterol [(4.12±0.64) vs (4.87±0.66) mmol/L], triglyceride [(1.42±0.31) vs (1.63±0.42) mmol/L] and low-density lipoprotein cholesterol [(2.27±0.61) vs (3.04±0.59) mmol/L]

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通信作者: 冯曲波, E-mail: 269684799@qq.com

(all $P<0.05$), reduced ultrasound imaging score [(6.18±1.34) vs (7.25±1.46)] and NAS score [(3.27±0.54) vs (3.85±0.73)] (both $P<0.05$), and lower inflammatory factors, that is, serum interleukin-6 [(109.43±11.87) vs (129.75±10.96) $\mu\text{g/L}$], tumor necrosis factor- α [(51.26±6.05) vs (63.18±6.72) $\mu\text{g/L}$] and transforming growth factor- β [(6.03±1.92) vs (8.45±2.21) $\mu\text{g/L}$] (all $P<0.05$) when compared with the control group. There was no significant difference in the incidence of adverse reactions between the 2 groups ($P>0.05$). **Conclusion** Compound diisopropylamine dichloroacetate combined with ornithine aspartate shows effective efficacy in the adjuvant treatment of NASH in the elderly, and has a certain clinical value in clinical practice.

【Key words】 non-alcoholic steatohepatitis; compound diisopropylamine dichloroacetate; ornithine aspartate; atorvastatin

Corresponding author: FENG Qu-Bo, E-mail: 269684799@qq.com

非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)是指除酒精及其他不明因素所致,以肝内细胞脂肪过度堆积为主要特征的疾病。我国NASH发病率约为31%^[1],老年人体内脂肪含量相对增加,肝脏血流量降低,肝脏代谢功能下降,易引发NASH^[2]。老年性NASH的发病率呈不断上升趋势^[3]。对于老年性NASH,临床上主要采用改变生活方式、减肥手术及药物治疗等方式进行治疗^[4]。他汀类药物为治疗NASH的常用药物,对肝脂肪变性有一定治疗作用,但存在一定的肝毒性。有临床研究表明,保肝药物对肝功能的恢复具有良好的促进作用^[5]。复方二氯醋酸二异丙胺和门冬氨酸鸟氨酸作为保肝药物中的代表药物,前者可改善肝脏能量代谢及肝细胞功能,促进受损肝细胞的修复^[6],后者可激活 γ -谷氨酰转移酶(γ glutamyl-transferase, GGT),清除对人体有害的自由基,促进肝细胞的修复与再生^[7]。基于此,本研究在他汀类药物治疗的基础上,对联合复方二氯醋酸二异丙胺和门冬氨酸鸟氨酸辅助治疗老年性NASH的效果进行分析,以期对临床老年NASH患者的联合药物治疗提供更多思路。

1 对象与方法

1.1 研究对象

选取2019年1月至2019年12月于四川省林业中心医院治疗住院的老年性NASH患者95例。以确定研究对象为起点,多点追踪至研究结束,共脱落3例,最终纳入患者92例。脱落原因:主动要求退出1例,病情急剧恶化1例,死亡1例。采用随机数表法将患者分为对照组与观察组,每组各46例。对照组男性31例,女性15例,平均年龄(67.28±4.53)岁;观察组男性30例,女性16例,平均年龄(68.05±4.72)岁。2组患者基线资料比较,差异无统计学意义($P>0.05$)。

纳入标准:(1)符合《肝癖(非酒精性脂肪性肝炎)诊疗方案》^[8]中关于NASH的西医诊断标准;(2)入组前2周末服用保肝类药物。排除标准:(1)合并严重心肝肾功能障碍;(2)对本次所

用药物过敏者或不耐受。本研究经四川省林业中心医院伦理委员会审查批准。

1.2 方法

对照组患者给予阿托伐他汀(厂家:辉瑞制药有限公司,国药准字:H20051408)治疗,202 mg/片,口服给药,1片/次,1次/d,连续给药3个月。观察组在对照组的基础上给与复方二氯醋酸二异丙胺(厂家:山西省临汾健民制药厂,国药准字:H14023585)联合门冬氨酸鸟氨酸(厂家:福安药业股份有限公司,国药准字:H20113459)进行治疗。复方二氯醋酸二异丙胺含二氯醋酸二异丙胺20 mg、葡萄糖酸钙19.5 mg,口服给药,温水吞服,2片/次,3次/d;取门冬氨酸鸟氨酸10 g溶解于250 ml 0.9%的氯化钠溶液中,静脉滴注给药,1次/d,连续给药3个月。

1.3 观察指标

(1)丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)及GGT等肝功能指标;(2)总胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)及低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)等血脂指标;(3)超声影像学评分,主要包括肝脏形态、轮廓、结构及近场回声4个条目,总分为0~12分,评分越高,病情越严重;(4)采用非酒精性脂肪性肝病活动度积分(no-nalcoholic fatty liver disease activity score, NAS)判断NASH的病情严重程度,主要包括肝脂肪病变、坏死灶及肝脏气球样变3个条目,总分为0~8分,评分越高,病情越严重;(5)血清中白细胞介素-6(interleukin-6, IL-6)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)及转化生长因子- β (transforming growth factor- β , TGF- β)等炎症因子水平;(6)患者不良反应发生情况。

1.4 统计学处理

采用SPSS 26.0统计学软件进行数据分析。计量资料以均数±标准($\bar{x}\pm s$)表示,组间比较采用独立样本 t 检验;计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 2 组患者治疗前后肝功能指标比较

与治疗前相比,2 组患者治疗后 ALT、AST 及 GGT 均显著降低(均 $P<0.05$)。与对照组相比,治疗后观察组患者 ALT、AST 及 GGT 均显著降低(均 $P<0.05$;表 1)。

2.2 2 组患者治疗前后血脂水平比较

与治疗前相比,2 组患者治疗后 TC、TG 及 LDL-C 水平均显著下降($P<0.05$)。与对照组相比,治疗后观察组患者 TC、TG 及 LDL-C 水平均显著下降($P<0.05$;表 2)。

2.3 2 组患者治疗前后超声影像学评分比较

与治疗前相比,2 组患者治疗后超声影像学评分均显著下降($P<0.05$)。与对照组相比,治疗后观察组超声影像学评分显著下降($P<0.01$)。其中,对照组、观察组治疗前的超声影像学总评分分别为

(10.05±2.32)、(9.88±2.17)分,治疗后的超声影像学总评分分别为(7.25±1.46)、(6.18±1.34)分。

2.4 2 组患者治疗前后 NAS 积分比较

与治疗前相比,2 组患者治疗后 NAS 积分均显著下降($P<0.05$)。与对照组相比,治疗后观察组 NAS 积分显著下降($P<0.05$)。其中,对照组、观察组治疗前的 NAS 评分分别为(4.36±0.77)、(4.24±0.79)分,治疗后的 NAS 评分分别为(3.85±0.73)、(3.27±0.54)分。

2.5 2 组患者治疗前后炎症因子水平比较

与治疗前相比,2 组患者治疗后 IL-6、TNF- α 及 TGF- β 等炎性因子水平均显著下降($P<0.05$)。与对照组相比,治疗后观察组炎症因子水平显著下降($P<0.05$;表 3)。

2.6 2 组患者不良反应情况比较

2 组患者不良反应发生率比较,差异无统计学意义($P>0.05$;表 4)。

表 1 2 组患者治疗前后肝功能指标比较

Table 1 Comparison of liver function indexes between two groups before and after treatment ($n=46$, U/L, $\bar{x}\pm s$)

Group	ALT		AST		GGT	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	92.63±11.52	53.29±6.84 *	76.42±6.94	34.61±4.27 *	96.54±8.52	41.25±3.59 *
Control	90.35±12.07	65.73±7.25 *	77.58±6.86	45.73±5.12 *	95.83±8.19	64.74±5.52 *
t	1.008	8.465	0.806	11.313	0.407	24.195
P value	0.316	<0.01	0.422	<0.01	0.685	<0.01

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyltransferase. Compared with before treatment, * $P<0.05$.

表 2 2 组患者治疗前后的血脂水平比较

Table 2 Comparison of blood lipid level between two groups before and after treatment ($n=46$, mmol/L, $\bar{x}\pm s$)

Group	TC		TG		LDL-C	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	5.79±1.03	4.12±0.64 *	2.06±0.75	1.42±0.31 *	3.86±0.94	2.27±0.61 *
Control	5.82±0.98	4.87±0.66 *	2.13±0.68	1.63±0.42 *	3.93±0.87	3.04±0.59 *
t	0.143	5.533	0.469	2.728	0.371	6.154
P value	0.887	<0.01	0.640	<0.01	0.712	<0.01

TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol. Compared with before treatment, * $P<0.05$.

表 3 2 组患者治疗前后炎症因子水平比较

Table 3 Comparison of inflammatory factors between two groups before and after treatment ($n=46$, $\mu\text{g/L}$, $\bar{x}\pm s$)

Group	IL-6		TNF- α		TGF- β	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	146.25±29.16	109.43±11.87 *	87.39±9.27	51.26±6.05 *	15.23±3.08	6.03±1.92 *
Control	149.71±30.23	129.75±10.96 *	85.46±8.73	63.18±6.72 *	15.39±2.97	8.45±2.21 *
t	0.559	8.530	1.028	8.941	0.254	5.606
P value	0.578	<0.01	0.307	<0.01	0.800	<0.01

IL-6: interleukin-6; TNF- α : tumor necrosis factor- α ; TGF- β : transforming growth factor- β . Compared with before treatment, * $P<0.05$.

表 4 2 组患者不良反应情况比较

Table 4 Comparison of adverse reactions between two groups [n=46, n(%)]

Group	Vomiting	Headache	Dizziness	Abdominal pain	Gum swelling	Total incidence rate
Observation	2(4.35)	3(6.52)	2(4.35)	1(2.17)	2(4.35)	10(21.74)
Control	3(6.52)	1(2.17)	2(4.35)	2(4.35)	0(0.00)	8(17.39)

3 讨 论

NASH 为临床上较为常见的代谢性障碍综合征,患者明确无过量饮酒史,病理发展与酒精性肝损伤相似^[8]。流行病学研究表明,我国 NASH 发病增长率一直居高不下^[9]。患者常伴有疼痛、肥胖、乏力及消化系统紊乱等表现,若得不到及时有效的治疗,可能会发展为肝硬化甚至肝癌^[10,11]。

轻度老年性 NASH 患者可通过调节生活方式控制病情的发展,但已存在肝损伤的患者则需要进行药物治疗^[12]。老年性 NASH 患者病情较为复杂,老年人往往合并多种慢性疾病,需要同时服用多种药物,应注意用药安全。他汀类药物被广泛应用于 NASH 的治疗中,通过干扰肝脏细胞脂肪变性、氧化及炎症反应等过程,发挥降脂及抗炎的作用,但单纯应用阿托伐他汀在发挥降脂的同时存在一定程度的肝毒性^[13]。而复方二氯醋酸二异丙胺与门冬氨酸鸟氨酸作为保肝药物单一应用于脂肪肝患者中均获得了良好的治疗效果^[14-16]。故本研究在阿托伐他汀基础上,采用新的联合用药方案(复方二氯醋酸二异丙胺联合门冬氨酸鸟氨酸)辅助治疗老年性 NASH,旨在从临床疗效、安全性方面验证该方案的可行性。结果发现,2 组患者的肝功能指标、血脂指标均有所改善,且观察组优于对照组($P<0.05$)。与对照组相比,观察组超声影像学评分、NAS 积分及炎症因子水平均显著降低($P<0.05$),与张逸强等^[17]结果相似。分析原因可能是阿托伐他汀能够阻断胆固醇的合成,降低血脂水平;复方二氯醋酸二异丙胺可增加肝细胞氧摄取,使血液乳酸水平降低,调节机体酸碱平衡并补充能量,从而改善肝脏机能,促进肝脏细胞的修复^[14];门冬氨酸鸟氨酸可激活肝脏解毒的关键酶并直接参与肝细胞中氨的代谢,彻底清除有害自由基及肝脏细胞中的脂肪^[15]。在老年性 NASH 治疗中三药联用发挥了降脂、保肝、解毒的协同及促进作用。石振东等^[18]应用阿托伐他汀联合二氯醋酸二异丙胺治疗老年非酒精性脂肪肝患者,未见明显不良反应。但本研究观察组与对照组不良反应率差异无统计学意义($P>0.05$),可能与本研究的样本量偏少、用药治疗时间偏短有关。未来还需进行大样本量研究,延长联合药物治疗时间,以进一步探讨联合用药治疗

NASH 的有效性与安全性。

综上所述,复方二氯醋酸二异丙胺联合门冬氨酸鸟氨酸辅助治疗老年性 NASH 的效果显著,具有一定的临床应用价值。

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