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不同剂量易善复治疗肝硬化的疗效及安全性研究

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摘要 目的:探讨不同剂量的多烯磷脂酰胆碱(易善复)对肝硬化的治疗效果及其安全性。**方法:**以 2016 年 ~2017 年在我院就诊的 70 例单纯肝炎后肝硬化(VC)和酒精性肝硬化(AC)患者为研究对象,采用随机数字表法将其随机分为小剂量组和大剂量组,每组 35 例。小剂量组予易善复 10 mL+5%葡萄糖注射液 250 mL 静滴,大剂量组予易善复 20 mL+5%葡萄糖注射液 250 mL 静滴。观察两组治疗前后临床症状、血尿常规、肾功能、肝功能指标、腹腔彩超的变化情况。结果:两组患者治疗后肝功能指标谷丙转氨酶(ALT)、白蛋白(ALB)、总胆红素(TBIL)、谷草转氨酶(AST)、碱性磷酸酶(ALP)均较治疗前明显改善(P<0.05),且大剂量组各项指标水平均明显优于小剂量组(P<0.05);大剂量组治疗肝硬化的总有效率为 88.6%,显著高于小剂量组的(68.6%,P<0.05)。两组治疗过程中均未见明显药物副反应。**结论:**与小剂量易善复相比,大剂量易善复更能改善单纯肝炎后肝硬化和酒精性肝硬化患者的肝功能,提高药物疗效的同时不增加药物副反应,安全性高。

关键词:易善复;肝硬化;不同剂量;肝功能

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Research on the Efficacy and Safety of Different Doses of Essentiale in the Treatment of Liver Cirrhosis

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ABSTRACT Objective: To explore the efficacy and safety of different doses of Essentiale for patients with liver cirrhosis. **Methods:** 70 cases patients with viral cirrhosis (VC) and alcoholic cirrhosis (AC) treated in our hospital from 2106 to 2107 were selected and randomly divided into two groups (low dose group and high dose group), 35 cases in each group. The low dose group was given Essentiale 10 mL+5% Glucose Injection 250 mL, and the high dose group was given Essentiale 20 mL+5% Glucose Injection 250 mL. The clinical symptoms, blood routine, renal function, liver function and color Doppler ultrasound were observed and compared between two groups before and after treatment. **Results:** Compared with before treatment, the hepatic function index including alanine amino transferase (ALT), albumin (ALB), total bilirubin (TBIL), aspartate amino transferase (AST), alkaline phosphatase (ALP) were significantly improved in both groups of patients after treatment (P<0.05). And the level of indicators in high dose group were obviously better than those of the low dose group (P<0.05). The total effective rate of high dose group was 88.6%, which was significantly higher than that of the low dose group (68.6%, P<0.05). There was no abnormal reaction and obvious side effects of hematuria, blood glucose and blood lipid in both groups and no obvious side effects. **Conclusions:** Different doses of Essentiale had therapeutic effect on patients with liver cirrhosis, and compared with the low dose Essentiale, high dose Essentiale can more effectively improve the liver function of patients with liver cirrhosis, and improve the curative effect without increasing the drug adverse reactions, which is worthy of clinical application.

Key words: Essentiale; Liver cirrhosis; Different doses; Liver function

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前言

肝硬化是各种慢性肝病发展的晚期阶段,由于多种因素使肝细胞发生损伤、变性、坏死,进而有肝细胞再生及纤维结缔组织增生,肝纤维化和假小叶的形成[1,2]。常见的肝硬化类型有肝炎性肝硬化(viral cirrhosis,VC)和酒精性肝硬化(alcoholic cirrhosis,AC),肝硬化的病因、发病率和发病特征等受多种因素影响,如年龄、地域和国家等。在西方国家几乎超过 2/3 的肝硬化为 AC,而在我国则主要为 VC[3-5]。肝硬化的治疗难度大,目前除了肝移植外几无根治方法[6]。多烯磷脂酰胆碱注射液(易善复)是大豆提取物[7],多年来用于慢性肝病的治疗,尤其是对脂肪性肝病有确切疗效[8,9]。林春兰等[10]研究观察到加倍剂量的易善复治疗肝纤维化的疗效明显优于常规剂量,但不同剂量易善复治疗肝硬化目前国内尚无研究报道。本研究比较了大剂量与小剂量易善复治疗肝硬化的疗效,以期对临床治疗

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工作提供参考。

1 资料和方法

1.1 研究对象

选择 2016 年 ~2017 年就诊的 70 例单纯 VC 与 AC 患者。纳入标准符合中华医学会肝病学分会制订的诊断标准[11]。VC 诊断标准:有慢性肝炎病史和(或)HBV、HCV 抗原抗体标记或其 DNA 检查阳性,肝功受损,有门脉高压表现,肝硬化与肝炎病毒感染有关,与饮酒等其它因素无关,影像学检查证实有肝硬化改变。AC 诊断标准:有长期(>5 年)饮酒史,酒精摄入量>40 g/d;无肝炎病史,HV 标记阴性;肝功受损,有门脉高压表现;影像学检查证实有肝硬化改变。排除标准:药物性肝硬化、胆汁淤积性肝硬化、代谢性肝硬化、血吸虫性肝硬化及非酒精性脂肪性肝病等其它原因引起的肝硬化; 合并程度严重的黄疸、肝性脑病或肝肾综合症,不能通过综合保肝对症治疗得到有效缓解;血小板<30× 10^9/L,白细胞计数<2× 10^9/L。

采用随机数字表法将入选肝硬化患者分为两组, 每组 35 例。大剂量组:男 20 例,女 15 例,年龄 29~71 岁,平均(54.1± 8.4)岁,VC 30 例,AC 5 例;小剂量组:男 19 例,女 16 例,年龄 27~73 岁,平均(54.6± 6.7)岁,VC 31 例,AC 4 例;两组性别、年龄、肝硬化类型比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

两组均接受基本的护肝、支持及对症治疗,小剂量组予易善复(赛诺菲制药有限公司,国药准字 H20059010)10 mL+5%葡萄糖注射液 250 mL 静滴,1 次 /d,连续 2~3 周;大剂量组予易善复 20 mL+5%葡萄糖注射液 250 mL 静滴,1 次 / 天,连续 2~3 周。

1.3 观察指标

观察治疗前后患者临床症状变化, 主要症状包括黄疸、腹水、腹胀、肝区胀痛或刺痛、乏力、纳差等;进行血、尿常规、电解质、肝功能(ALT、ALB、TBIL、AST、ALP 等)检查及腹部彩超检查;治疗期间密切观察患者有无出现副反应,对于药物过敏或腹泻严重的患者酌情予以停药处理并退出研究。本研究所选患者中,无药物过敏或腹泻严重者。

1.4 疗效判定

显效:黄疸、腹水、腹胀等临床症状完全消失,肝功能指标恢复正常范围;有效:临床症状明显减轻,肝功能指标改善>50%;无效:临床症状无减轻或加重,肝功能指标改善<50%[12]。

1.5 统计学方法

采用 SPSS18.0 统计软件进行数据处理, 计数资料以%表示,行 x^2 检验;计量资料以 $\bar{x}\pm s$ 表示,行 t 检验,P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后肝功能指标的变化比较

两组治疗后血清 ALT、TBIL、AST、ALP 水平均较治疗前明显降低(P<0.05),而血清 ALB 水平明显升高,且大剂量组血清 ALT、TBIL、AST、ALP 水平显著低于小剂量组(P<0.05),ALB 水平明显高于对照组(P<0.05),见表 1。

表 1 两组治疗前后肝功能指标的变化比较

Table 1 Comparison of the changes of liver function between the two groups before and after treatment

Groups	Cases	ALT(U/L)		ALB(g/L)		TBIL(μmmol/L)		AST(U/L)		ALP(U/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Hige dose group	35	84.9± 20.1	34.2± 5.5*	36.3± 4.8	50.4± 6.5*	44.5± 6.9	24.0± 4.2*	94.9± 30.1	44.0± 7.2*	194.5± 40.1	74.2± 12.5*
Low dose group	35	84.6± 22.4	49.5± 7.3*	37.6± 5.1	41.3± 7.1*	43.8± 5.4	29.7± 4.5*	94.6± 27.4	63.7± 9.3*	194.8± 40.4	103.7± 15.3*
P		0.580	0.000	0.272	0.000	0.310	0.002	0.337	0.000	0.697	0.000

Note: Compared with before treatment,*P<0.05.

2.2 两组临床疗效比较

两组临床疗效比较结果见表 2 所示,大剂量易善复组对肝硬化患者的总有效率为 88.6%,显著高于小剂量组(68.6%,P<0.05)。

表 2 两组临床疗效比较【例(%)】

Table 2 Comparison of two groups of clinical efficacy[n(%)]

Groups	Cases	Effective	Valid	Invalid	The total effective
Hige dose group	35	10(28.6)	21(60.0)	4(11.4)	31(88.6)
Low dose group	35	4(11.4)	20(51.7)	11(31.4)	24(68.6)
P					0.001

2.3 两组不良反应发生情况的比较

两组治疗过程中未见血尿常规、血糖、血脂等异常反应,均无明显药物副反应。

3 讨论

肝硬化是全球性疾病,在发达国家该病已成为致死的第 5 大元凶,是所有慢性肝脏发展的最终结果。我国目前的现状是肝炎病毒感染仍然是导致肝硬化的首要原因,其次为慢性酒精中毒,而肝炎后肝硬化中又以乙型肝炎后肝硬化居多,其次为丙型肝炎后肝硬化[13-15]。肝硬化的治疗难度大,容易进展为肝癌,VC 患者进展为肝癌的危险性要高于 AC, 而 AC 患者更易发生自发性腹膜炎[16]。酒精是肝硬化患者发生自发性腹膜炎的易感因素, 研究显示 AC 患者的小肠内多存在细菌过度生长[17,18], 而自发性腹膜炎的发生正与小肠内细菌生长及肠道运动功能的变化有关[19-21]。肝硬化病死率高,目前除了肝移植外没有其它有效根治方法,而肝移植由于治疗费用高、供体有限等原因的限制不能普及,所以如何延缓肝硬化患者的病情是临床医生十分关心的问题。

在慢性炎症或肝细胞损害后的组织修复过程中,细胞外基质的合成超过其降解,因而开始大量沉积,肝窦内皮细胞筛孔消失,毛细血管化,从而导致肝功能逐渐减退,并出现小叶改建、假小叶及再生结节形成。随着肝损伤的加重,严重部位往往会出现纤维化并发展为肝硬化。过去研究认为肝硬化是不可逆转的,但随着研究的深入,多个动物实验与临床研究显示疾病早期如治疗得当仍能阻止疾病的进展。抗肝纤维化和硬化的手段主要包括:去除肝损伤诱发因素、抑制肝星状细胞激活与增生、增加肝脏细胞外基质降解、促进肝细胞再生、诱导分化治疗及干细胞治疗等[22-27]。

易善复的主要活性成分为 1,2 二亚酰磷脂胆碱,与内源性磷脂具有高度相似的化学结构,生物利用度高,主要进入肝细胞。其作用机制为:结合肝窦内皮细胞膜、肝细胞膜及细胞器膜,促进肝细胞和膜功能恢复正常;维持细胞膜的稳定,从而减轻经各种途径介导的细胞毒作用,如有丝分裂素介导的淋巴细胞毒作用、潜在抗原或抗体依赖的细胞介导的细胞毒作用,能影响肝星形细胞增殖,提高胶原酶的活性,抑制纤维组织增生,减轻炎症浸润[28-29];能提高过氧化氢酶、胱甘肽还原酶及超氧化物歧化酶的活性,减少自由基,减轻脂质过氧化损伤,阻止肝细胞脂肪变性、坏死,促进受损的肝细胞得到修复,使肝细胞再生;提高肝细胞内线粒体酶与浆膜中的膜蛋白酶的活性,阻止肝细胞炎症纤维化。

易善复在欧洲国家使用多年, 在我国临床也应用广泛,其主要适应症是脂肪性肝病。国内大量研究表明其对病毒性肝炎、肝纤维化、各类肝硬化、胆汁阻塞亦具有良好疗效,并能预防胆结石复发, 但各研究在剂量上并不统一, 一般为 10~20 mL, 未对剂量与疗效间的相关性进行深究。本研究比较了 10 mL 易善复与 20 mL 易善复治疗肝硬化的疗效,结果显示大剂量易善复在改善肝功能指标、提高临床总有效率等方面明显优于小剂量易善复。虽然本研究两组均未发生明显药物副反应,但有报道显示个别患者可能对药物中的苯甲醇过敏而出现胃肠道反应、头痛、惊厥、昏迷等[30,31]。因此,在应用过程中要注意以下几点:① 一般用 5%或 10%葡萄糖注射液进行稀释,禁止用生理盐水、林格液等电解质溶液,对糖尿病患者可用 5%木糖醇溶液; ② 如果用其它液体配制, 应保证混合液的 pH 在 7.5 以上,控制滴速,最好在前 10 min 内保持每分钟 20 滴,观察患者无任何不良反应后再增加滴速至每分钟 30~40 滴,静滴过程中要保持溶液澄清;③ 因药物中含苯甲醇等,所以不适用于早产儿和新生儿。

综上所述,与常规剂量相比,大剂量易善复更能改善肝硬化患者的肝功能,提高疗效,且不增加药物副反应,未来期待大样本、多中心的进一步研究。

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