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丁二磺酸腺苷蛋氨酸联合熊去氧胆酸对妊娠期肝内胆汁淤积症患者肝功能及妊娠结局的影响*

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摘要 目的：探讨丁二磺酸腺苷蛋氨酸联合熊去氧胆酸对妊娠期肝内胆汁淤积症（ICP）患者肝功能及妊娠结局的影响。**方法**：选取2016年1月至2017年10月我院接诊的96例ICP患者，按照随机数字表法分为观察组和对照组，每组各48例，两组患者均给予常规基础治疗，对照组在此基础上给予熊去氧胆酸治疗，观察组在对照组基础上给予丁二磺酸腺苷蛋氨酸治疗，比较两组患者瘙痒、黄疸改善时间及治疗前后胆酸和肝功能指标检测结果，观察并对比两组母婴预后情况。**结果**：观察组瘙痒改善时间及黄疸改善时间均低于对照组（*P<0.05*）。两组患者治疗前总胆汁酸（TBA）、甘胆酸（CG）、谷丙转氨酶（ALT）、谷草转氨酶（AST）、总胆红素（TBiL）、直接胆红素（DBiL）水平对比差异无统计学意义（*P>0.05*）；两组患者治疗后TBA、CG、ALT、AST、TBiL、DBiL水平均低于治疗前，且观察组低于对照组（*P<0.05*）。观察组羊水污染、胎儿窘迫、早产、剖宫产及新生儿Apgar评分<7分发生率均低于对照组（*P<0.05*），两组患者产后出血、死胎发生率对比差异无统计学意义（*P>0.05*）。**结论**：丁二磺酸腺苷蛋氨酸联合熊去氧胆酸能够有效改善ICP症状和肝功能，降低不良母婴预后发生风险，可作为优选治疗方案。

关键词：妊娠期肝内胆汁淤积症；丁二磺酸腺苷蛋氨酸；熊去氧胆酸；肝功能；妊娠结局

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Effect of Ademetionine 1,4-Butane Disulfonate Combined with Ursodeoxycholic Acid on Liver Function and Pregnancy Outcome in Patients with Intrahepatic Cholestasis during Pregnancy*

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ABSTRACT Objective: To investigate the effect of ademetionine 1,4-Butane Disulfonate combined with ursodeoxycholic acid on liver function and pregnancy outcome in patients with intrahepatic cholestasis during pregnancy (ICP). **Methods:** A total of 96 patients with ICP, who were admitted to Panyu District Central Hospital of Guangzhou from January 2016 to October 2017, were selected and randomly divided into observation group (n=48) and control group (n=48). The patients in the two groups were given routine basic treatment, on the basis of which, the control group was given ursodeoxycholic acid, and the observation group was given ademetionine 1,4-Butane Disulfonate treatment on the basis of the control group's therapy. The improvement time of itching and jaundice and the results of bile acid and liver function indexes before and after treatment in the two groups were compared. The prognosis of maternal and infant in the two groups was observed and compared. **Results:** The improvement time of the itching and the jaundice in the observation group was less than that in the control group (*P<0.05*). There were no significant differences in the levels of total bile acids (TBA), glucocholic acid (CG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBiL) and direct bilirubin (DBiL) between the two groups before treatment (*P>0.05*). After treatment, the levels of TBA, CG, ALT, AST, TBiL and DBiL in the two groups were lower than those before treatment, and the observation group was lower than the control group (*P<0.05*). The incidence of amniotic fluid pollution, fetal distress, premature delivery, cesarean section and neonatal Apgar score <7 scores of the observation group were lower than those of the control group (*P <0.05*). There was no significant difference in the incidence of postpartum hemorrhage and stillbirth between the two groups (*P >0.05*). **Conclusion:** Ademetionine 1,4-butanedisulfonate combined with ursodeoxycholic acid can effectively improve the symptoms and liver function of ICP and reduce the risk of poor maternal and infant prognosis, which can be used as a preferred treatment plan.

Key words: Intrahepatic cholestasis of pregnancy; Ademetionine 1,4-Butane Disulfonate; Ursodeoxycholic acid; Liver function; Pregnancy outcome

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前言

妊娠期肝内胆汁淤积症(intrahepatic cholestasis of pregnancy,ICP)多发于妊娠中晚期,是一种严重影响围产儿预后的妊娠期并发症[1,2]。有研究显示,ICP 患者存在胆汁酸异常升高、肝功能受损等现象,若不能及时有效的治疗,则容易引发胎儿窘迫、早产,甚至死亡等现象[3,4]。ICP 患者主要表现为皮肤瘙痒、黄疸等症状,同时其转氨酶、血胆汁酸水平均异常升高,但关于其发病原因尚不十分清楚[5,6]。根据 ICP 病理变化,加强产前监护、适当的时候终止妊娠是改善预后的重要方案。熊去氧胆酸为有机化合物,是治疗 ICP 的常用药物,其主要功能是抑制血液与肝细胞中胆汁酸水平,改善胆汁淤积与肝功能,但其在改善围产儿预后方面仍有待提高[7,8]。因此,研究有效的治疗方案,从而改善 ICP 患者肝功能及妊娠结局具有重要意义。丁二磺酸腺苷蛋氨酸是人体组织和体液中普遍存在的一种生理活性分子,主要功能是防止胆汁淤积[9]。基于此,我院开展了熊去氧胆酸加用丁二磺酸腺苷蛋氨酸治疗 ICP,有效提升了 ICP 的治疗效果,并在改善母婴预后方面效果显著,现将其临床优势进行分析,报道如下。

1 资料与方法

1.1 一般资料

选取 2016 年 1 月至 2017 年 10 月我院接诊的 96 例 ICP 患者,纳入标准:(1)符合《妊娠期肝内胆汁淤积症诊疗指南》[10]中关于 ICP 相关诊断标准,经实验室检查总胆汁酸(total bile acid,TBA)、肝功能并结合临床表现确诊者;(2)均为初产妇;(3)均为单胎,胎位均为头位。排除标准:(1)合并患有其他妊娠期并发症者;(2)其他原因所致的皮肤瘙痒、TBA 异常升高者;(3)合并消化系统疾病或其他重要脏器功能异常者;(4)依从性差,无法配合完成本研究者。按照随机数字表法分为观察组和对照组,每组各 48 例,其中观察组年龄 21-35 岁,平均(27.26± 4.40)岁,病情:轻度(10 μmol/L<TBA<39 μmol/L)37 例、重度(TBA≥ 40 μmol/L)11 例;对照组年龄 22-38 岁,平均(26.83± 4.51)岁,病情:轻度 38 例、重度 10 例。两组患者的年龄、病情等基线资料比较无统计学意义(*P>0.05*),具有可比性。本研究经我院伦理委员会审核通过,患者及家属签署知情同意书。

1.2 方法

两组患者入院时均依据《妊娠期肝内胆汁淤积症诊疗指南》[10]给予常规基础治疗,包括高渗葡萄糖、吸氧、能量合剂、维生素等,治疗期间密切监控胎儿情况。

对照组在此基础上给予熊去氧胆酸(国药准字:H20150365;生产单位:德国霍克药厂)治疗,250 mg/ 次,3 次 /d,口服,连续治疗 20d。

观察组在对照组基础上给予丁二磺酸腺苷蛋氨酸注射液(国药准字:H20143203;生产单位:浙江震元制药有限公司)治疗,500 mg/ 次,1 次 /d,静滴,连续治疗 20d。

1.3 观察指标

比较两组患者症状(瘙痒、黄疸)改善时间,瘙痒改善判断依据:瘙痒间断发作或瘙痒难忍转变为偶有轻微瘙痒或瘙痒消失;黄疸改善判断依据:黄疸消退,皮肤颜色恢复正常。比较两组患者胆酸和肝功能指标检测结果,分别于治疗前、治疗 20d 后采集所有患者空腹静脉血 2 mL,37℃水浴 10 min,2000 r/min 离心 10 min,分离血清,待测。采用酶联免疫吸附法检测血清 TBA、甘胆酸(glucocholic acid,CG)水平,试剂盒购自盛世中方(北京)生物科技有限公司;采用比色法检测谷丙转氨酶(alanine transaminase,ALT)、谷草转氨酶(aspartate aminotransferase,AST)水平,试剂盒购自上海容创生物技术有限公司;采用钒酸盐氧化法检测总胆红素(total bilirubin,TBiL)、直接胆红素(direct bilirubin,DBiL)水平,试剂盒购自上海钰博生物科技有限公司。所有操作严格按照试剂盒说明书操作。观察并对比两组母婴预后情况,包括羊水污染、胎儿窘迫、早产、剖宫产、产后出血、死胎及新生儿阿普加(Apgar)评分 <7 分的发生率。

1.4 统计学方法

使用 SPSS 19.0 进行统计学处理,母婴预后等计数资料以百分率表示,组间比较用 x^2 检验,症状改善时间、胆酸及肝功能指标等计量资料以均数± 标准差表示,组间比较用 t 检验,检验标准设置为 α=0.05。

2 结果

2.1 两组患者症状改善时间

观察组瘙痒改善时间及黄疸改善时间均低于对照组(*P< 0.05*),见表 1。

表 1 两组症状改善时间比较(d,$\bar{x}\pm s$)

Table 1 Comparison of the symptom improvement time in two groups(d,$\bar{x}\pm s$)

Groups	n	Itching improvement time	Jaundice improvement time
Observation group	48	3.57± 0.86	13.22± 3.03
Control group	48	5.66± 1.13	21.65± 5.19
t		10.197	9.718
P		0.000	0.000

2.2 两组患者治疗前后胆酸及肝功能指标检测结果

两者患者治疗前 TBA、CG、ALT、AST、TBiL、DBiL 水平对比差异无统计学意义(*P>0.05*);两组患者治疗后 TBA、CG、ALT、AST、TBiL、DBiL 水平均低于治疗前,且观察组低于对照组(*P<0.05*),见表 2。

2.3 两组患者母婴预后情况对比

观察组羊水污染、胎儿窘迫、早产、剖宫产及新生儿 Apgar 评分 <7 分发生率均低于对照组(*P<0.05*),两组患者产后出血、死胎发生率对比差异无统计学意义(*P>0.05*)。见表 3。

表 2 两组胆酸及肝功能指标对比($\bar{x}\pm s$)

Table 2 Comparison of the cholic acid and liver function indexes between two groups($\bar{x}\pm s$)

Groups	Time	TBA(μmol/L)	CG(mg/L)	ALT(U/L)	AST(U/L)	TBiL(μmol/L)	DBiL(μmol/L)
Observation group(n=48)	Before treatment	38.75± 3.76	15.44± 2.77	122.65± 16.74	104.02± 14.73	17.14± 2.33	13.35± 1.08
	After treatment	10.84± 2.02△ *	4.77± 0.95△ *	49.45± 5.73△ *	40.28± 4.95△ *	6.95± 0.91△ *	4.01± 0.88△ *
Control group (n=48)	Before treatment	38.70± 3.69	15.41± 2.73	118.41± 17.05	104.11± 13.92	17.09± 2.15	13.29± 0.99
	After treatment	14.33± 3.17△	7.05± 1.10△	62.07± 8.80△	56.64± 7.07△	12.44± 1.26△	10.44± 1.03△

Note: compare with before treatment, △ $P<0.05$, compare with the control group, *$P<0.05$.

表 3 两组母婴预后情况对比[n(%)]

Table 3 Comparison of maternal and infant prognosis between two groups[n(%)]

Groups	n	Amniotic fluid pollution	Fetal distress	Premature	Caesarean	Postpartum hemorrhage	Stillbirth	Neonatal Apgar score <7 scores
Observation group	48	2(4.17)	2(4.17)	3(6.25)	6(12.50)	0(0.00)	0(0.00)	2(4.17)
Control group	48	8(16.67)	8(16.67)	10(20.83)	15(31.25)	1(2.08)	1(2.08)	9(18.75)
x^2		4.019	4.019	4.360	4.937	1.011	1.011	5.031
P		0.045	0.045	0.037	0.026	0.315	0.315	0.025

3 讨论

我国 ICP 发病率较高,且呈一定地域性,发病率最高的地区约为 12%左右[11]。ICP 发病机制复杂,目前尚无明确研究结果,但大多数学者认为主要和妊娠期性激素水平的改变、遗传有关[12]。ICP 症状十分典型,患者在妊娠中晚期出现明显的瘙痒以及胆汁酸与肝酶异常升高现象,通过胆汁酸检测与肝功能检查即可确诊,一般在分娩后可快速恢复,并不会影响母体健康[13]。但有文献报道指出[14],ICP 对胎儿危害较大,使围产儿发病率和死亡率增高,因此需要及时采取治疗干预控制相关指标的异常改变。临床研究也表明[15,16],ICP 发病后胎盘绒毛膜侧会出现胆汁沉降,导致滋养细胞分裂增长速度加快,造成绒毛间隙变小影响胎儿血供,最终引发胎儿缺氧甚至胎心骤停等不良情况的发生。国外有关文献报道也证实[17-19],ICP 患者胎儿窘迫、早产、新生儿窒息的发生风险较普通孕妇显著升高,且新生儿 Apgar 评分也会出现明显降低,严重影响围产儿预后。因此,及时进行药物治疗,控制胆酸和肝功能异常对改善母婴预后具有重要意义。

本研究结果显示,观察组瘙痒改善时间及黄疸改善时间均低于对照组($P<0.05$),说明丁二磺酸腺苷蛋氨酸与熊去氧胆酸有一定协同作用,二者联用可明显提升对 ICP 的治疗效果。分析其原因,主要是丁二磺酸腺苷蛋氨酸为甲基供体和生理性巯基化合物的前体,其可增强 Na^+-K^+-ATP 酶活性,调节胆汁分泌和运转,还可以合成生物多胺,调控肝细胞再生、增殖,加快肝功能修复[20-22]。丁二磺酸腺苷蛋氨酸治疗 ICP 能够抑制雌激素对胆盐、胆汁等代谢的影响,从而改善患者胆汁淤积情况,同时能够改善肝酶水平,保护肝功能,用药后短期间患者瘙痒等症状得到显著改善,达到较好的治疗效果[23,24]。此外,两组患者治疗后 TBA、CG、ALT、AST、TBiL、DBiL 水平均低于治疗前,且观察组低于对照组($P<0.05$),由此可见,丁二磺酸腺苷蛋氨酸联合熊去氧胆酸可改善 ICP 患者肝功能,因为熊去氧胆酸无药物毒性,能够通过促进内源性胆汁酸分泌抑制血液和肝细胞中胆酸水平升高和肠道对内源性胆酸的重吸收,改善胆汁淤积状态,对 ICP 疗效显著[25-27]。本研究结果还显示,观察组羊水污染、胎儿窘迫、早产、剖宫产及新生儿 Apgar 评分 <7 分发生率均低于对照组($P<0.05$),因为熊去氧胆酸属于亲水性二羟基胆酸化合物,能够保护肝脏、发挥疏水性胆汁酸替代作用,改善母婴跨滋养层胆汁酸转运功能,对缓解患者症状和改善围产儿预后有确切效果[28,29]。也有研究显示[30],熊去氧胆酸还有一定抗氧化应激和细胞凋亡作用,与传统的地塞米松、磷酸肌酸钠等方案相比疗效更稳定且副作用更低,证实了熊去氧胆酸的确切效果。

综上所述,与单用熊去氧胆酸相比,联合应用丁二磺酸腺苷蛋氨酸治疗 ICP 能够降低瘙痒缓解时间和黄疸消退时间,改善患者 TBA、CG、ALT、AST、TBiL、DBiL 水平,降低羊水污染、胎儿窘迫、早产、剖宫产及新生儿 Apgar 评分 <7 分的发生率,临床上可考虑将两种药物联合应用治疗 ICP。

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