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熊去氧胆酸对婴儿肝炎综合征患儿血清炎症因子和肝功能的影响*

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摘要 目的:探讨熊去氧胆酸对婴儿肝炎综合征患儿血清炎症因子和肝功能的影响。**方法:**选取我院自2013年5月-2015年5月收治的婴儿肝炎综合征患儿91例,随机分为对照组(n=47)和观察组(n=44),对照组患儿给予常规护肝、利胆等治疗,观察组患儿在对照组的基础上给予熊去氧胆酸治疗,两组均治疗3周。比较两组患儿治疗前后的血清炎症因子及肝功能指标水平,观察两组患儿用药后的临床治疗效果及不良反应发生情况。**结果:**治疗后,所有患儿的血清肿瘤坏死因子- α (TNF- α)、白细胞介素-6 (IL-6)、总胆红素(TBil)、直接胆红素(DBil)、丙氨酸转氨酶(ALT)、谷氨酰转肽酶(GGT)、总胆汁酸(TBA)水平均低于治疗前,且观察组低于对照组($P<0.05$)。观察组患儿治疗后总有效率高于对照组($P<0.05$)。两组患儿总不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**熊去氧胆酸可以减轻婴儿肝炎综合征患儿的炎症反应,改善其肝功能,疗效显著且安全性好。

关键词:熊去氧胆酸;婴儿肝炎综合征;患儿;炎症因子;肝功能;疗效

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Effects of Ursodeoxycholic Acid on Serum Inflammatory Factors and Liver Function in Infants with Infantile Hepatitis Syndrome*

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ABSTRACT Objective: To investigate the effect of ursodeoxycholic acid on serum inflammatory factors and liver function in infants with infantile hepatitis syndrome. **Methods:** 91 infants with infantile hepatitis syndrome who were treated in our hospital from May 2013 to May 2015 were selected, and they were randomly divided into control group (n=47) and observation group (n=44), the control group were given routine liver protection and gallbladder treatment, the observation group were given ursodeoxycholic acid on the basis of the control group, and the two groups were treated for 3 weeks. The levels of serum inflammatory factors and liver function indexes were compared between the two groups before and after treatment. The clinical effects and adverse reactions of two groups after medication were observed. **Results:** After treatment, the levels of serum tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), total bilirubin (TBil), direct bilirubin (DBil), alanine transaminase (ALT), glutamyl transaminopeptidase (GGT) and total bile acid (TBA) in all infants were lower than those before treatment, and the observation group was lower than the control group ($P<0.05$). The total effective rate of the observation group after treatment was higher than that of the control group ($P<0.05$). There was no significant difference in the incidence of the total adverse reactions between the two groups ($P>0.05$). **Conclusion:** Ursodeoxycholic acid can reduce the inflammatory reaction and improve the liver function of infants with hepatitis syndrome, the curative effect is remarkable, and the safety is good.

Key words: Ursodeoxycholic acid; Infantile hepatitis syndrome; Infants; Inflammatory factors; Liver function; Curative effect

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前言

婴儿肝炎综合征是儿科常见疾病,多发于新生儿或婴幼儿^[1,2]。该病起病较早,较易引起肝脏肿大、质地变硬、肝细胞性黄疸等并发症,严重损害肝脏细胞的功能^[3,4]。婴儿肝炎综合征的发病机制较为复杂,主要与先天性机体代谢异常、宫腔或妊娠期感染、肝胆管发育畸形以及其他危险因素有关^[5]。近年来,感染巨细胞病毒被认为是婴儿肝炎综合征的第一发病因素,该病毒可以导致机体形成非特异性多核巨细胞,从而使机体产生病

理反应^[6,7]。婴儿肝炎综合征的治疗主要以抗病毒、消炎、保肝、消除黄疸等常规治疗手段为主,但是临床效果不尽满意^[8]。熊去氧胆酸是近几年临床上新应用的治疗婴儿肝炎综合征药物,可以有效缓解患儿的黄疸以及肝脏功能的病症,深受临床医务人员和患者的青睐^[9,10]。本研究通过探讨熊去氧胆酸对婴儿肝炎综合征患儿血清炎症因子和肝功能的影响,旨在为更好地诊治婴儿肝炎综合征提供数据支持,阐述结果如下。

1 资料与方法

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1.1 一般资料

选取我院自 2013 年 5 月 -2015 年 5 月收治的婴儿肝炎综合征患儿 91 例,纳入标准:(1)所有患儿均符合全国小儿病毒性肝炎防治座谈会制定的婴儿肝炎综合征的诊断标准^[1];(2)所有患儿家属均知情同意且签署知情同意书;(3)无胆道阻塞性黄疸者;(4)HBV 阳性者。排除标准:(1)胆道先天性闭锁者;(2)胆总管囊肿者;(3)药物性肝炎者;(4)伴有呼吸、泌尿、循环、消化、血液、神经、免疫系统其他全身性系统疾病的患儿。将所有患儿随机分为对照组和观察组,其中,对照组 47 例,男性 26 例,女性 21 例,年龄 36-159d,平均(66.57±16.53)d,病程 23-52d,平均(38.70±10.36)d。观察组 44 例,男性 24 例,女性 20 例,年龄 35-162d,平均(68.38±15.92)d,病程 21-53d,平均(37.05±9.65)d。两组患儿在年龄、性别、病程等一般资料比较差异无统计学意义($P>0.05$),具有可比性。本研究经我院伦理委员会审核通过。

1.2 研究方法

对照组患儿给予常规护肝、利胆及补充脂溶性维生素等治疗,并维持水、电解质等酸碱平衡。观察组患儿在对照组的基础上给予熊去氧胆酸片(国药准字 H42021791,武汉人福药业有限责任公司,规格:50 mg)口服治疗,每日 1 次,每次 1 片,3 周为一个疗程。所有患儿均治疗一个疗程。治疗期间,严密观察、监测所有患儿的血压、心率、呼吸等情况,根据患儿情况,及时调整用药剂量。

1.3 观察指标

1.3.1 血清炎症因子、肝功能指标的检测及不良反应统计 治疗前后,均采集两组患儿的清晨空腹静脉血 6 mL,室温下静置 25 min,在离心机下离心 15 min,转速为 3000 r/min,分离获得血清,留置 4 mL 血清冻存于 -80℃ 环境下保存。(1)采用酶联

免疫吸附法测定患儿血清肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、白细胞介素-6(Interleukin -6, IL-6)水平,所有检测试剂盒均购自于天津市灏洋生物制品科技有限责任公司,所有操作均按试剂盒说明书进行。(2)采用深圳迈瑞生物医疗电子股份有限公司生产的迈瑞 BS-480 全自动生化分析仪测定患儿肝功能指标,包括丙氨酸转氨酶(Alanine aminotransferase, ALT)、谷氨酰转肽酶(Glutamyl transpeptidase, GGT)、直接胆红素(Direct bilirubin, DBil)、总胆红素(Total bilirubin, TBil)、总胆汁酸(Total bile acids, TBA)水平,记录两组患儿治疗期间出现的不良反应。

1.3.2 疗效判定 (1)显效:患儿彻底无黄疸现象,恢复正常的肝功能,肝脏大小恢复到正常;(2)有效:患儿黄疸现象减轻,肝功能有所恢复,肝脏大小接近正常;(3)无效:患儿黄疸现象未改变甚至加重,肝功能未恢复甚至恶化,肝脏大小严重偏离正常。总有效率=(显效病例数+有效病例数)/总病例数×100%。

1.4 统计学方法

采用 SPSS19.0 进行统计学处理,炎症因子、肝功能指标水平等计量资料以均数±标准差($\bar{x}\pm s$)表示,采用 t 检验,总有效率、不良反应发生率、性别比例等计数资料采用百分比(%)表示,采用 χ^2 检验。检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组患儿血清炎症因子水平比较

治疗前,两组患儿的血清 TNF- α 、IL-6 水平比较差异无统计意义($P>0.05$)。治疗后,所有患儿的血清 TNF- α 、IL-6 水平均低于治疗前,且观察组低于对照组($P<0.05$)。见表 1。

表 1 观察组和对照组患儿血清炎症因子水平比较($\bar{x}\pm s$, ng/L)

Table 1 Comparison of serum inflammatory factors levels between the observation group and the control group ($\bar{x}\pm s$, ng/L)

Groups	TNF- α		IL-6	
	Before treatment	After treatment	Before treatment	After treatment
Observation group(n=44)	356.53±60.48	202.10±49.21 ^a	49.09±8.23	30.27±5.45 ^a
Control group(n=47)	348.39±59.38	269.67±51.83 ^a	51.36±7.93	40.69±6.53 ^a
t	0.648	6.368	1.340	8.234
P	0.519	0.000	0.184	0.000

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

2.2 两组患儿肝功能指标水平比较

治疗前,两组患儿的血清 TBil、DBil、ALT、GGT、TBA 水平均无显著性差异($P>0.05$)。治疗后,所有患儿的血清 TBil、

DBil、ALT、GGT、TBA 水平均低于治疗前,且观察组低于对照组($P<0.05$)。见表 2。

表 2 观察组和对照组患儿肝功能指标水平比较($\bar{x}\pm s$)

Table 2 Comparison of liver function indexes levels between the observation group and the control group ($\bar{x}\pm s$)

Groups	Time	TBil(mol/L)	DBil(mol/L)	ALT(U/L)	GGT(U/L)	TBA(mol/L)
Observation group (n=44)	Before treatment	168.34±38.45	112.43±22.32	116.76±24.46	217.39±51.06	49.09±8.23
	After treatment	82.12±19.18 ^{ab}	35.82±10.05 ^{ab}	58.80±14.51 ^{ab}	87.43±26.58 ^{ab}	30.27±5.45 ^{ab}
Control group (n=47)	Before treatment	170.90±39.84	110.56±21.87	118.33±25.98	220.09±50.66	51.36±7.93
	After treatment	119.74±31.34 ^a	70.09±17.63 ^a	85.87±20.33 ^a	139.49±39.54 ^a	40.69±6.53 ^a

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

2.3 观察组和对照组患儿治疗效果比较

(P<0.05)。见表 3。

与对照组相比,治疗后观察组患儿总有效率升高

表 3 观察组和对照组患儿治疗效果比较[n(%)]

Table 3 Comparison of the therapeutic effects between the observation group and the control group [n (%)]

Groups	Excellence	Effective	Invalid	Total effective rate
Observation group(n=44)	23(52.27)	17(38.64)	4(9.09)	40(90.91)
Control group(n=47)	16(34.04)	19(40.43)	12(25.53)	35(74.47)
χ^2				4.239
P				0.040

2.4 观察组和对照组患儿不良反应发生情况比较

学意义(P>0.05)。见表 4。

观察组和对照组患儿总不良反应发生率比较差异无统计

表 4 观察组和对照组患儿不良反应发生情况比较[n(%)]

Table 4 Comparison of adverse reactions between the observation group and the control group[n(%)]

Groups	Vomiting and diarrhea	Constipation	Erythra	Total incidence of adverse reactions
Observation group(n=44)	9(20.45)	4(9.09)	2(4.55)	15(34.09)
Control group(n=47)	8(17.02)	5(10.64)	1(2.13)	14(29.79)
χ^2				0.194
P				0.660

3 讨论

婴儿肝炎综合征病情较复杂,高发年龄段集中于 1 周岁以内,且患儿多表现出黄疸、肝脏病理学改变、高血清胆红素等症状^[12]。该病的病因较多,目前公认的第一病因是病毒感染,其他诸如大肠杆菌、肺炎链球菌、弓形体感染以及基因遗传等因素均可引起该病的发生^[13,14]。以抗感染、护肝、退黄疸为主的常规治疗手段虽能改善婴儿肝炎综合征的病情,但效果不甚理想。有研究显示^[15],熊去氧胆酸对婴儿肝炎综合征疗效较好,故该药在当前婴儿肝炎综合征的救治过程中备受关注。熊去氧胆酸是一种亲水性胆酸,无毒性,且对肝脏和胆囊均有良好的保护作用,主要用于成人淤胆型肝炎的治疗^[16,17]。该药的药理学作用较为复杂,主要为以下几个方面:(1)其对机体胆酸代谢的关键信号通道具有激活作用,可减少胆汁酸的合成与分泌,抑制小肠对疏水性胆汁酸的重吸收,使血清胆汁酸浓度降低,减少对肝脏的毒副作用^[18];(2)对钙通道、蛋白激酶 C 通道具有激活作用,增强蛋白激酶活性,提升胆汁淤积肝脏细胞的分泌水平,减少胆汁淤积^[19];(3)对机体的免疫系统具有调节作用,并可以抗氧化,延缓肝细胞的凋亡进程^[20]。

本研究结果显示,熊去氧胆酸治疗婴儿肝炎综合征患儿具有良好的效果,可以改善患儿血清 IFN- α 、IL-6 水平以及肝功能 TBil、DBil、ALT、GGT、TBA 的水平,提高治疗总有效率。主要原因有:(1)血清 TNF- α 是一种重要的炎性介质,由巨噬细胞因感染等多种因素被激活后而分泌的一种物质,既适量时可以抗感染、增强免疫功能、抗击疾病,大量时又能介导炎症反应,损伤机体组织器官,引发疾病^[21,22]。本研究中,观察组血清 TNF- α 水平较低,有利于在机体内发挥抗感染、提高免疫力、

抗击疾病的作用,有利于婴儿肝炎综合征患儿病症的改善。(2)血清 IL-6 是由多种细胞反应生成的一种细胞因子,生物学活性功能较多,可以传递信息,加速 B 细胞、T 细胞以及成纤维细胞的增殖、分化进程,对急性期蛋白的合成起到诱导作用,故在机体炎症反应中扮演重要的角色^[23,24];其水平的降低,表明婴儿肝炎综合征患儿机体炎症反应减轻。血清 TNF- α 、IL-6 可以介导众多疾病的进展,这其中就包括婴儿肝炎综合征,故其对炎症反应具有很强的指示作用,其水平的降低,预示婴儿肝炎综合征患儿病情的好转^[25,26]。(3)血 TBil、DBil、ALT、GGT、TBA 是肝功能的常见检测指标,GGT 的水平变化与碱性磷酸酶的变化趋势相符合,可以通过其水平判断是否有胆汁淤积的存在,TBA 的水平对肝脏的合成与分泌具有很好的指示作用;TBil、DBil 和 TBA 升高可间接反映肝脏排泄功能出现异常,而 ALT、AST 和 GGT 升高多提示肝脏细胞损害,细胞内肝酶释放入血,是肝功能受损的生化表现^[27,28]。因此,可以通过检测血 TBil、DBil、ALT、GGT、TBA 的水平,全面判断婴儿肝炎综合征患儿的肝脏功能情况。本研究中患儿血 TBil、DBil、ALT、GGT、TBA 水平的显著下降,提示婴儿肝炎综合征患儿的肝功能显著好转。此外,在本研究中,只有少数患儿出现呕吐、腹泻、便秘、皮疹等不良反应,且两组患儿不良反应发生情况无统计学差异,说明熊去氧胆酸对婴儿肝炎综合征患儿安全性较好^[29,30]。

综上所述,熊去氧胆酸联合常规疗法对婴儿肝炎综合征患儿疗效显著,能够改善肝功能,降低炎症反应,且不良反应少。

参考文献(References)

- [1] Wang G, Feng D. Dynamic relationship between infantile hepatitis syndrome and cytomegalovirus infection[J]. Exp Ther Med, 2017, 13 (6): 3443-3447

- [2] Wang X, Qian L, Jia L, et al. Utility of Shear Wave Elastography for Differentiating Biliary Atresia From Infantile Hepatitis Syndrome[J]. J Ultrasound Med, 2016, 35(7): 1475-1479
- [3] Yasmeen S, Siddique N, Athar Abbas M, et al. Fiber gene based molecular and biological characterization of hydropericardium-hepatitis syndrome associated avian adenoviruses [J]. Iran J Vet Res, 2017, 18(3): 190-196
- [4] Sugiyura A, Wada S, Mori H, et al. Successful Treatment for Chronic Hepatitis C-Autoimmune Hepatitis Overlap Syndrome due to Daclatasvir and Asunaprevir[J]. Case Rep Gastroenterol, 2017, 11(2): 305-311
- [5] Sun Y, Du T, Liu B, et al. Seroprevalence of avian hepatitis E virus and avian leucosis virus subgroup J in chicken flocks with hepatitis syndrome, China[J]. BMC Vet Res, 2016, 12(1): 261
- [6] Leonardsson H, Hreinsson JP, Löve A, et al. Hepatitis due to Epstein-Barr virus and cytomegalovirus: clinical features and outcomes[J]. Scand J Gastroenterol, 2017, 52(8): 893-897
- [7] Lei JH, Tian Y, Luo HY, et al. Guillain-Barré syndrome following acute co-super-infection of hepatitis E virus and cytomegalovirus in a chronic hepatitis B virus carrier[J]. J Med Virol, 2017, 89(2): 368-372
- [8] Zhang Xiao-jun, Yang Yun. To observe the curative effect of He-Ne laser irradiation in the treatment of infantile hepatitis syndrome in children[J]. Laser Journal, 2014, 35(8): 99-100
- [9] Zhang H, Li S, Yang J, et al. A meta-analysis of ursodeoxycholic acid therapy versus combination therapy with corticosteroids for PBC-AIH-overlap syndrome: evidence from 97 monotherapy and 117 combinations[J]. Prz Gastroenterol, 2015, 10(3): 148-155
- [10] Fang YQ, Lv DX, Jia W, et al. Case-control study on prednisolone combined with ursodeoxycholic acid and azathioprine in pure primary biliary cirrhosis with high levels of immunoglobulin G and transaminases: efficacy and safety analysis [J]. Medicine (Baltimore), 2014, 93(20): e104
- [11] Peng Hong, Dong Guo-qing. Etiological examination and clinical analysis of infantile hepatitis syndrome [J]. Chinese Journal of Misdiagnostics, 2003, 3(5): 686-687
- [12] Cho HH, Kim WS, Choi YH, et al. Ultrasonography evaluation of infants with Alagille syndrome: In comparison with biliary atresia and neonatal hepatitis[J]. Eur J Radiol, 2016, 85(6): 1045-1052
- [13] Serghini M, Labidi A, Khsiba A, et al. Cytomegalovirus infection simulating an overlap syndrome: autoimmune hepatitis -primary biliary cirrhosis[J]. Tunis Med, 2014, 92(10): 652-653
- [14] Chan A, Bazerbachi F, Hanson B, et al. Cytomegalovirus hepatitis and pancreatitis in the immunocompetent [J]. Ochsner J, 2014, 14(2): 295-299
- [15] Quigley G, Al Ani M, Nadir A. Occurrence of Jaundice Following Simultaneous Ursodeoxycholic Acid Cessation and Obeticholic Acid Initiation[J]. Dig Dis Sci, 2018, 63(2): 529-532
- [16] Harms MH, Lammers WJ, Thorburn D, et al. Major Hepatic Complications in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis: Risk Factors and Time Trends in Incidence and Outcome [J]. Am J Gastroenterol, 2018, 113 (2): 254-264
- [17] Di Guida F, Pirozzi C, Magliocca S, et al. Galactosylated Pro-Drug of Ursodeoxycholic Acid: Design, Synthesis, Characterization, and Pharmacological Effects in a Rat Model of Estrogen-Induced Cholestasis[J]. Mol Pharm, 2018, 15(1): 21-30
- [18] Alaca N, Özbeyli D, Uslu S, et al. Treatment with milk thistle extract (Silybum marianum), ursodeoxycholic acid, or their combination attenuates cholestatic liver injury in rats: Role of the hepatic stem cells[J]. Turk J Gastroenterol, 2017, 28(6): 476-484
- [19] Reig A, Sesé P, Parés A. Effects of Bezafibrate on Outcome and Pruritus in Primary Biliary Cholangitis With Suboptimal Ursodeoxycholic Acid Response [J]. Am J Gastroenterol, 2018, 113 (1): 49-55
- [20] Sombetzki M, Fuchs CD, Fickert P, et al. 24-nor-ursodeoxycholic acid ameliorates inflammatory response and liver fibrosis in a murine model of hepatic schistosomiasis[J]. J Hepatol, 2015, 62(4): 871-878
- [21] Wu X, Xu W, Feng X, et al. TNF- α mediated inflammatory macrophage polarization contributes to the pathogenesis of steroid-induced osteonecrosis in mice [J]. Int J Immunopathol Pharmacol, 2015, 28(3): 351-361
- [22] Wang Jie, Sun Hao-miao, Wang Hong-qing, et al. Serum IL-18 and TNF- α levels change before and after treatment in CMV hepatitis baby and its significance [J]. Anhui Medical Journal, 2015, 36(12): 1517-1519
- [23] Motawi T, Shaker OG, Hussein RM, et al. Polymorphisms of α 1-antitrypsin and Interleukin-6 genes and the progression of hepatic cirrhosis in patients with a hepatitis C virus infection [J]. Balkan J Med Genet, 2017, 19(2): 35-44
- [24] Chen Z, Li YX, Fu HJ, et al. Hepatitis B Virus Core Antigen Stimulates IL-6 Expression via p38, ERK and NF- κ B Pathways in Hepatocytes[J]. Cell Physiol Biochem, 2017, 41(1): 91-100
- [25] Schleker T, Jacobsen EM, Mayer B, et al. Preserved in vitro immunoreactivity in children receiving long-term immunosuppressive therapy due to inflammatory bowel disease or autoimmune hepatitis [J]. Mol Cell Pediatr, 2018, 5(1): 1
- [26] Li J, Yang C, Zhang S, et al. Ginsenoside Rg1 inhibits inflammatory responses via modulation of the nuclear factor- κ B pathway and inhibition of inflammasome activation in alcoholic hepatitis [J]. Int J Mol Med, 2018, 41(2): 899-907
- [27] Wang Z, Sheng L, Yang Y, et al. The Management of Autoimmune Hepatitis Patients with Decompensated Cirrhosis: Real-World Experience and a Comprehensive Review [J]. Clin Rev Allergy Immunol, 2017, 52(3): 424-435
- [28] Arain SQ, Talpur FN, Channa NA, et al. Serum lipids as an indicator for the alteration of liver function in patients with hepatitis B [J]. Lipids Health Dis, 2018, 17(1): 36
- [29] 赵攀, 熊艺茹, 陈婧, 等. 肝纤维化程度及自身抗体表达对熊去氧胆酸单药治疗自身免疫性肝病重叠综合征患者临床疗效的影响[J]. 现代生物医学进展, 2016, 16(8): 1521-1523
- Zhao Pan, Xiong Yi-ru, Chen Jing, et al. Impact of Fibrosis and Autoantibody on the Efficacy of Ursodeoxycholic Acid Monotherapy in Patients with Autoimmune Hepatitis and Primary Biliary Cirrhosis Overlap Syndrome[J]. Progress in Modern Biomedicine, 2016, 16(8): 1521-1523
- [30] Torisu Y, Nakano M, Takano K, et al. Clinical usefulness of ursodeoxycholic acid for Japanese patients with autoimmune hepatitis [J]. World J Hepatol, 2017, 9(1): 57-63