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碳酸氢钠 + 载药微球经肝动脉化疗栓塞治疗中晚期肝癌的临床效果 *

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摘要 目的:探讨碳酸氢钠 + 载药微球经肝动脉化疗栓塞治疗中晚期肝癌的临床效果及安全性。**方法:**选择 2015 年 2 月到 2018 年 6 月在我院诊治的中晚期肝癌患者 78 例,根据随机数字表法将其均分为两组,每组各 39 例。对照组给予载药微球经肝动脉化疗栓塞治疗,实验组给予碳酸氢钠 + 载药微球经肝动脉化疗栓塞治疗,比较两组的临床疗效,治疗前后 CD3⁺CD4⁺、CD3⁺CD8⁺T 细胞比例的变化,治疗期间不良反应的发生情况及预后。**结果:**治疗后,实验组与对照组的总有效率分别为 74.4% 和 43.6%,实验组显著高于对照组($P < 0.05$)。实验组治疗期间的发热、腹痛、腹胀、呕吐等不良反应发生情况与对照组的对比差异无统计学意义($P > 0.05$)。两组治疗前后 CD3⁺CD4⁺T 比例对比差异无统计学意义($P > 0.05$),两组治疗后的 CD3⁺CD8⁺T 比例显著低于治疗前,且实验组明显低于对照组($P < 0.05$)。治疗后,实验组的躯体功能、心理功能、社会功能、共性症状及副作用评分都低于对照组($P < 0.05$)。**结论:**碳酸氢钠 + 载药微球经肝动脉化疗栓塞治疗中晚期肝癌能提高治疗效果,改善机体的免疫功能,提高患者的生活质量,且不会增加不良反应。

关键词:碳酸氢钠;载药微球;肝动脉化疗栓塞;肝癌

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Effects of Sodium Bicarbonate + drug-loaded Microspheres in the Treatment of Advanced Hepatocellular Carcinoma by Transcatheter Arterial Chemoembolization*

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ABSTRACT Objective: To investigate the clinical efficacy and safety of sodium bicarbonate+drug-loaded microspheres in the treatment of advanced hepatocellular carcinoma by transcatheter arterial chemoembolization. **Methods:** 78 patients with advanced hepatocellular carcinoma who were treated in a certain hospital from February 2015 to June 2018 were selected and were equally divided into the experimental group and control group according to the random number table method. There were 39 cases in each group. The control group were treated with transcatheter arterial chemoembolization, the experimental group were treated with sodium bicarbonate and drug-loaded microspheres via transcatheter arterial chemoembolization. These indexes were compared in the two groups which include the clinical efficacy, the changes of CD3⁺CD4⁺, CD3⁺CD8⁺ T cell ratio before and after treatment, the occurrence of adverse reactions and prognosis during treatment. **Results:** After treatment, the total effective rates of the experimental group and the control group were 74.4% and 43.6%, respectively, and the experimental group were significantly higher than the control group ($P < 0.05$). There were no significant difference in the incidence of adverse reactions such as fever, abdominal pain, bloating, vomiting and the control group during the treatment group ($P > 0.05$). There were no significant difference in the proportion of CD3⁺CD4⁺T between the two groups before and after treatment ($P > 0.05$), and the proportion of CD3⁺CD8⁺T after treatment were significantly lower than that before treatment in the two group ($P < 0.05$), and the experimental group were significantly lower than the control group ($P < 0.05$). After treatment, the physical function, psychological function, social function, common symptoms and side effects of the experimental group were lower than the control group ($P < 0.05$). **Conclusion:** The treatment of sodium bicarbonate + drug-loaded microspheres by transcatheter arterial chemoembolization can improve therapeutic effect, immune function of the body and the quality of life of patients, and no increase adverse reactions in advanced hepatocellular carcinoma.

Key words: Sodium bicarbonate; Drug-loaded microspheres; Transcatheter arterial chemoembolization; Hepatocellular carcinoma

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前言

肝癌(Hepatocellular carcinoma)是起源于肝脏上皮或间叶组织的恶性肿瘤,恶性程度较高,就诊时大多为中晚期,因此预后比较差^[1]。肝癌的病因及机制尚未明确,研究显示主要与接触化学物质、病毒性肝炎、酒精、环境等因素有关^[2-3]。由于肝癌主要由肝动脉供血,采用肝动脉化疗栓塞可引起肿瘤组织缺血、缺氧而坏死,同时还可避免肿瘤周围正常肝组织受到严重损害^[4-5]。有研究表明肝动脉化疗栓塞治疗后肝癌的反应率可达35%以上,并可显著提高患者的中位生存期及生存率^[6,7]。

载药微球经肝动脉化疗栓塞通过其靶血管栓塞肝癌的供血动脉,不仅可提高肿瘤治疗的效果,并且缓慢的释放抗肿瘤化疗药物可建立一个可控的局部化疗药物释放系统,能提高肿瘤组织的局部化疗药物浓度,提高提高化疗的精确性与安全性^[8,9]。碳酸氢钠可通过改变肿瘤细胞或组织局部酸碱度来抑制肿瘤细胞生长,也可维持机体酸碱平衡和电解质平衡,通过细胞凋亡功能蛋白抑制肝癌生长^[10-12]。本研究主要探讨了碳酸氢钠+载药微球经肝动脉化疗栓塞治疗中晚期肝癌的效果,以明

确该方法的应用价值,现总结报道如下。

1 资料与方法

1.1 一般资料

选择2015年2月到2018年6月在我院诊治的中晚期肝癌患者78例,纳入标准:患者知情同意本研究;年龄18-70岁,性别不限,预计生存期 ≥ 6 个月;病理活检确诊为肝癌或临床确诊患者,临床分期 $\geq$ II期;肝脏占位直径 >2 cm;至少有1个可测量病灶,且单结节病灶直径 ≥ 5 cm;病灶不可行外科手术切除,具有化疗指征;肝功能Child-Pugh分级为A级/B级;治疗前血常规、凝血功能、肾功能代偿范围;研究得到医院伦理委员会的批准;临床资料完整。排除标准:合并门静脉血栓形成的患者;孕妇或哺乳期妇女;有严重的凝血功能障碍且无法纠正的患者;复查及随访不规律。

根据入院的顺序及随机数字表法将患者分为实验组与对照组,各39例,两组的一般资料对比差异无统计学意义($P>0.05$),具有可比性。见表1。

表1 两组一般资料的对比

Table 1 Comparison of the general data between the two groups

Groups	n	Gender(Male Female)	Age(year)	Maximum diameter of the lesion(cm)	BMI(kg/m ²)	Type of lesion (single/multiple)
Test group	39	21/18	58.14 $\pm$ 10.83	6.93 $\pm$ 1.24	21.13 $\pm$ 2.49	30/9
Control group	39	22/17	58.11 $\pm$ 8.92	6.24 $\pm$ 1.31	20.98 $\pm$ 1.11	32/7
t/ χ^2		0.052	0.054	0.782	0.333	0.315
P		0.820	0.973	0.233	0.872	0.575

1.2 治疗方法

对照组:给予载药微球经肝动脉化疗栓塞治疗,准备直径为100-300 μ m CalliSpheres 载药微球1瓶(国药准字20153771072,苏州恒瑞迦俐生生物医药科技有限公司),用20 μ L注射器抽出微球及生理盐水。将盐酸吡柔比星40-60 mg用5%葡萄糖溶液稀释到2-3 mL。使用装有CalliSpheres微球的20 mL注射器和盐酸吡柔比星的10 mL注射器联通,将微球和盐酸吡柔比星混合到一个20 μ L注射器中,每隔5 min摇匀1次,共3次。然后以1:1的比例加入非离子型对比剂并混匀。造影找到肿瘤供血动脉后予进行化疗灌注,以1 mL/min的速度缓慢匀速注入Collispheres载药微球,透视下观察造影剂流速,尽量彻底栓塞肿瘤的所有供血动脉,待流速停滞时可停滞栓塞。

实验组:给予碳酸氢钠+载药微球经肝动脉化疗栓塞治疗,在栓塞前采用5%碳酸氢钠+生理盐水30 mL进行栓塞治疗。每1个月栓塞1次,共持续3次。

1.3 观察指标

(1)疗效标准:以实体肿瘤疗效评价标准进行判定,完全缓解(Complete response, CR):所有目标病灶均消失;部分缓解(Partial response, PR):目标病灶直径减少至少30%;疾病进展(Progressive disease, PD):目标病灶病灶长径总和增加 $\geq 20\%$ 或出现新病灶;疾病稳定(Stable disease, SD):目标病灶未达至

PR或有增加但未达到PD。(完全缓解+部分缓解)/本组例数 $\times 100.0\%$ =总有效率。(2)记录两组在治疗期间出现的发热、腹痛、腹胀、呕吐等不良反应情况。(3)在治疗前后采用流式细胞术检测外周血T淋巴细胞亚群CD3⁺CD4⁺T、CD3⁺CD8⁺T的比例。(4)治疗前后,采用癌症患者生命质量测定量表体系(Quality of life instruments for cancer patients)中肝癌量表进行调查,包括躯体功能、心理功能、社会功能、共性症状及副作用等四个模块,分数越高,生活质量越低。

1.4 统计学分析

数据选择SPSS20.00软件进行统计学分析,计量资料以($\bar{x}\pm s$)表示,组间对比采用t检验;计数数据以百分比表示,组间比较行卡方检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组总有效率的对比

治疗后,实验组治疗总有效率为74.4%,显著高于对照组($P<0.05$)。见表2。

2.2 两组不良反应发生情况的对比

两组治疗期间的发热、腹痛、腹胀、呕吐等不良反应发生情况比较差异无统计学意义($P>0.05$)。见表3。

2.3 两组治疗前后T淋巴细胞亚群变化的对比

两组治疗前后CD3⁺CD4⁺T比例对比差异无统计学意义

($P>0.05$), 两组治疗后的 CD3⁺CD8⁺T 比例显著低于治疗前,且 试验组明显低于对照组($P<0.05$)。见表 4。

表 2 两组治疗总有效率对比(例,%)

Table 2 Comparison of the total total effective rate between the two groups (n, %)

Groups	n	CR	PR	SD	PD	Total efficiency
Test group	39	19	10	6	4	29(74.4%)
Control group	39	9	8	14	8	17(43.6%)
χ^2						7.63
P						0.006

表 3 两组不良反应的发生情况对比(例,%)

Table 3 Comparison of the incidence of adverse reactions between the two groups (n, %)

Groups	n	Heat	Stomach ache	Bloating	Vomiting
Test group	39	4(10.3%)	5(12.8%)	4(10.3%)	6(15.4%)
Control group	39	5(12.8%)	4(10.3%)	4(10.3%)	5(12.8%)
χ^2		0.126	0.126	0.000	0.106
P		0.723	0.723	1.000	0.745

表 4 两组治疗前后 T 淋巴细胞亚群变化对比($\bar{x}\pm s$)

Table 4 Comparison of the changes of T lymphocyte subsets before and after treatment between two groups($\bar{x}\pm s$)

Groups	n	CD3 ⁺ CD4 ⁺ T		t	P	CD3 ⁺ CD8 ⁺ T		t	P
		Before treatment	After treatment			Before treatment	After treatment		
Test group	39	51.44 $\pm$ 5.33	51.49 $\pm$ 4.55	0.038	0.977	40.20 $\pm$ 5.24	28.48 $\pm$ 5.23	11.423	0.000
Control group	39	51.40 $\pm$ 4.59	52.00 $\pm$ 5.14	0.245	0.786	41.42 $\pm$ 3.49	33.72 $\pm$ 4.21	6.333	0.010
t		0.033	0.452			0.332	5.294		
P		0.966	0.577			0.762	0.016		

2.4 两组治疗前后生活质量评分的对比

状及副作用评分均显著低于对照组($P<0.05$)。见表 5。

治疗后,实验组的躯体功能、心理功能、社会功能、共性症

表 5 两组治疗后生活质量评分的对比(分, $\bar{x}\pm s$)

Table 5 Comparison of the quality of life scores between two groups after treatment (points, $\bar{x}\pm s$)

Groups	n	Physical function	Psychological function	Social function	Common symptoms and side effects
Test group	39	48.22 $\pm$ 11.43	38.44 $\pm$ 9.24	41.88 $\pm$ 8.24	29.31 $\pm$ 7.29
Control group	39	62.10 $\pm$ 10.94	51.49 $\pm$ 10.42	60.33 $\pm$ 7.42	38.29 $\pm$ 8.11
t		5.699	9.193	10.438	6.832
P		<0.05	<0.05	<0.05	<0.05

3 讨论

我国是肝癌的高发地区,全球每年新增的 50 多万肝癌病例中,约 50 %发生在我国^[13]。手术切除是根治性治疗肝癌的首选方法,但是多数肝癌患者发现时已发展为中晚期,错过了手术治疗的时机^[14,15]。肝动脉栓塞化疗是不可行手术切除肝癌的首选治疗方法,化疗药物经肝动脉直接到达肝脏,可达到栓塞肿瘤血管的作用,从而达到延长患者中位生存期,提高生活质量的目的^[16]。但肝动脉栓塞化疗难以彻底的消灭肿瘤细胞,术

后癌组织残存相当常见;并且肝动脉栓塞化疗所致的缺氧是重要的刺激信号,可刺激残存肿瘤细胞,促进血管生成,加快了肿瘤的生长,给治疗带来一定的负面影响^[17,18]。

在肝动脉栓塞化疗中,载药微球具有更小的毒性和更好的栓塞治疗效果,其主要以正负电荷离子交换的形式负载药物,能更加直观即时的控制栓塞过程^[19]。特别是化疗药物的吸附速度与微球大小及配药浓度有关,微球越小,吸附速度越快,配药浓度越高,吸附速度越快。但是配药浓度太大造成栓塞造影剂容量不足影响栓塞效果,微球太小容易造成误栓且用量较大。

本研究均采用 100-300 μm 直径的表柔比星,能具备足够容量和造影剂混合进行缓慢充分栓塞,也能够提高载药速度^[20,21]。碳酸氢钠能改变肝癌组织细胞内环境酸碱度,其 pH 值和氯离子含量方面更加接近于生理值,可抑制肝癌肿瘤生长^[22]。本研究显示实验组与对照组的治疗总有效率分别为 74.4%和 43.6%,两组治疗期间发热、腹痛、腹胀、呕吐等不良反应发生情况对比差异无统计学意义,表明碳酸氢钠的应用并不会增加不良反应的发生,且可提高治疗效果。

肝癌患者多处于免疫抑制状态,外周血淋巴细胞亚群检测发现 CD3⁺CD4⁺T 淋巴细胞占淋巴细胞比例低于正常人,CD3⁺CD8⁺T 淋巴细胞占淋巴细胞比例高于正常人,可在一定程度上可导致肿瘤进展^[23]。肝动脉栓塞治疗可以在一定程度上改善患者细胞免疫的抑制状态,但是持续效果有待进一步提高^[24]。特别是传统肝动脉栓塞治疗缺乏手术操作的标准化和均质性,使得药物容易从治疗区域逃逸从而达不到指定效果。载药微球通过加载表柔比星后经肝动脉靶向栓塞肝癌组织的供血动脉,从而缓慢释放化疗药物,也可有效改善机体的免疫状况。碳酸氢钠的加入可稳定机体的细胞内和组织间液的 pH 值,维持体内酸碱调节系统平衡^[25]。并且碳酸氢钠还能刺激机体产生免疫反应,抵抗因肝癌导致的免疫减弱效应^[26]。本研究显示两组治疗后的 CD3⁺CD8⁺T 比例显著低于治疗前,且试验组明显低于对照组,表明碳酸氢钠的应用能提高机体的免疫功能。

传统的经肝动脉栓塞治疗是经肿瘤供血肝动脉灌注抗肿瘤药物制成的乳化剂,能提高局部抗肿瘤药物浓度,使肿瘤组织缺血坏死纤维化^[27,28]。载药微球经肝动脉化疗栓塞可针对性地对肿瘤供血动脉进行栓塞,增加肿瘤组织的缺血坏死程度;并且可以避免损伤正常肝组织,尽可能地做到真正去血管化^[29,30]。碳酸氢钠可破坏肿瘤的微环境,去除癌细胞里面乳酸分解出的氢离子,切断葡萄糖供应,使癌细胞更少地利用葡萄糖,从而加速癌细胞死亡^[31]。本研究显示实验组治疗后的躯体功能、心理功能、社会功能、共性症状及副作用评分都低于对照组。并且碳酸氢钠可影响细胞因子及受体结构、分布,从而影响细胞因子的活力,从而促进发挥治疗效果,提高患者的生活质量^[32]。但本研究也有一定的不足,如随访时间比较短,样本量偏少,具体的作用机制未做探讨,这均需在后续研究中进行深入分析。

综上所述,碳酸氢钠+载药微球经肝动脉化疗栓塞治疗中晚期肝癌能提高治疗效果,改善机体的免疫功能,提高患者的生活质量,且不会增加不良反应。

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