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抗病毒治疗乙型肝炎相关慢加急性肝衰竭患者的临床研究

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摘要 目的:探讨抗病毒治疗乙型肝炎相关慢加急性肝衰竭(acute on chronic liver failure,ACLF)的临床意义。**方法:**回顾性分析2007年8月~2013年8月我院收治的乙型肝炎相关慢加急性肝衰竭的住院患者80例，按照患者有无接受抗病毒治疗分为抗病毒治疗组(A组)50例和未抗病毒治疗组(B组)30例,分析患者接受治疗后的近期与远期疗效、并发症及生存率。**结果:**①出院时A组好转率70%;B组好转率33.3%。两组比较差异有统计学意义（x^2=10.243,P=0.001＜0.05)。②治疗14周后A组乙肝病毒DNA阴转率72%;B组阴转率30%,两组比较差异有统计学意义(x^2=13.440,P=0.000＜0.05)。③A组出现细菌感染45例,电解质紊乱41例,消化道出血5例,肝性脑病10例,肝肾综合征10例,B组出现细菌感染30例,电解质紊乱27例,消化道出血6例,肝性脑病10例,肝肾综合征12例,两组比较差异无统计学意义(x^2=2.755,P=0.097＞0.05)。④随访5年,A组存活36例,死亡14例,12、36和60个月累积生存率分别为78.5%、71.2%、71.2%,B组存活5例，死亡25例,12、36和60个月累积生存率分别为35.4%、27.5%、27.5%,两组比较差异有统计学意义(P＜0.05)。**结论:**对乙型肝炎相关慢加急性肝衰竭患者给予抗病毒治疗可明显改善预后,提高生存率。

关键词:乙型肝炎相关慢加急性肝衰竭;乙型肝炎病毒;拉米夫定;恩替卡韦

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Clinical Studies on Anti-viral Therapy for the Hepatitis B Patients with Acute on Chronic Liver Failure

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ABSTRACT Objective: To explore the clinical significance of anti-viral therapy for the hepatitis B patients with acute on chronic liver failure. **Methods:** 80 cases of hepatitis B patients with acute on chronic liver failure in our hospital from August 2007 to August 2013 were selected for retrospective analysis, and were divided into antiviral treatment group (group A of 50 cases) and non-antiretroviral treatment group (group B of 30 cases). Recent and long-term efficacy, complications and survival rates and other indicators were analyzed after treatment. **Result:** ①The improvement rate of Group A was 70%, while 33.3% for Group B ,the difference was statistically significant x^2 = 10.243, P= 0.001＜0.05). ② The HBV DNA negative rate of group A after 14 weeks of treatment was 72%, while 30% for Group B, the difference was statistically significant (x^2= 13.440, P=0.000＜0.05). ③ In group A, there were 45 cases of bacterial infection, 41 cases of electrolyte disorder, 5 cases of gastrointestinal bleeding in, 10 cases of hepatic encephalopathy, while group B had 10 cases of hepatorenal syndrome, 30 cases of bacterial infections, 27 cases of electrolyte disorder, 6 cases of gastrointestinal bleeding, 10 cases of hepatic encephalopathy, 12 cases of hepatorenal syndrome, the difference was not statistically significant (x^2= 2.755, P= 0.097 > 0.05). ④Follow-up of 5 years showed that 36 cases survived in group A while 14 cases died, the cumulative survival rates at 12, 36 and 60 month were 78.5%, 71.2%, 71.2% respectively ; There were 5 cases of surviving in group B and 25 cases of death, the cumulative survival rates at 12, 36 and 60 month was 35.4%, 27.5%, 27.5%, the difference was statistically significant (P<0.05). **Conclusion:** Anti-viral therapy can significantly improve the prognosis and survival rate in hepatitis B patients with acute on chronic liver failure.

Key words: Hepatitis B combined with acute on chronic liver failure; Hepatitis B virus; Lamivudine; Entecavir

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前言

慢加急性肝衰竭临床表现包括凝血机制障碍、肝性脑病、黄疸、腹水等,是在慢性肝病为基础上发生的急性或亚急性肝功能失代偿，在我国乙型肝炎病毒感染是本病的主要病因[1,2]。乙型肝炎相关慢加急性肝衰竭病情进展快,病死率高,预后不良,临床上为最大程度降低并发症发生率,提高患者生存率,多采取内科治疗基础上予抗病毒治疗的原则[3]。为此,本文着重研究抗病毒治疗乙型肝炎相关慢加急性肝衰竭患者的临床疗效,现报道如下。

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1 资料和方法

1.1 一般资料

病例为 2007 年 8 月 ~2013 年 8 月我院消化内科收治的确诊为乙型肝炎相关慢加急性肝衰竭的住院患者 80 例，所有患者诊断均符合《肝衰竭诊疗指南》(2006 年中华医学会制定)。其中男 54 例,女 26 例,年龄 19~70 岁,平均 46.8 ± 2.1 岁。根据患者有无接受抗病毒治疗分为抗病毒治疗组(A 组)和未抗病毒治疗组(B 组),其中 A 组 50 例,B 组 30 例。A 组中 HBeAg 阳性 28 例和阴性 22 例;B 组中 HBeAg 阳性 16 例和阴性 14 例。两组患者治疗初期各指标比较，差异无统计学意义（均 P＞0.05),见表 1。

表 1 两组患者治疗初期各指标比较

Table 1 Comparison of indexes of early treatment between two groups

指标 Indexes	A 组(n=50) Group A(n=50)	B 组(n=30) Group B(n=30)	T/x^2	P
年龄(岁) Age(years)	45.2± 1.8	45.9± 2.2	1.548	0.126
HBeAg 阳性(n)HBeAg Positive(n)	27	16	0.003	0.954
ALT(U/L)	601.3± 654.7	367.2± 714.6	1.496	0.138
TBil(μmol/L)	226.7± 141.2	265.4± 129.3	1.224	0.225
PTA(%)	44.1± 18.2	44.5± 19.1	0.093	0.925

1.2 治疗方法

两组患者均接受常规保肝支持治疗,A 组患者在常规治疗基础上由主管医生依照患者病情及个人意愿进行个体化选择抗病毒药物,用药种类包括拉米夫定(20 例,口服,0.1g/ 次,1 次 /d，国药准字 H20030581，由葛兰素史克制药有限公司生产)、恩替卡韦（18 例，口服,0.5g/ 次,1 次 /d，国药准字 H20052237,由中美上海施贵宝制药有限公司生产)、替比夫定(10 例,口服,0.6 g/ 次,1 次 /d,国药准字 H20070028,由北京诺华制药有限公司生产)及拉米夫定联合阿德福韦酯(2 例,拉米夫定同上，阿德福韦酯片，口服,10 mg/ 次,1 次 /d，国药准字 H20080365,由江苏天士力帝益药业有限公司生产)。对两组患者入院后病历资料及随访 5 年内的病情变化资料进行记录并观察。

1.3 观察指标及疗效判定

观察指标包括患者接受治疗后的谷丙转氨酶(ALT)、谷草转氨酶(AST)、总胆红素(TBil)及凝血酶原活动度(PTA),试剂盒均由由上海实业科华公司生产，另外观察近期与远期疗效、并发症及生存率等,疗效判定参照中华传染病与寄生虫病学会人工肝学组指定的《人工肝支持系统的适应症、禁忌症及疗效判断标准》。

1.4 统计方法

采用 SPSS13.0 统计软件进行数据分析，计量资料采用均数 ± 标准差($\bar{x} \pm s$)表示,计量资料比较采用 t 检验,计数资料比较采用 x^2 检验,非正态分布则采用秩和检验,生存率分析采用 Log-Rank 检验。以 P＜0.05 认为差异有统计学意义。

2 结果

2.1 两组患者近期疗效比较

2.1.1 出院时好转率比较 两组患者入院时均存在不同程度的乏力、纳差、腹胀等表现,出院时 A 组临床症状明显好转者 35 例,好转率 70%;B 组好转 10 例,好转率 33.3%,两组比较差异有统计学意义(x^2=10.243,P=0.001)。

2.1.2 生化指标变化趋势比较 两组患者在治疗 4 周时均有“胆酶分离”,其中在 2 周前 A 组和 B 组均表现为 ALT、AST 下降较快,TBil 上升较快,PTA 上升较慢,2 周后 A 组 PTA 上升变快,ALT、AST 下降变慢，TBil 上升变慢,B 组 PTA 上升变快，ALT 下降变慢,而 AST 则上升,TBil 上升加快。见图 1-3。

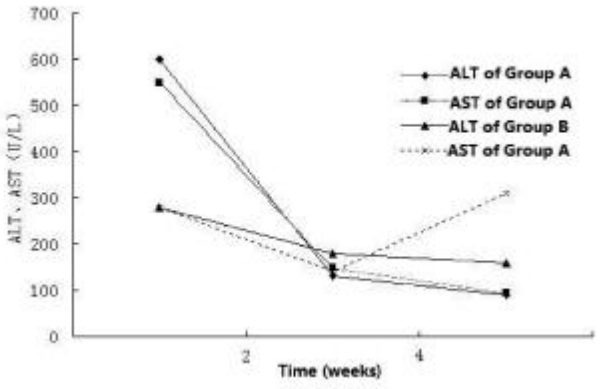

图 1 两组患者 ALT 与 AST 变化趋势图

Fig. 1 ALT and AST trend chart between two groups

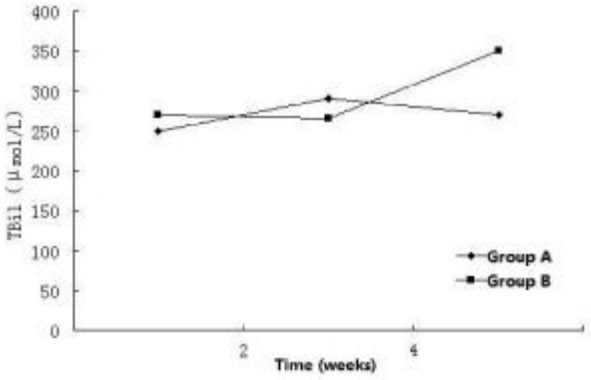

图 2 两组患者 TBil 变化趋势图

Fig. 2 TBil trend chart between two groups

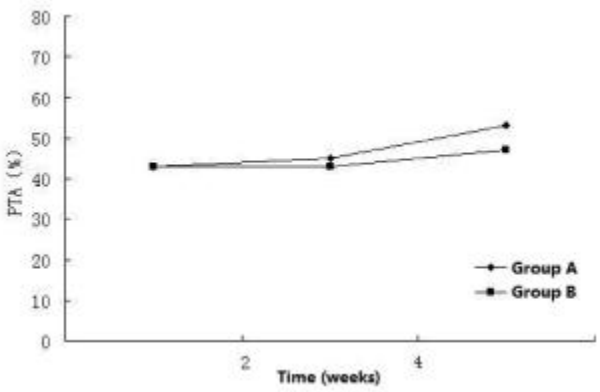

图 3 两组患者 PTA 变化趋势图

Fig. 3 PTA trend chart between two groups

2.2 两组患者远期疗效比较

2.2.1 病毒学指标比较 治疗 14 周后 A 组乙肝病毒 DNA 转阴 36 例，阴转率 72%；B 组乙肝病毒 DNA 转阴 9 例，阴转率 30%。两组比较差异有统计学意义(x^2=13.440，P=0.000)。24 周内 HBeAg 阳性转阴者 20 例，B 组则无转阴病例。

2.2.2 并发症比较 A 组出现细菌感染 45 例，电解质紊乱 41 例，消化道出血 5 例，肝性脑病 10 例，肝肾综合征 10 例；B 组出现细菌感染 30 例，电解质紊乱 27 例，消化道出血 6 例，肝性脑病 10 例，肝肾综合征 12 例，经统计分析，两组比较差异无统计学意义(x^2=2.755，P=0.097)。

2.2.3 疾病转归及生存率比较 随访 5 年，A 组存活 36 例，死亡 14 例，12、36 和 60 个月累积生存率分别为 78.5%、71.2%、71.2%，B 组存活 5 例，死亡 25 例，12、36 和 60 个月累积生存率分别为 35.4%、27.5%、27.5%，两组比较差异有统计学意义(P<0.05)，见图 4。

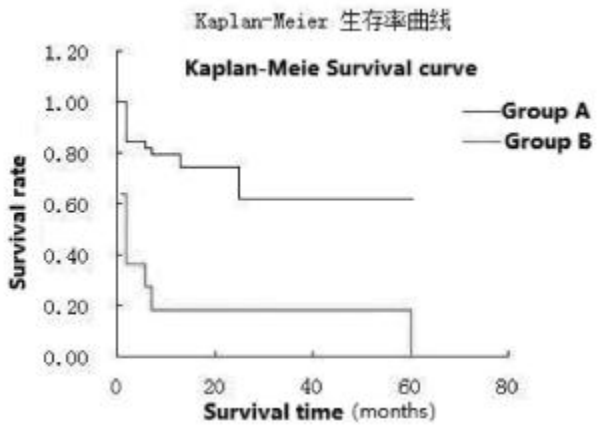

图 4 生存率曲线

Fig. 4 Survival rate curve

3 讨论

乙型肝炎相关慢加急性肝衰竭的发病机制目前仍不甚明朗，但学者普遍认为乙型肝炎感染所引起的肝细胞免疫病理损伤[4-8]及 T 淋巴细胞毒性反应所生成的炎性因子[9-11]是造成急性肝损伤的直接原因，而经循环途径内毒素导致的中性粒细胞障碍则是致肝损害的次要原因，在双重毒性作用下，多器官功能衰竭、肝脏再生能力下降、败血症等病症接踵而至。由此可推断，乙型肝炎病毒感染是乙型肝炎相关慢加急性肝衰竭发生发展的主要原因[12-14]。对本病的治疗，多数研究认为可给予抗病毒治疗已达到尽快恢复肝功能，避免肝衰竭的目的[15]。如某研究发现通过对乙型肝炎相关慢加急性肝衰竭患者给予拉米夫定抗病毒治疗后，17 例患者中有 14 例恢复了肝功能，避免了肝移植手术[16]。这主要是因为拉米夫定或其他抗病毒药物可快速抑制乙肝病毒的复制，阻止损伤面积的继续扩大，从而达到提高短期存活率，并有效降低了复发率[17,18]。不过对此学术界并未达成广泛共识，有报道指出给予恩替卡韦抗病毒治疗同对照组之间在短期疗效上并无显著性差异，且即便短期能够抑制乙肝病毒复制，仍可能不会阻止肝功能衰竭的进程[19]。

本组研究中发现，抗病毒治疗在短期与长期疗效上均有较大价值，相比未接受抗病毒治疗的患者，疗效及转归更好。在早期治疗过程中肝细胞难免要受到乙肝病毒的持久性破坏，故经过一段时间抗病毒治疗方可起效，而远期 DNA 阴转率及生存率比较显示，相比对照组明显较高，与既往研究结果类似[20]。由此可见通过抗病毒治疗可明显降低患者多种死亡风险因素发生的可能，改善预后，提高生存率。

总之，通过我们的研究可认为对乙型肝炎相关慢加急性肝衰竭患者给予抗病毒治疗可明显改善预后，提高生存率，且使用安全，在考虑治疗本病时可以将此作为首选。

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