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S-腺苷蛋氨酸治疗胆汁淤积性肝病伴抑郁/焦虑的临床效果研究*

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摘要 目的:研究S-腺苷蛋氨酸治疗胆汁淤积性肝病伴抑郁/焦虑患者的临床效果。**方法:**选择2011年3月～2013年3月我院收治的51例不同病因的胆汁淤积性肝病(药物性肝损害13例、慢性乙型肝硬化14例、酒精性肝硬化11例、自身免疫性肝病6例、肝癌5例、胆管癌2例)并抑郁/焦虑的患者,予S-腺苷蛋氨酸1.0 g治疗2周,应用SDS/SAS量表分别评估和比较治疗前后各组患者抑郁/焦虑程度的评分情况。**结果:**S-腺苷蛋氨酸治疗后,所有组别胆汁淤积性肝病肝病改善的临床总有效率94.12%,其中药物性肝损害、慢性乙型肝硬化、酒精性肝硬化、自身免疫性肝硬化总有效率均为100.00%,肝癌的有效率为60.00%,胆管癌的有效率为50.00%,药物性肝损害患者临床疗效与其他各组有差异(P<0.05);药物性肝病患者SDS和SAS评分均较治疗前显著降低(P<0.05)。而慢性乙型肝硬化、酒精性肝硬化、自身免疫性肝病、肝癌、胆管癌患者SDS和SAS评分与治疗前相比均无统计学差异(P>0.05)。**结论:**S-腺苷蛋氨酸可改善药物性胆汁淤积性肝病并轻、中度抑郁/焦虑患者的肝功能,并有效减轻其抑郁/焦虑情绪。

关键词:胆汁淤积;焦虑;抑郁;S-腺苷蛋氨酸

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Research on S-adenosylmethionine in the Treatment of Patients of Cholestatic Liver Diseases Associated with Anxiety/depression*

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ABSTRACT Objective: To study the clinical effects of S-adenosyl methionine for patients with cholestatic liver disease associated with depression or anxiety. **Methods:** 51 patients with different causes of cholestatic liver diseases (13 cases of drug-induced liver injury, 14 cases of chronic hepatits B cirrhosis, 11 cases of alcoholic cirrhosis, 6 cases of autoimmune liver disease, 5 cases of hepatocellular carcinoma and 2 cases of cholangiocarcinoma) and depression or anxiety were selected in our hospital from March 2011 to March 2013 and treated with intravenous use of S-adenosyl methionine 1.0 g for 2 weeks. Then, Zung's SDS / SAS assessment were applied to compare the effects in these groups. **Results:** After treatment with S-adenosylmethionine, the total effetive ratio of all cholestatic liver diseases was 94.12%, including 100.00% in drug-induced liver injury, chronic hepatits B cirrhosis, alcoholic cirrhosis and autoimmune liver disease, 60.00% in hepatocellular carcinoma and 50.00% in cholangiocarcinoma. There was significant statistical differences between drug-induced cholestatic liver disease and the other groups (P<0.05). Scores of SDS and SAS significantly decreased in patients with drug-induced cholestatic liver disease after treated with S-adenosylmethionine (P<0.05), however, it seemed no change in chronic cholestatic liver disease (cirrhosis, autoimmune liver disease) as well as in hepatobiliary cancer (hepatocellular carcinoma, cholangiocarcinoma) . **Conclusion:** S-adenosylmethionine could improve the liver function in patients with drug-induced cholestatic liver disease associated with mild and moderate depression or anxiety, and effectively better their depressive or anxious mood.

Key words: Cholestasis; Anxiety; Depression; S-adenosylmethionine

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胆汁淤积性肝病患者多伴有抑郁、焦虑症状,可能由疾病的痛苦、社会经济的压力、药物治疗作用缓慢和黄疸持续等引起。近来研究发现S-腺苷蛋氨酸(S-adenosyl-L-methionine, SAMe)具有保肝及抗抑郁双重作用。本研究通过对我院2011年3月～2013年3月收治的51例不同病因所致的胆汁淤积性肝病并抑郁/焦虑患者予SAMe治疗,旨在进一步评估

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SAMe 抗胆汁淤积性肝病并抑郁 / 焦虑的临床疗效，现报道如下。

1 资料与方法

1.1 病例来源

选择 2011 年 3 月～2013 年 3 月在青岛市立医院消化内科及肝胆外科住院的胆汁淤积性肝病患者 51 例，其中男 27 例，女 24 例，平均年龄(54.96± 13.85)岁。病因：药物性肝损害 13 例，慢性乙型肝硬化 14 例，酒精性肝硬化 11 例，自身免疫性肝病 6 例，肝癌 5 例，胆管癌 2 例。TBIL 均大于 100 μmol/l (192.86± 71.61)。

1.2 治疗方法

各胆汁淤积型肝病伴抑郁或焦虑患者经 S- 腺苷蛋氨酸(思美泰，Transemtil，德国基诺药厂生产)1.0 g 加入 5%葡萄糖液 250 mL 静滴，每日一次，治疗 2 周。

1.3 临床疗效评价方法

抑郁焦虑量表由美国 Zung 编制，各量表均由 20 条构成，简称 SDS、SAS 量表，因使用简便，应用颇广，是目前精神医学界最常用的抑郁自测量表之一。应用 SDS / SAS 量表对各组胆汁淤积性肝病病人治疗前均予 SDS 及 SAS 量表评分，将总分乘以 1.25 后为最后得分，根据最后得分，确定抑郁、焦虑症状的分级 (在 50 分以下为正常，50-59 分提示轻度，60-69 分提示中度，70 分以上提示重度)。

显效：治疗后主要症状(厌食油腻、上腹不适、尿黄、皮肤瘙痒) 消失，TBIL 较治疗前下降≥ 2/3；有效：治疗后症状改善，TBIL 较治疗前下降 >1/3；无效：症状无好转或加重，TBIL 下降 <1/3 者。

1.4 统计学分析

应用 SPSS 12.0 软件包进行统计学分析，计量资料采用成组 t 检验，有序分类资料采用 Ridit 分析检验及秩和检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 各组胆汁淤积性肝病患者治疗后的临床疗效比较

胆汁淤积性肝病患者总计 51 例，显效 31 例，有效 17 例，无效 3 例，有效及显效率为 94.12%，药物性肝损害 13 例，显效 13 例，显效率为 100.00%；慢性乙型肝硬化 14 例，显效 8 例，有效 6 例，有效及显效率为 100.00%，；酒精性肝硬化 11 例，显效 7 例，有效 4 例，有效及显效率为 100.00%；自身免疫性肝病 6 例，显效 3 例，有效 3 例，有效及显效率为 100.00%；肝癌 5 例，有效 3 例，无效 2 例，有效率 60.00%；胆管癌 2 例，有效 1 例，无效 1 例，有效率 50.00%(见表 1)。药物性肝损害患者治疗后临床疗效明显优于其余各组胆汁淤积性肝病患者临床疗效，差异有统计学意义(P< 0.05)，慢性乙型肝硬化、酒精性肝硬化、自身免疫性肝病三者之间疗效比较无显著差异(P> 0.05)。

表 1 各组胆汁淤积性肝病患者治疗后的临床疗效

Table 1 Comparison of the clinical effects between groups of patients with different cholestatic liver diseases

	Total cases	ObviousMarked effective cases (rate %)(%)	Eeffective cases (rate %)(%)	NegitiveInvalid cases (rate%)(%)	Ttotal effective cases (rate) (%)
Drug-induced liver injury	13	13(100)	0(0)	0(0)	13(100.00)
Chronic hepatits B cirrhosis	14	8(57.9)	6(42.1)	0(0)	14(100.00)
Alcoholic cirrhosis	11	7(63.6)	4(36.4)	0(0)	11(100.00)
Autoimmune liver disease	6	3(50)	3(50)	0(0)	6(100.00)
Hepatocellular carcinoma	5	0(0)	3(60)	2(40)	3(60.00)
Cholangiocarcinoma	2	0(0)	1(50)	1(50)	1(50.00)
cholestatic liver disease	51	31(60.8)	17(33.3)	3(5.9)	48(94.12)

2.2 各组胆汁淤积性肝病患者治疗后的抑郁 / 焦虑症状疗效比较

药物性肝损害伴抑郁病人 13 例(轻度 8 例、中度 3 例、重度 2 例)，治疗后，1 例重度患者好转为轻度，其余患者无抑郁症状；药物性肝损害伴焦虑病人 13 例(轻度 8 例、中度 4 例、重度 1 例)，治疗后，1 例重度患者改善为轻度，其余患者全部治愈。治疗前后，药物性肝损害抑郁、焦虑症状明显改善(应用 Ridit 分析：抑郁及焦虑患者治疗后 Ridit=0.5，P<0.05)。慢性乙肝肝硬化病人中 8 例抑郁病人(轻度 6 例，中度 2 例)治疗后 1 例中度患者好转为轻度，2 例轻度患者抑郁症状消失，11 例焦虑病人(轻度 9 例，中度 1 例，重度 1 例)治疗后 3 例轻度患者焦虑症状消失；酒精性肝硬化中 7 例抑郁病人(轻度 3 例，中度 3 例，重度 1 例)治疗后 1 例中度患者好转为轻度，1 例患者症抑郁状消失，10 例焦虑病人(轻度 6 例，中度 2 例，重度 2 例)治疗后 1 例重度患者好转为轻度，2 例轻度患者焦虑症状消失；自身免疫性肝病抑郁病人 3 例(轻度 2 例，中度 1 例)治疗后 1 例中度患者好转为轻度，1 例轻度患者抑郁症状消失，焦虑病人 6 例(轻度 3 例，中度 3 例)治疗后 1 例中度好转为轻度；三组治疗前后，抑郁、焦虑症状改善无统计学意义 (应用 Ridit 分析：P> 0.05)。肝癌及胆管癌患者抑郁 / 焦虑症状无改善，(见表 2)。

2.3 各组胆汁淤积性肝病患者治疗前后抑郁 / 焦虑量表评分比较

如表 3 所示，SAMe 治疗后，药物性肝损害伴抑郁患者 SDS 和 SAS 评分均较治疗前显著降低(P<0.05)，而慢性乙型肝硬化、酒精性肝硬化、自身免疫性肝病、肝癌、胆管癌患者 SDS 和 SAS 评分与治疗前相比均无统计学差异(P>0.05)，表明 S- 腺苷蛋氨酸对改善药物性肝损害患者伴抑郁、焦虑症状具有显著疗效。

表 2 各组肝病患者 SAMe 治疗前后 SDS / SAS 疗效比较(病例数)

Table 2 Comparison of the SDS/SAS efficacy between groups of patients with different liver diseases(number of cases)

	Before Therapy			After Therapy			Before Therapy			After Therapy		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Drug-induced liver injury*	8	3	2	1	0	0	8	4	1	1	0	0
Chronic hepatits B cirrhosis	6	2	0	5	1	0	9	1	1	6	1	1
Alcoholic cirrhosis	3	3	1	3	2	1	6	2	2	5	2	1
Autoimmune liver disease	2	1	0	2	0	0	3	3	0	4	2	0
Hepatocellular carcinoma	1	1	1	1	0	2	2	1	1	2	1	1
Cholangiocarcinoma	0	1	1	0	1	1	0	0	2	0	0	2

SDS:Depression score sheet;SAS:Anxiety score sheet;*P<0.05

表 3 各组肝病患者治疗前后 SDS / SAS 量表评分比较($\bar{x}\pm s$)

Table 3 Comparison of the SDS/SAS scores between groups of patients with different liver diseases ($\bar{x}\pm s$)

	SDS		SAS	
	Before Therapy	After Therapy	Before Therapy	After Therapy
Drug-induced liver injury	62.44± 11.44	32.79± 6.66 *	58.17± 5.02	32.88± 8.50*
Chronic hepatits B cirrhosis	49.97± 5.51	50.94± 5.42	55.42± 1.51	52.50± 5.24
Alcoholic cirrhosis	62.14± 6.11	58.21± 10.45	61.08± 7.18	56.50± 9.36
Autoimmune liver disease	58.33± 1.91	50.83± 6.41	59.17± 5.28	4.79± 4.70
Hepatocellular carcinoma	67.92± 11.27	67.50± 9.92	65.00± 17.05	62.50± 11.59
Cholangiocarcinoma	69.38± 4.42	68.13± 9.72	76.25± 3.54	72.50± 1.77

Compared with the same group before SAMe therapy, * P<0.05

3 讨论

S- 腺苷蛋氨酸(S-adenosyl-L-methionine,SAMe)是一种天然分子,存在于人体所有细胞中,在肝脏、肾上腺以及松果体中的浓度较高,在大脑中亦均匀分布,是重要的甲基供体,具有转甲基、转氨丙基和转硫等多种生理作用,其抗氧化、解毒及促进肝细胞再生等作用被广泛应用于治疗肝病所致的肝内胆汁淤积、肝纤维化等。近年来,研究发现其对改善肝病患者情绪,治疗肝病患者抑郁症等方面[1,2]具有重要的作用,并逐渐引起人们的重视[3-6]。SAMe 抗抑郁作用的机制尚未完全明确[7-10],但目前研究多认为 SAMe 作为膜磷脂、髓磷脂、胆碱、儿茶酚胺和其他分子的甲基供体对脑功能具有重要作用,影响受体的功能、膜的流动性及神经递质的产生[11]。内源性 SAMe 可促进神经元膜流动性,脑脊液中低叶酸、低 SAMe 水平均可致神经元膜的流动性的降低 [12],导致在膜结合的底物受体亲合性和转运的中断,从而引发神经系统疾患,尤其是抑郁症状。SAMe 可加强大脑多巴胺和 5- 羟色胺神经递质代谢和信息传递功能,在精神分裂症和情感障碍患者中发现 SAMe 的代谢异常,无法合成人体正常所需的 SAMe 量,因此必须从外源补充[13]。

在国外,SAMe 于 20 世纪 70 年代末应用于抑郁症的治疗,在欧洲是一种重要的治疗抑郁症的处方药,在俄罗斯被广泛用于有抑郁症状的肝病患者,在美国用于抑郁症的营养补充剂[14]。SAMe 静脉用药和肌肉注射均可有效改善患者的抑郁症状,口服用药也可提高患者脑脊液中 SAMe 浓度,表明其可通过血脑屏障而发挥作用。Y.Levkovitz 等[15]研究表明,将 46 名对 SRI 无应答的重度抑郁症患者进行 6 周随机、对照、双盲试验,通过口服 SAMe 治疗,患者记忆相关的认知症状得到明显改善。抑郁症患者血清和脑脊髓液中有低水平的 SAMe,因此补充 SAMe、多巴胺以及其他神经递质具有很好的抗抑郁作用[16]。临床上应用 SAMe 治疗抑郁症,无依赖性,毒副作用轻微[17],尤其适合于伴有慢性肝脏疾病或身体状况不佳的患者及老年人。SAMe 对于轻、中度抑郁症状短期的治疗有效,但并不能取代中、重度抑郁症患者传统的抗抑郁药物[11],表明 SAMe 可作为抗抑郁治疗的一种辅助治疗[18]。

在我国,最早将 SAMe 应用于抑郁症的治疗开始于 20 世纪 90 年代,主要用于治疗老年患者、严重肝脏疾病者以及存在酒精中毒性肝脏损害的抑郁症患者等[19]。张海燕等[1]将 SAMe 组与苦黄注射液组的肝内胆汁淤积患者的情志改变和临床疗效作对比,结果显示两组在改善肝功能、退黄疸方面均有效,但通过 SAS 和 SDS 量表对上述患者情志进行分析,SAMe 组具有明显的抗抑郁、焦虑作用,两组间差异有显著性意义。

本实验中,药物性肝损害患者在接受 SAMe 治疗后,抑郁焦虑症状改善明显,而肝硬化患者稍有改善,肝癌及胆管癌患者无明显作用,且 SAMe 对轻、中度胆汁淤积性肝病患者治疗作用优于重度患者,这些可能与抑郁 / 焦虑形成原因、病程以及机体免疫力等多种因素相关。SAMe 应用剂量、给药途径、用药疗程对抑郁 / 焦虑的影响仍需我们进一步大样本研究明确。我们期待:通过抗氧化自由基及促进肝细胞再生等途径治疗胆汁淤积的同时改善患者脑中神经元膜的流动性及促进兴奋性神经递质的产生,发挥 SAMe 护肝及抗抑郁的双重作

用,为人类的“生理-心理”疾病的治疗带来更广阔的应用前景。

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