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熊去氧胆酸联用思美泰对妊娠期肝内胆汁淤积症重症患者瘙痒程度、妊娠结局及肝功能的影响 *

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摘要 目的:探讨熊去氧胆酸联用思美泰对妊娠期肝内胆汁淤积症(ICP)重症患者瘙痒程度、妊娠结局及肝功能的影响。**方法:**选取2016年6月到2017年12月期间在我院接受治疗的ICP重症患者76例,根据随机数字表法将患者均分为研究组(n=38)和对照组(n=38)。对照组采用熊去氧胆酸进行治疗,研究组采用熊去氧胆酸联用思美泰进行治疗。比较两组患者治疗前、治疗7d后的Ribaha皮肤瘙痒程度评分、天冬氨酸氨基转移酶(AST)、丙氨酸氨基转移酶(ALT)、总胆汁酸(TBA)、血清总胆红素(TB)的水平,比较两组患者的妊娠结局。**结果:**治疗7d后两组患者的瘙痒程度评分均明显降低,且研究组低于对照组($P<0.05$)。治疗7d后两组患者的AST、ALT、TBA、TB水平均明显降低,且研究组患者的AST、ALT、TBA、TB水平低于对照组,差异有统计学意义($P<0.05$)。两组患者的新生儿窒息发生率和新生儿体质量比较无统计学差异($P>0.05$),研究组患者早产、胎儿窘迫、羊水胎粪污染的发生率低于对照组,差异有统计学意义($P<0.05$)。**结论:**熊去氧胆酸联用思美泰可有效缓解ICP重症患者的瘙痒程度,改善肝功能和妊娠结局,临床疗效显著,具有积极的临床意义。

关键词:妊娠期肝内胆汁淤积症;熊去氧胆酸;思美泰;瘙痒程度;妊娠结局;肝功能

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The Effects of Ursodeoxycholic Acid Combined with Transmetil on Pruritus, Pregnancy Outcome and Liver Function in Patients with Severe Intrahepatic Cholestasis of Pregnancy*

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ABSTRACT Objective: To investigate the effects of ursodeoxycholic acid combined with transmetil on the itching degree, pregnancy outcome and liver function in patients with severe intrahepatic cholestasis of pregnancy (ICP). **Methods:** 76 patients with severe ICP who were treated in our hospital from June 2016 to December 2017 were enrolled. The patients were divided into study group (n=38) and control group (n=38) according to the random number table method. The control group was treated with ursodeoxycholic acid, and the study group was treated with ursodeoxycholic acid combined with transmetil. The levels of Ribaha skin itching degree score, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bile acid (TBA), serum total bilirubin (TB) before treatment and 7 days after treatment were compared between the two groups. The pregnancy outcomes of the two groups were compared. **Results:** 7 days after treatment, the itching degree scores of the two groups were significantly lower, and the study group was lower than that of the control group ($P<0.05$). 7 days after treatment, the levels of AST, ALT, TBA and TB in the two groups were significantly lower, and the levels of AST, ALT, TBA and TB in the study group were lower than those in the control group, the difference was statistically significant ($P<0.05$). There was no significant difference between the two groups in the incidence of neonatal asphyxia and neonatal body mass ($P>0.05$). The incidence of premature labor, fetal distress and meconium stained amniotic fluid in the study group were lower than those in the control group, and the difference was statistically significant ($P<0.05$). **Conclusion:** The ursodeoxycholic acid combined with transmetil can effectively relieve itching degree in patients with severe ICP, and it can improve liver function and pregnancy outcomes, the clinical effect is significant, it has positive clinical significance.

Key words: Intrahepatic cholestasis of pregnancy; Ursodeoxycholic acid; Transmetil; Itching degree; Pregnancy outcome; Liver function

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前言

妊娠期肝内胆汁淤积症(Intrahepatic cholestasis of pregnancy, ICP)是妊娠中晚期的并发症之一,患者主要表现为皮肤瘙痒和黄疸,且临床检验通常伴有胆汁酸升高以及肝功能生化指标异常^[1,2]。ICP对胎儿有严重的影响,可导致胎儿窘迫、胎儿早产、羊水胎粪污染等,尤其是ICP重症患者对胎儿的影响极大,可明显增加胎儿的发病率和死亡率^[3,5],因此探究有效的治疗方法具有重要的临床意义。熊去氧胆酸是一种非细胞毒性二羟胆酸,英国皇家妇产科医师学会指南中指出熊去氧胆酸可有效改善ICP患者的瘙痒症状和肝功能,是临床治疗ICP的一线用药^[6]。腺苷蛋氨酸商品名为思美泰,是一种参与甲基转移的辅助底物,为临床治疗ICP的二线用药或联合治疗药物^[7,9]。本研究旨在探讨熊去氧胆酸联用思美泰对ICP重症患者瘙痒程度、妊娠结局及肝功能的影响,以为临床治疗ICP重症患者提供参考。

1 资料与方法

表1 两组患者一般资料比较($\bar{x} \pm s$)

Table 1 Comparison of general information between the two groups of patients($\bar{x} \pm s$)

Groups	n	Ages (year)	Body mass(kg)	Gestational weeks (weeks)	Pregnancies (times)
Control group	38	28.94± 5.21	53.42± 6.87	32.16± 1.14	1.46± 0.38
Study group	38	27.68± 5.39	51.58± 6.45	32.57± 1.08	1.57± 0.42
t		1.036	1.204	0.847	1.197
P		0.304	0.233	0.400	0.235

1.2 治疗方法

两组患者均给予基础治疗,包括补液、营养支持,且进行低脂饮食,叮嘱患者注意休息,必要时吸氧。对照组在此基础上采用熊去氧胆酸片(沈阳东昂制药有限公司,国药准字H21021236,规格:50 mg)进行治疗,口服,250 mg/次,2次/d。研究组在对照组的基础上联用思美泰(浙江震元制药有限公司,国药准字H20143203,规格:500 mg)进行治疗,将1000 mg思美泰与500 mL 5%的葡萄糖溶液混合,静脉滴注,1次/d。两组均以7 d为1个疗程,一直持续治疗到分娩为止。

1.3 观察指标

在治疗前、治疗7 d后采用Ribaha皮肤瘙痒程度评分标准评价两组患者的瘙痒程度^[10],若患者无瘙痒则得0分;若患者感觉偶尔瘙痒则得1分;若患者出现间断性瘙痒,且无症状波动,则得2分;若患者出现间断性瘙痒,且有症状波动,则得3分;若患者出现持续性瘙痒则得4分。在治疗前、治疗7 d后抽

1.1 临床资料

选取我院于2016年6月至2017年12月期间收治的ICP重症患者76例,纳入标准:(1)所有患者均符合《妇产科学》第8版中关于ICP的诊断标准^[10],且均为重症患者,即发病时孕周不足34周或入院治疗时病程≥3周,且总胆汁酸(Total bile acid, TBA)≥50 μmol/L,直接胆红素≥6 μmol/L,血清总胆红素(Serum total bilirubin, TB)≥21 μmol/L,天冬氨酸氨基转移酶(Aspartate aminotransferase, AST)≥200 U/L,丙氨酸氨基转移酶(Alanine aminotransferase, ALT)≥200 U/L。(2)未合并其他妊娠期并发症;(3)均为单胎妊娠;(4)患者及其家属均已知晓本次研究,且已在知情同意书上签字。排除标准:(1)合并严重器质性疾病以及肝脏疾病者;(2)合并恶性肿瘤者;(3)高龄产妇;(4)入院前接受过药物治疗者;(5)入院时孕周已足37周,且存在胎动异常、羊水过少的现象的ICP重症患者。根据随机数字表法将患者均分为研究组(n=38)和对照组(n=38)。纳入病例基线资料比较无差异($P>0.05$),见表1。本研究已通过我院伦理委员会的审核。

取两组患者的空腹静脉血4 mL,室温下静置30 min,3000 r/min离心10 min,提取血清,采用全自动生化分析仪(日本Olympus,型号:AU5400)检测AST、ALT、TBA、TB的水平。观察两组患者的妊娠结局,包括早产、胎儿窘迫、羊水胎粪污染、新生儿窒息、新生儿体质量等。

1.4 统计学方法

采用SPSS20.0进行数据分析,以率的形式表示计数资料,进行卡方检验,以均值±标准差的形式表示计量资料,进行t检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组瘙痒程度比较

治疗前两组瘙痒程度评分比较无差异($P>0.05$),治疗7 d后两组瘙痒程度评分均明显降低,且研究组于对照组($P<0.05$),见表2。

表2 两组患者Ribaha皮肤瘙痒程度评分比较($\bar{x} \pm s$)

Table 2 Comparison of Ribaha skin itching degree scores between the two groups of patients($\bar{x} \pm s$)

Groups	n	Ribaha skin itching degree scores(score)	
		Before treatment	7 days after treatment
Control group	38	3.24± 0.58	1.02± 0.54 [#]
Study group	38	3.31± 0.62	0.63± 0.45 [#]
t		0.508	3.420
P		0.613	0.001

Note: compared with before treatment, [#] $P<0.05$.

2.2 两组肝功能指标比较

两组治疗前 AST、ALT、TBA、TB 水平比较无差异 ($P>0.05$), 治疗 7d 后两组患者的 AST、ALT、TBA、TB 水平均明显

降低, 且研究组患者的 AST、ALT、TBA、TB 水平低于对照组, 差异有统计学意义 ($P<0.05$), 见表 3。

表 3 两组患者肝功能指标比较($\bar{x}\pm s$)

Table 3 Comparison of liver function indexes between the two groups($\bar{x}\pm s$)

Groups	n	AST(U/L)		ALT(U/L)		TBA(μ mol/L)		TB(μ mol/L)	
		Before treatment	7 days after treatment	Before treatment	7 days after treatment	Before treatment	7 days after treatment	Before treatment	7 days after treatment
Control group	38	312.26 $\pm$ 103.58	131.02 $\pm$ 32.58 [#]	323.73 $\pm$ 113.25	143.26 $\pm$ 29.57 [#]	73.21 $\pm$ 20.14	42.12 $\pm$ 10.36 [#]	36.27 $\pm$ 9.98	22.62 $\pm$ 6.43 [#]
Study group	38	301.31 $\pm$ 98.65	97.25 $\pm$ 28.67 [#]	312.58 $\pm$ 109.54	101.26 $\pm$ 30.25 [#]	70.06 $\pm$ 19.68	31.08 $\pm$ 9.65 [#]	35.18 $\pm$ 9.65	18.54 $\pm$ 5.48 [#]
t		0.472	4.797	0.436	6.120	0.690	4.807	0.484	2.977
P		0.638	0.000	0.664	0.000	0.493	0.000	0.630	0.004

Note: compared with before treatment, [#] $P<0.05$.

2.3 两组患者妊娠结局的比较

两组患者的新生儿窒息发生率和新生儿体质量比较无统

计学差异 ($P>0.05$), 研究组患者早产、胎儿窘迫、羊水胎粪污染的发生率低于对照组, 差异有统计学意义 ($P<0.05$), 见表 4。

表 4 两组患者妊娠结局的比较

Table 4 Comparison of pregnancy outcomes between the two groups of patients

Groups	n	Incidence rate[n(%)]				Neonatal body mass (kg)
		Premature labor	Fetal distress	Meconium stained amniotic fluid	Neonatal asphyxia	
Control group	38	8(21.05)	10(26.32)	13(34.21)	3(7.89)	3.11 $\pm$ 0.56
Study group	38	2(5.26)	3(7.89)	5(13.16)	1(2.63)	3.26 $\pm$ 0.48
χ^2/t		4.145	4.547	4.659	0.264	1.254
P		0.042	0.033	0.031	0.607	0.214

3 讨论

ICP 的首发症状为无皮肤损伤的瘙痒, 通常患者手掌和脚掌先出现瘙痒感, 之后会慢慢向肢体近端延伸, 瘙痒严重者甚至可发展到面部, 并且患者的瘙痒感白昼轻、夜间剧烈, 严重影响患者的日常生活^[12-14]。目前 ICP 的具体发病机制尚不明确, 但已证明与妊娠期孕妇体内雌激素水平明显升高有关, 雌激素水平升高可导致 $\text{Na}^+\text{-K}^+\text{-ATP}$ 酶的活性下降, 进而影响能量供给, 导致胆酸代谢障碍, 雌激素还可通过与肝细胞表面的雌激素受体相结合来影响肝细胞蛋白质合成, 造成胆汁回流, 进而导致肝小叶内胆汁淤积, 影响患者肝功能^[15-17]。ICP 最严重的危害是其会对胎儿的生长、发育造成严重的影响, 尤其是 ICP 重症患者, 胆汁酸水平过高会导致胎儿类固醇物质代谢出现障碍, 造成脱氢表雄酮高表达, 通过胎盘形成大量的雌二醇, 进而诱发早产^[18-20]; 此外 ICP 可导致胎盘滋养细胞肿胀、绒毛间质水肿, 进而造成绒毛间腔狭窄, 影响胎儿与母体之间的血流交换, 进而影响胎儿的生长、发育^[21-23]; 另一方面, 高浓度的胆汁酸会刺激胎儿的结肠运动, 促进胎儿排出胎粪, 增加羊水胎粪污染的概率^[24]。因此, 临床在治疗 ICP 重症患者时的主要思路就是改善患者的瘙痒症状和肝功能, 避免不良妊娠结局。

熊去氧胆酸是一种无毒性的亲水胆酸, 可通过以下几点治

疗 ICP^[25-27]: (1) 能竞争性地抑制回肠吸收毒性内源性胆酸; (2) 拮抗疏水性胆汁酸的细胞毒性, 进而起到保护细胞和细胞膜的作用; (3) 抑制毒性胆酸引起的枯否细胞激活, 降低肝细胞的氧化损伤; (4) 有效缓解胎盘绒毛胆汁淤积状态, 改善胎儿环境。腺苷蛋氨酸可通过转巯基反应促进胆酸的硫酸化, 有效降低血中胆酸的水平, 并且腺苷蛋氨酸经甲基化作用可灭活儿茶酚雌激素, 进而改善雌激素水平过高造成的不良影响, 恢复 $\text{Na}^+\text{-K}^+\text{-ATP}$ 酶的活性, 进而防止肝内胆汁淤积^[28,29]。由于熊去氧胆酸和思美泰治疗 ICP 的作用机制不同, 这为两种药物联合治疗 ICP 提供了可能。本研究结果显示, 治疗 7d 后两组瘙痒程度评分均明显降低, 且研究组低于对照组 ($P<0.05$), 治疗 7d 后两组患者的 AST、ALT、TBA、TB 水平均明显降低, 且研究组患者的 AST、ALT、TBA、TB 水平低于对照组 ($P<0.05$), 说明熊去氧胆酸联用思美泰可有效改善 ICP 重症患者的瘙痒症状和肝功能。周凡等人的研究显示^[30], 熊去氧胆酸联用腺苷蛋氨酸治疗 ICP 的疗效优于单独使用熊去氧胆酸治疗, 与本研究结果一致。在妊娠结局方面, 研究组患者早产、胎儿窘迫、羊水胎粪污染的发生率低于对照组 ($P<0.05$), 提示熊去氧胆酸联用思美泰可有效改善 ICP 重症患者的不良妊娠结局, 这可能与两种药物联合可有效降低 TBA 水平有关, 进而有效降低了高浓度的 TBA 对胎儿生长、发育的影响。

综上所述,熊去氧胆酸联用思美泰治疗 ICP 重症患者可有效缓解患者的瘙痒程度,改善肝功能,减少不良妊娠结局的发生率,临床疗效优于熊去氧胆酸单独治疗,然而本研究由于选取的病例数过少仍存在一定的局限性,熊去氧胆酸联用思美泰治疗 ICP 重症患者的有效性和安全性还有待更大样本量的研究进行验证。

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