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更昔洛韦联合大剂量丙种球蛋白治疗婴儿巨细胞病毒性肝炎的疗效观察

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摘要 目的:研究更昔洛韦联合大剂量丙种球蛋白治疗婴儿巨细胞病毒性(CMV)肝炎的临床疗效,为婴儿 CMV 肝炎的抗菌治疗提供理论依据。**方法:**选取我院自 2009 年 7 月至 2016 年 1 月收治的 103 例 CMV 肝炎婴儿,根据随机数字表法分为治疗组 58 例,对照组 45 例。两组患儿均常规给予退黄、保肝药物治疗,对照组在此基础上给予更昔洛韦治疗,治疗组给予大剂量丙种球蛋白联合更昔洛韦治疗。对比观察两组患儿治疗后黄疸消退情况、肝功能变化、血 CMV-IgM 和尿 CMV-DNA 转阴情况、肝和脾 B 超变化、治疗效果及不良反应情况。**结果:**治疗组患儿黄疸消退时间、血 CMV-IgM 和尿 CMV-DNA 转阴时间均短于对照组(P＜0.05);治疗组肝功能指标包括总胆红素(TBIL)、直接胆红素(DBIL)、丙氨酸氨基转移酶(ALT)、γ- 谷氨酰转肽酶(GGT)水平均较对照组和治疗前降低(P＜0.05);治疗后两组肝、脾明显减小,且治疗组减小更显著,差异有统计学意义(P＜0.05);治疗组中血 CMV-IgM 转阴率、尿 CMV-DNA 转阴率、治疗总有效率均高于对照组(P＜0.05);治疗组不良反应发生率低于对照组(P＜0.05)。**结论:**更昔洛韦联合大剂量丙种球蛋白治疗婴儿 CMV 肝炎临床效果良好,可以有效缓解黄疸症状,恢复肝脏功能,肝、脾回缩明显,不良反应少,值得推广。

关键词:婴儿;巨细胞病毒;肝炎;更昔洛韦;丙种球蛋白;疗效

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Curative Effect of Gancicolovir Combined with High Dose Intravenous Immunoglobulin for Cytomegalovirus Hepatitis in Infants

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ABSTRACT Objective: To investigate the clinical curative effect of ganciclovir combined with high dose intravenous immunoglobulin in the treatment of cytomegalovirus (CMV) hepatitis in infants, and to provide a theoretical basis for antimicrobial treatment of cytomegalovirus hepatitis in infants. **Methods:** A total of 103 cytomegalovirus hepatitis infants, who were treated in, Sanya People's Hospital of Hainan Province from July 2009 to January 2016,were selected and randomly divided into treatment group(n=58) and control group (n=45). The Infants of the two groups were given routine treatment of jaundice and liver protecting drugs, on the basis of which, the control group was added ganciclovir, the treatment group were added high dose intravenous immunoglobulin combined with ganciclovir. The regression of jaundice, liver function, negative conversion of CMV-IgM and CMV-DNA, the size of liver and spleen, treatment effect and adverse reaction of the two groups were compared. **Results:** The time of jaundice regression, the time of blood CMV-IgM and urine CMV-DNA negative results in the treatment group was shorter than that in the control group (P<0.05). The liver function indexes of the treatment group, total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) levels included, were lower than those of the control group and before treatment (P<0.05). After treatment, liver and spleen of the two groups were markedly reduced, and the treatment group was reduced more significantly, the difference was statistically significant (P<0.05). The blood CMV-IgM negative rate, urine CMV-DNA negative rate and total effective rate of treatment group were significantly higher than those of the control group (P<0.05). There was a statistical differences between the two groups (P<0.05). The incidence of adverse reaction in the treatment group was lower than that in the control group (P<0.05). **Conclusion:** The ganciclovir combined with high dose intravenous immunoglobulin in the treatment of cytomegalovirus hepatitis in infants has good clinical curative effect. It can effectively alleviate the symptoms of jaundice, restore liver function, retract the volume of liver and spleen obviously, with less adverse reactions, which is worthy to be promoted.

Key words: Infant; Cytomegalovirus; Hepatitis; Ganciclovir; Intravenous immunoglobulin; Curative effect

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前言

婴儿巨细胞病毒性（Cytomegalovirus,CMV）肝炎是由人CMV引起的疾病,主要临床症状为患儿出现黄疸、肝脏肿大、肝功能异常,并可发展为肝功能衰竭甚至引起继发死亡的肝脏疾病[1,2]。CMV肝炎具有起病隐匿、缓慢持续进展的特点,如不及时治疗,易导致严重肝功能衰竭,同时还可引发患儿其他脏器发生暂时性或永久性损害,但到目前为止临床上尚无治疗婴儿CMV肝炎的统一标准和完善的方案。更昔洛韦是一种抗病毒药物,对CMV有较高的活性,是临床上治疗婴儿CMV肝炎的一线药物,但疗效不甚理想,同时还会导致患者骨髓抑制以及肝功能损害等副反应[3,4]。丙种球蛋白可增强人体的免疫力,而大剂量的丙种球蛋白除了可增强免疫力之外,还可中和机体内的毒素,阻断机体异常免疫反应,减少CMV对患者肝脏等的损害,提高机体对CMV的抵抗力。近年来更昔洛韦联合大剂量丙种球蛋白治疗CMV肝炎的报道逐渐增多,而且疗效确切[5,6]。我院儿科使用此方案治疗CMV肝炎,并与使用更昔洛韦治疗的患儿进行比较,分析更昔洛韦联合大剂量丙种球蛋白治疗婴儿CMV肝炎的临床疗效，以为临床治疗提供参考,现报道如下。

1 资料与方法

1.1 研究对象

选取我院自2009年7月至2016年1月收治的CMV肝炎患儿103例。所有患儿均符合《巨细胞病毒感染诊断方案》中的相关规定[7]。纳入标准:符合上述诊断标准者且乙肝全套及甲肝、丙肝抗体阴性,单纯疱疹病毒、EB病毒、风疹病毒均为阴性,所有患儿均表现为黄疸延迟消退,肝、脾肿大,谷丙转氨酶升高,血抗CMV-IgM阳性。排除标准:药物和中毒性肝炎、遗传代谢性疾病者;对本研究所用药物过敏者。根据随机数字表法将103例患儿分为治疗组(n=58)和对照组(n=45)。两组患儿性别、年龄、体重、出生后1min Apgar评分比较差异无统计学意义(P＞0.05),具有可比性,详见表1。本研究已征得患儿监护人的同意,且已签署相关临床研究知情同意书,并符合本院人体实验委员会制定的伦理学标准。

表1 两组患儿治疗前临床资料比较($\bar{x}\pm s$)

Table 1 Comparison of clinical data of two groups before treatment($\bar{x}\pm s$)

Groups	n	Sex (male / female)	Age(d)	Weight (kg)	Apgar scores (points)
Treatment group	58	31/27	66.00± 21.98	3.45± 0.57	7.41± 1.12
Control group	45	25/20	66.04± 21.13	3.48± 0.59	7.53± 1.47
t/x^2		0.045	0.010	0.226	0.468
P		0.831	0.992	0.822	0.641

1.2 治疗方案

患儿入院后均进行常规给予退黄、保肝药物治疗。对照组同时予以注射用更昔洛韦钠（南京海辰药业股份有限公司,国药准字:H20050156,规格:0.25 g)治疗,治疗前使用100 mL 5%葡萄糖溶液溶解,剂量为5 mg/kg,每12 h静脉滴注一次,间隔时间超过1 h,连续滴注14天;待尿CMV-DNA转阴后即进入维持期治疗：治疗组在对照组基础上联合大剂量丙种球蛋白(冻干静注人免疫球蛋白)(同路生物制药有限公司,国药准字:S19983038,规格:2.5 g)治疗400 mg/(kg·d)肌内注射,连用5天。

1.3 观察指标

于治疗前后抽取两组患儿外周静脉血检查肝功能:血清总胆红素（TBIL)、直接胆红素（DBIL)、丙氨酸氨基转移酶(ALT)、γ- 谷氨酰转肽酶(GGT)。治疗4周后分别采用酶联免疫吸附试验和聚合酶链式反应检测外周静脉血CMV-IgM和尿CMV-DNA,同时进行肝和脾的B超检查。

1.4 疗效评价标准[8]

疗效分为3个等级,治愈:黄疸症状完全消失,肝功能恢复正常,肝脏和脾脏体积基本正常;有效:黄疸症状基本消失,肝功能基本恢复正常,肝脏和脾脏体积略微缩小;无效:黄疸症状和肝功能无任何改善,肝脏和脾脏体积无变化。总有效率=(治愈+有效)例数/总例数。

1.5 统计学方法

研究中所有数据均在SPSS 19.0软件运行处理，黄疸消退时间、CMV-IgM、肝功能指标等计量资料用($\bar{x}\pm s$)表示,组间组内比较分别采用独立样本t和配对t检验,转阴率、总有效率等计数资料采用百分率(%)表示,组间比较用x^2检验。P<0.05为差异有统计学意义。

2 结果

2.1 两组症状转归情况

治疗组患儿黄疸消退时间、血CMV-IgM和尿CMV-DNA转阴时间明显低于对照组,差异有统计学意义(P<0.05),见表2。

表2 两组症状转归比较($\bar{x}\pm s$)

Table 2 Comparison of symptoms recovery of two groups($\bar{x}\pm s$)

Groups	n	Jaundice subsided time (d)	CMV-IgM negative turn time (d)	CMV-DNA negative turn time (d)
Treatment group	58	14.05± 3.29	11.26± 2.91	10.36± 2.48
Control group	45	22.98± 3.34	16.18± 3.30	17.71± 2.70
t	-	13.573	8.016	14.335
P	-	0.000	0.000	0.000

2.2 两组治疗前后肝功能变化情况

治疗前两组肝功能指标比较无差异(P>0.05),治疗后两组肝功能指标均降低,且治疗组 TBIL、DBIL、ALT、GGT 均低于对照组,差异有统计学意义(P<0.05),见表 3。

表 3 治疗前后肝功能指标比较($\bar{x}\pm s$)

Table 3 Comparison of liver function indexes before and after treatment($\bar{x}\pm s$)

Groups	n	TBIL(μmol/L)		DBIL(μmol/L)		ALT(U/L)		GGT(U/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group	58	151.07± 16.96	68.34± 5.560*	86.72± 16.14	33.81± 6.419*	121.60± 21.61	41.88± 5.47*	190.19± 30.81	66.19± 19.77*
Control group	45	150.56± 17.71	82.00± 5.641*	88.56± 14.96	50.18± 10.37*	123.09± 21.19	70.36± 7.218*	188.96± 30.19	92.18± 19.27*
t	-	0.149	11.129	0.590	9.841	0.349	22.782	0.203	6.690
P	-	0.881	0.000	0.557	0.000	0.728	0.000	0.839	0.000

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

2.3 两组肝、脾大小变化情况

治疗前两组肝、脾大小差异无统计学差异(P>0.05);治疗后两组肝、脾明显减小,且治疗组减小更显著,差异有统计学意义(P<0.05),见表 4。

表 4 两组肝脾大小比较($\bar{x}\pm s$)

Table 4 Comparison of size of liver and spleen in two groups($\bar{x}\pm s$)

Groups	n	Liver(cm)		Spleen(cm)	
		Before treatment	After treatment	Before treatment	After treatment
Treatment group	58	5.22± 0.69	2.50± 0.90*	3.50± 0.57	1.67± 0.46*
Control group	45	5.47± 0.68	3.55± 0.84*	3.50± 0.55	2.22± 0.50*
t	-	1.865	6.068	0.040	5.777
P	-	0.065	0.000	0.968	0.00

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

2.4 两组 CMV 转阴情况

2 组治疗 4 周后复查血 CMV-IgM 及尿 CMV-DNA,治疗组转阴率均显著高于对照组,差异有统计学意义(P<0.05),见表 5。

表 5 两组 CMV 转阴比较

Table 5 Comparison of CMV regression in two groups

Groups	n	CMV-IgM		CMV-DNA	
		Negative number	Negative conversion (%)	Negative number	Negative conversion (%)
Treatment group	58	53	91.38	44	75.86
Control group	45	32	71.11	19	42.22
x^2	-	-	7.218	-	12.072
P	-	-	0.007	-	0.001

2.5 两组疗效比较

治疗后两组患者症状均有所改善,治疗组总有效率高于对照组,差异有统计学意义(P<0.05),见表 6。

表 6 两组疗效比较

Table 6 Comparison of curative effect of two groups[n(%)]

Groups	n	Cure	Effective	Invalid	Total effective rate
Treatment group	58	35(60.34)	18(31.03)	5(8.62)	53(91.38)
Control group	45	18(40.00)	14(31.11)	13(28.89)	32(71.11)
x^2	-				7.218
P	-				0.007

2.6 不良反应比较

治疗组出现 3 例中性粒细胞减少症，发生率为 5.17%(3/58)，对照组出现 8 例，发生率为 17.78%(8/45)，采用停药 5 天的方法，两组患者粒细胞恢复正常。两组患者的肾功能及尿常规检查指标正常。治疗组不良反应发生率明显低于对照组，差异有统计学意义(x^2=4.221，P=0.040)。

3 讨论

CMV 属于疱疹病毒群，具有潜伏 - 活化的生物学特性，自身的逆转录酶作用于 RNA 转录为 DNA 的过程，保证其增殖，进入机体后，存活能力强[9-11]。人类是 CMV 的主要宿主，免疫功能正常的个体感染后常无症状，而免疫力低下的婴儿则会出现多脏器、多系统损伤。胎儿、新生儿以及小婴儿易受 CMV 感染，主要累及肝脏[12-14]。CMV 是引起婴儿肝炎综合征的主要病因，有文献报道，约 45.3%~78.5%婴儿肝炎综合征与 CMV 感染有关，CMV 肝炎临床主要表现为黄疸、肝功能损害、肝脾肿大，其中 10%~15%患者远期症状可能有神经系统后遗症，具体表现为智力、听力和视力障碍等[15-17]。目前，CMV 肝炎尚无特效药物，有报道称更昔洛韦联合大剂量丙种球蛋白治疗 CMV 肝炎具有很好的疗效[18,19]。

更昔洛韦是一种广谱抗 DNA 病毒药，是治疗 CMV 感染的首选药物[20]。GCV 为开环核苷类似物，在病毒和细胞蛋白激酶作用下转换为 GCV 三磷酸盐从而具有抗 CMV 活性，能竞争性移植病毒 DNA 聚合物，并通过替换 dGTP 合成新的病毒 DNA 链而终止其延长，抑制病毒的复制[21,22]。由于更昔洛韦初次磷酸化的蛋白激酶为 CMV UL97 基因编码，故在 CMV 感染细胞中其活化性比正常细胞高 100 倍，具有 CMV 高选择性[23,24]。丙种球蛋白中免疫球蛋白 G(IgG)及亚类与正常机体一致，给予人体大量的丙种球蛋白能够快速提高血清中 IgG 水平，在抵抗 CMV 病毒抗体的同时，还能够对巨噬细胞的 FC 受体产生封闭作用，结合病毒自身抗体，形成复合物，被机体清除，同时其具有抗炎及增加宿主抵抗力的作用[25-27]。除此之外，丙种球蛋白可以调节免疫功能，提高其免疫力，降低细菌感染的机率，有效控制 CMV 感染情况[28]。

本研究结果发现，联合用药治疗组患者治愈率达到 60.34%，总有效率达 91.38%，明显优于单用更昔洛韦对照组，说明更昔洛韦与大剂量丙种球蛋白联合使用治疗效果优于单独用药。进一步研究发现，治疗组患儿黄疸消退时间、血 CMV-IgM 和尿 CMV-DNA 转阴时间明显短于对照组，且治疗组肝、脾回缩幅度显著大于治疗组(P＜0.05)，说明两药联合使用可以快速减轻患者不适症状；肝功能指标恢复优于对照组(P＜0.05)，治疗组血 CMV-IgM、CMV-DNA 转阴率明显高于对照组(P＜0.05)，这说明联合用药有效抑制 CMV 活性，可能因为丙种球蛋能有效中和毒素，加速清楚 CMV，提高转阴率。联合用药治疗组出现中性粒细胞减少等不良反应少于对照组(P＜0.05)。说明了两种药物联用安全性优于更昔洛韦单用。可能因为大剂量丙种球蛋白仅能在短期内提高婴儿的免疫功能，还能促进髓鞘再生，保护神经系统，防止肝脏中的 CMV 扩散到神经系统，预防患儿出现后遗症[29]。也有研究发现[30]，更昔洛韦治疗期间，患儿脑脊液中 IgG 含量约为正常值的 2 倍，主要原因可能是当人体注射外源性 IgG 时，容易通过血脑屏障，影响屏障内外渗透压，但在停药后可恢复正常，本研究并未发现患儿出现脑水肿等情况。

综上所述，更昔洛韦联合大剂量丙种球蛋白治疗 CMV 肝炎的临床疗效优于单独使用更昔洛韦，在改善肝功指标的同时，使得肝脾体积回缩，CMV 转阴率也很高，疗效确切，值得临床推广与应用。

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