

doi: 10.13241/j.cnki.pmb.2018.15.027

胸腺肽 $\alpha 1$ 联合异甘草酸镁对肝癌经导管肝动脉化疗栓塞术后患者肝纤维化及红细胞免疫功能的影响 *

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摘要 目的:探讨胸腺肽 $\alpha 1$ 联合异甘草酸镁对肝癌经导管肝动脉化疗栓塞(TACE)术后患者肝纤维化及红细胞免疫功能的影响。方法:选择2015年1月至2016年12月间我院应用TACE治疗的肝癌患者84例,根据随机数字表法分为研究组和对照组各42例。两组患者均行TACE治疗,对照组同时给予胸腺肽 $\alpha 1$ 治疗,研究组则应用胸腺肽 $\alpha 1$ 联合异甘草酸镁治疗,疗程均为5d。比较两组治疗前、治疗5d后肝功能、肝纤维化指标,并观察患者治疗前、治疗后1个月、3个月、6个月红细胞C3b受体花环率(RBC-C3bRR)、红细胞免疫复合物花环率(RBC-ICR)。结果:治疗5d后两组患者谷氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)和总胆红素(TBIL)均显著降低,白蛋白(ALB)显著升高($P<0.05$),研究组患者ALT、AST、TBIL显著低于对照组,ALB显著高于对照组($P<0.05$)。治疗5d后两组患者血清透明质酸(HA)、III型前胶原氨基末端肽(PCIII)、层粘连蛋白(LN)、IV型胶原(CIV)均显著降低($P<0.05$),研究组患者血清HA、LN、PCIII和CIV显著低于对照组($P<0.05$)。与治疗前比较,治疗后1个月、3个月、6个月研究组患者的RBC-C3bRR显著升高,RBC-ICR显著降低($P<0.05$),且研究组患者RBC-C3bRR显著高于对照组,RBC-ICR显著低于对照组($P<0.05$)。结论:胸腺肽 $\alpha 1$ 联合异甘草酸镁可以有效的缓解肝癌TACE术后患者肝纤维化和肝功能损伤,促进红细胞免疫功能的提升,有助于肝癌TACE术后患者的康复。

关键词: 胸腺肽 $\alpha 1$; 肝癌; 红细胞免疫; 肝纤维化; 经导管肝动脉化疗栓塞

中图分类号: R735.7 **文献标识码:** A **文章编号:** 1673-6273(2018)15-2926-04

Effect of Thymosin $\alpha 1$ Combined with Magnesium Isoglycyrrhizinate on Liver Fibrosis and Erythrocyte Immune Function in Patients with Liver Cancer after TACE*

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ABSTRACT Objective: To investigate the effect of thymosin $\alpha 1$ combined with Magnesium Isoglycyrrhizinate on liver fibrosis and erythrocyte immune function in patients with liver cancer after transcatheter arterial chemoembolization (TACE) for liver cancer. **Methods:** 84 patients with liver cancer treated with TACE in our hospital from January 2015 to December 2016 were selected, which were divided into the study group and the control group according to the random number table method, 42 cases in each group. The patients of two groups were treated with TACE, while the control group was treated with thymosin $\alpha 1$, the study group was treated with thymosin $\alpha 1$ and Magnesium Isoglycyrrhizinate, the course of treatment was 5 days. The liver function and liver fibrosis indexes of two groups were compared before treatment and five days after treatment, and the red blood cell C3b receptor rosette (RBC-C3bRR) and the red blood cell immune complex rosette (RBC-ICR) were observed before treatment, one months, three months, six months after treatment. **Results:** Five days after treatment, the levels of alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin (TBIL) in the two groups were significantly decreased, and the level of albumin (ALB) was significantly increased ($P<0.05$), the ALT, AST and TBIL in the study group were significantly lower than that in the control group, the ALB was significantly higher than that in the control group ($P<0.05$). Five days after treatment, the levels of serum hyaluronic acid (HA), procollagen type III amino-terminal propeptide (PCIII), laminin (LN) and collagen IV (CIV) were significantly decreased in the two groups ($P<0.05$), the serum HA, LN, PCIII and CIV in the study group were significantly lower than those in the control group ($P<0.05$). Compared with before treatment, the RBC-C3bRR in the study group was significantly increased and the RBC-ICR decreased significantly one months, three months, six months after treatment ($P<0.05$), and the RBC-C3bRR in the study group was significantly higher than that in the control group, the RBC-ICR was significantly lower than that in the control group ($P<0.05$). **Conclusion:** Thymosin $\alpha 1$ combined with Magnesium

* 基金项目:湖北省卫生计生委西医类重点项目(WJ2015MA028)

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(收稿日期:2017-11-15 接受日期:2017-12-11)

Isoglycyrrhizinate can effectively alleviate liver fibrosis and liver function damage in patients with liver cancer after TACE, promote the immune function of red blood cell, it has good therapeutic effect on the rehabilitation of patients with liver cancer after TACE.

Key words: Thymosin α 1; Liver cancer; Erythrocyte immune; Liver fibrosis; Transcatheter arterial chemoembolization

Chinese Library Classification(CLC): R735.7 **Document code:** A

Article ID: 1673-6273(2018)15-2926-04

前言

肝癌是消化系统常见的恶性肿瘤,其患病率和死亡率均较高。有报道显示,肝癌5年生存率仅为5%,死亡率位居我国恶性肿瘤的第2位,严重威胁人们健康^[1-3]。肝癌经导管肝动脉化疗栓塞(transcatheter arterial chemoembolization, TACE)是目前临床上治疗肝癌的常见方法,其主要原理是将肝癌供血动脉栓塞,导致瘤体坏死,从而达到治疗目的,但患者在进行TACE治疗后可能导致肝功能损伤,并引起肝纤维化,影响治疗效果^[4-6]。近年来有研究发现,TACE治疗无法将体内癌细胞完全清除,残留的癌细胞主要通过集体免疫功能杀灭,而TACE在抑制肿瘤细胞生长的同时也会造成机体免疫功能降低,因而需要干预治疗^[7]。胸腺肽 α 1是由28个氨基酸组成的多肽类激素,具有增强免疫功能、抗肿瘤、抗病毒的功效,是TACE治疗的常用药物^[8,9]。异甘草酸镁是肝细胞保护剂,具有改善肝功能、保护肝细胞膜和抗炎的功效,联合胸腺肽 α 1可能发挥更好的治疗效果^[10,11]。为探讨胸腺肽 α 1联合异甘草酸镁对TACE术后患者肝纤维化及红细胞免疫功能的影响,笔者进行了对照研究,现报道如下。

1 资料和方法

1.1 临床资料

选择2015年1月至2016年12月间我院应用TACE治疗的肝癌患者84例,纳入标准:(1)所有患者均符合第八届全国肝癌学术会议制定的《原发性肝癌的临床诊断与分期标准》^[12];(2)患者首次进行TACE治疗,术前肝功能Child-Pugh分级A级、B级;(3)病历资料完整;(4)术后未发生感染或死亡。排除标准:(1)合并严重心、肺、肾功能不全者;(2)肝癌病灶超过肝脏面积4/5以上者;(3)近3周发生感染性疾病、免疫系统疾病或使用免疫制剂治疗者;(4)存在凝血机制障碍者。按照随机数字表法将患者分为研究组和对照组各42例。其中研究组男性28例,女性14例,年龄42~80岁,平均年龄(61.82 $\pm$ 6.43)岁;肝功能Child-Pugh分级:A级29例、B级13例。对照组男性27例,女性15例,年龄43~79岁,平均年龄(60.64 $\pm$ 6.31)岁;肝功能Child-Pugh分级:A级28例、B级14例。两组患者年龄、性别构成、肝功能Child-Pugh分级比较无统计学差异($P>0.05$),具有可比性。本研究经医院伦理委员会审批同意。

1.2 方法

两组均行TACE治疗,患者术前常规进行肝、肾功能检查、血常规检查、凝血功能检查和心电图检查,并根据腹部CT确定肿瘤病灶情况。患者呈仰卧位,右侧腹股沟韧带下1 cm作为穿刺点,穿刺点局部麻醉,Seldinger穿刺,通过股动脉将5F-Co-bra送至肝总动脉,CT下进行诊断造影,观察肝癌病灶位置、大小、数量和血供情况。将导管选择性的进入肝动脉,在透视条件

下将化疗药物悬浊液注入病灶内,药物用量根据肿瘤大小和血流情况而定。拔出导管,穿刺点压迫止血,包扎。术后常规进行补液、保肝和抗感染治疗。对照组同时给予胸腺肽 α 1治疗,分别于术后当天、术后3 d、术后5 d给予胸腺肽 α 1(成都地奥九泓制药厂生产,国药准字H20020532,规格1 mg,批号:141205)1.6 mg/次,皮下注射,1次/d。研究组则应用胸腺肽 α 1联合异甘草酸镁(江苏正大天晴药业股份有限公司生产,国药准字H20140092,规格10 mL: 50 mg,批号:150231)治疗,分别于术后当天、术后3 d、术后5 d给予胸腺肽 α 1 1.6 mg/次,皮下注射,1次/d,术前1周、术后3 d应用异甘草酸镁100 mg/次静脉滴注,1次/d,两组疗程均为5 d。

1.3 观察指标

1.3.1 肝功能指标 分别于治疗前、治疗5 d后抽取患者清晨空腹静脉血8 mL,其中4 mL应用DDG-3300K肝功能检查仪进行肝功能检查,检查指标包括:谷氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、白蛋白(ALB)和总胆红素(TBIL)。

1.3.2 肝纤维化指标 取4 mL清晨空腹静脉血经3500 r/min离心10 min,离心半径16 cm,分离血清,应用酶联免疫吸附法检测肝纤维化指标,包括:透明质酸(HA)、III型前胶原氨基末端肽(PIII)、层粘连蛋白(LN)、IV型胶原(CIV),试剂盒购自上海酶联生物医药有限公司。

1.3.3 红细胞免疫功能 分别于治疗前、治疗后1个月、治疗后3个月、治疗后6个月抽取患者清晨空腹静脉血2 mL,经3500 r/min离心10 min,离心半径16 cm,收集红细胞,混入红细胞冻存液后加入液氮中保存。应用酵母菌玫瑰花环法测定红细胞C3b受体花环率(RBC-C3bRR),应用酵母菌玫瑰花环法测定红细胞免疫复合物花环率(RBC-ICR),试剂盒购自第二军医大学免疫学教研室。

1.4 统计学方法

所有数据应用SPSS25.0进行统计分析,一般资料等计数资料以率(%)表示,进行 χ^2 检验;肝功能指标等计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)表示,两个样本之间数据比较应用t检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者肝功能指标比较

治疗前两组患者ALT、AST、ALB和TBIL比较无统计学差异($P>0.05$),治疗5 d后两组患者ALT、AST、TBIL均显著降低,ALB显著升高($P<0.05$),研究组患者ALT、AST、TBIL显著低于对照组,ALB显著高于对照组($P<0.05$)。见表1。

2.2 两组患者肝纤维化指标比较

治疗前两组患者血清HA、LN、PIII和CIV比较无统计学差异($P>0.05$),治疗5 d后两组患者血清HA、LN、PIII和CIV均显著降低($P<0.05$),研究组患者血清HA、LN、PIII和CIV显著低于对照组($P<0.05$)。见表2。

表 1 两组患者肝功能指标比较($\bar{x} \pm s$)

Table 1 Comparison of liver function indexes between the two groups ($\bar{x} \pm s$)

Groups	ALT(U/L)		AST(U/L)		ALB(g/L)		TBIL(μ mol/L)	
	Before treatment	Five days after treatment	Before treatment	Five days after treatment	Before treatment	Five days after treatment	Before treatment	Five days after treatment
Study group (n=42)	142.53 $\pm$ 6.25	89.52 $\pm$ 14.28*	110.24 $\pm$ 7.18	42.65 $\pm$ 6.14*	41.08 $\pm$ 6.09	50.78 $\pm$ 6.17*	65.83 $\pm$ 4.75	28.35 $\pm$ 4.23*
Control group (n=42)	143.43 $\pm$ 6.15	112.64 $\pm$ 18.31*	111.33 $\pm$ 7.34	72.78 $\pm$ 6.07*	40.38 $\pm$ 6.33	45.28 $\pm$ 5.32*	66.12 $\pm$ 4.31	44.54 $\pm$ 4.35*
t	0.293	3.220	0.253	2.839	0.135	2.784	0.225	2.839
P	0.882	0.000	0.901	0.008	0.945	0.028	0.908	0.008

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

表 2 两组患者肝纤维化指标比较($\bar{x} \pm s$)

Table 2 Comparison of hepatic fibrosis indexes between the two groups ($\bar{x} \pm s$)

Groups	HA(μ g/L)		LN(μ g/L)		PCIII(μ mol/L)		CIV(μ mol/L)	
	Before treatment	Five days after treatment	Before treatment	Five days after treatment	Before treatment	Five days after treatment	Before treatment	Five days after treatment
Study group (n=42)	273.43 $\pm$ 78.32	107.23 $\pm$ 42.32*	158.53 $\pm$ 56.34	84.23 $\pm$ 23.54*	187.86 $\pm$ 56.97	120.78 $\pm$ 26.54*	212.86 $\pm$ 75.38	102.45 $\pm$ 52.13*
Control group (n=42)	269.32 $\pm$ 76.05	165.24 $\pm$ 46.78*	153.09 $\pm$ 53.75	125.34 $\pm$ 31.67*	185.34 $\pm$ 58.32	153.59 $\pm$ 30.12*	214.52 $\pm$ 68.35	141.58 $\pm$ 56.56*
t	0.302	3.156	0.357	3.021	0.227	2.856	0.206	3.128
P	0.804	0.000	0.794	0.000	0.908	0.005	0.912	0.000

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

2.3 两组患者红细胞免疫功能比较

两组患者治疗前 RBC-C3bRR、RBC-ICR 比较无统计学差异(P>0.05),与治疗前比较,治疗后 1 个月、3 个月、6 个月研究

组RBC-C3bRR 显著升高、RBC-ICR 显著降低(P<0.05),且研究组患者 RBC-C3bRR 显著高于对照组,RBC-ICR 显著低于对照组(P<0.05)。见表 3。

表 3 两组患者红细胞免疫功能比较($\bar{x} \pm s$)

Table 3 Comparison of red blood cell immune function between the two groups ($\bar{x} \pm s$)

Groups	RBC-C3bRR(n/100RBC)				RBC-ICR(n/100RBC)			
	Before treatment	One months after treatment	Three months after treatment	Six months after treatment	Before treatment	One months after treatment	Three months after treatment	Six months after treatment
Study group (n=42)	18.67 $\pm$ 1.78	23.23 $\pm$ 2.12*	25.75 $\pm$ 2.34*	30.12 $\pm$ 3.43*	14.74 $\pm$ 2.56	11.89 $\pm$ 2.18*	8.98 $\pm$ 2.12*	8.05 $\pm$ 2.96*
Control group (n=42)	18.23 $\pm$ 1.96	19.02 $\pm$ 1.54	19.38 $\pm$ 1.64	20.03 $\pm$ 2.05	14.23 $\pm$ 2.78	14.05 $\pm$ 2.88	13.73 $\pm$ 2.78	12.97 $\pm$ 2.16
t	1.077	10.412	14.447	16.381	0.875	3.875	8.805	8.702
P	0.285	0.000	0.000	0.000	0.384	0.000	0.000	0.000

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

3 讨论

肿瘤的生长主要依赖于肿瘤新生血管的形成,当肿瘤生长到 1~2 mm³ 时,由于血供降低,肿瘤缺氧,导致肿瘤周围微环境 pH 值降低,刺激肿瘤细胞分泌血管生成因子,加速新生血管形成^[13-15]。而通过 TACE 治疗可以有效的阻断肿瘤血流供应,导致肿瘤细胞缺血、缺氧,进而达到抑制肿瘤生长,促进肿瘤细胞坏死的作用。然而在 TACE 治疗过程中,不可避免的导致正常肝脏细胞坏死,并引发肝功能损伤。有报道显示,TACE 术后肝功能损伤发生率约为 32.73%~58.42%,其中大部分患者肝功能可

自主恢复,但部分患者可能存在严重肝功能降低,甚至导致死亡^[16-18]。肝纤维化是 TACE 术后另一重要的并发症,有研究表明,TACE 中使用的化疗药物和碘油等均可造成肝细胞损害,引起肝纤维化^[19,20]。因此如何降低 TACE 对患者肝功能和肝纤维化的影响是目前研究的热点问题。

胸腺肽 α 1 是一种免疫调节剂,它可以促进淋巴细胞成熟,提高 NK 细胞和 T 淋巴细胞活性,诱导毒性 T 淋巴细胞活化,从而起到增强患者免疫功能的功效,对抗病毒和抗肿瘤有很好的效果^[21]。异甘草酸镁是临床上常用的肝细胞保护剂,具有抗炎、改善肝功能的作用^[22]。本研究结果治疗 5d 后两组患者

ALT、AST、TBIL 均显著降低,ALB 显著升高($P<0.05$),研究组患者 ALT、AST、TBIL 显著低于对照组,ALB 显著高于对照组($P<0.05$)。表明应用胸腺肽 $\alpha 1$ 联合异甘草酸镁可以有效的改善肝癌 TACE 术后患者肝功能。肝纤维化是肝功能损害的病理特征之一,也是 TACE 术后常见的并发症^[23,24]。研究表明,肝纤维化是一个慢性过程,涉及到肝内胶原、糖蛋白和蛋白聚糖的增加,而血清 HA、LN、PCIII 和 CIV 水平可以反映肝脏纤维化程度^[25,26]。本研究从两组患者治疗前、治疗 5d 后肝纤维化指标变化来看,治疗 5d 后两组患者血清 HA、LN、PCIII 和 CIV 均显著降低($P<0.05$),研究组患者血清 HA、LN、PCIII 和 CIV 显著低于对照组($P<0.05$)。表明研究组经过治疗后肝纤维化得到有效的控制,效果优于对照组。我们认为这可能是由于胸腺肽 $\alpha 1$ 通过增强患者免疫功能有效的降低了肝脏损伤,而异甘草酸镁通过保护肝细胞、降低炎症反应起到了延缓和抑制肝纤维化改变的作用,这对促进肝癌患者 TACE 术后康复,降低术后并发症有积极意义。红细胞是机体重要的血细胞,具有识别、粘附、杀伤抗原、参与免疫调控的作用,也是机体免疫系统的重要成员。研究发现,红细胞免疫功能主要通过细胞膜表面 C3b 受体实现,通过 C3b 受体与循环免疫复合粘附,然后通过吞噬细胞进行免疫反应是红细胞免疫功能实现的主要方式^[27]。而 RBC-C3bRR、RBC-ICR 是反映红细胞免疫功能的重要指标,本研究中治疗后 1 个月、3 个月、6 个月研究组 RBC-C3bRR 显著升高、RBC-ICR 显著降低($P<0.05$),且研究组患者 RBC-C3bRR 显著高于对照组,RBC-ICR 显著低于对照组($P<0.05$)。表明研究组治疗后红细胞免疫功能更佳,这对降低肝细胞损伤,杀灭参与癌细胞有重要作用。我们推测研究组治疗后红细胞免疫功能的恢复与胸腺肽 $\alpha 1$ 的应用以及肝细胞功能的恢复有关。

综上所述,胸腺肽 $\alpha 1$ 联合异甘草酸镁可以有效的缓解肝癌 TACE 术后患者肝纤维化和肝功能损伤,促进红细胞免疫功能的提升,对肝癌 TACE 术后患者康复有很好的治疗作用。

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