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肝癌疼痛与血浆 VEGF、BDNF、FGF-2 水平的相关性研究 *

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摘要 目的:研究肝癌疼痛与血浆血管内皮生长因子(VEGF)、脑源性神经营养因子(BDNF)、纤维细胞生长因子 -2(FGF-2)水平的相关性。**方法:**选择我院 2018 年 10 月 ~2019 年 7 月收治的 30 例肝癌疼痛患者作为研究对象,依据疼痛程度分为 4 例轻度疼痛组、19 例中度疼痛组、7 例重度疼痛组, 同期纳入 30 例肝癌无痛患者和 30 例健康对照组, 比较各组血浆 VEGF、BDNF 和 FGF-2 水平,并分析肝癌疼痛患者血浆 VEGF、BDNF 和 FGF-2 水平和数字评分法(NRS)评分的相关性。**结果:**肝癌疼痛组血浆 VEGF、BDNF、FGF-2 水平显著高于肝癌无痛组及对照组(P<0.05)。重度疼痛组血浆 VEGF、BDNF、FGF-2 水平显著高于中度疼痛组及轻度疼痛组(P<0.05)。治疗后,肝癌疼痛患者血浆 VEGF、BDNF、FGF-2 水平显著低于治疗前(P<0.05)。肝癌疼痛患者血浆 VEGF、BDNF、FGF-2 水平和 NRS 评分呈显著正相关(r 值分别为 0.619、0.571、0.563,P 值均 <0.001)。**结论:**肝癌疼痛患者血浆 VEGF、BDNF 和 FGF-2 水平较肝癌无痛者明显上升,且和疼痛程度显著相关。

关键词:肝癌疼痛;血管内皮生长因子;脑源性神经营养因子;纤维细胞生长因子 -2
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A Correlative Study on the Plasma VEGF, BDNF and Fgf-2 Levels with Liver Cancer Pain*

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ABSTRACT Objective: To study the correlation between liver cancer pain and plasma levels of vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF) and fibroblast growth factor-2 (FGF-2). **Methods:** Thirty patients with liver cancer pain admitted to our hospital from October 2018 to July 2019 were selected as the research object. According to the degree of pain, they were divided into 4 cases in mild pain group, including 19 cases in moderate pain group and 7 cases in severe pain group. At the same time, 30 painless patients with liver cancer and 30 healthy control groups were included. The levels of plasma VEGF, BDNF and FGF-2 were compared between different groups, and the correlation between the levels of plasma VEGF, BDNF and FGF-2 in patients with liver cancer pain and the score of digital scoring method (NRS) was analyzed. **Results:** The plasma VEGF, BDNF and FGF-2 levels in liver cancer pain group were significantly higher than those in liver cancer patients without pain and control group (P<0.05). The plasma VEGF, BDNF and FGF-2 levels in the severe pain group were significantly higher than those in the moderate pain group and the mild pain group (P<0.05). After treatment, the plasma levels of VEGF, BDNF and FGF-2 in patients with liver cancer pain were significantly lower than before treatment (P<0.05). The plasma VEGF, BDNF, FGF-2 levels and NRS scores were significantly positively correlated liver cancer pain (r values were 0.619, 0.571 and 0.563, P values<0.001). **Conclusion:** The plasma VEGF, BDNF and FGF-2 levels in patients with liver cancer pain are significantly higher than those in liver cancer patients without pain, and are significantly related to the degree of pain.

Key words: Liver cancer pain; Vascular endothelial growth factor; Brain-derived neurotrophic factor; Fibroblast growth factor-2
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前言

疼痛是晚期肝癌患者的主要并发症之一,研究显示[1,2]大部分晚期癌症患者以疼痛为主要症状,且为肿瘤直接浸润所致的疼痛,明显影响患者的生存质量。临床研究表明[3,4]对于可能治愈的癌症患者, 良好的镇痛干预能够显著改善患者一般状态,顺利完成抗肿瘤治疗计划,起到治愈作用。对于难以治愈的癌症患者,有效止痛能够改善患者的生存质量,对生存期的延长可能起到积极作用[5]。但目前有关肝癌疼痛的发生机制尚未明确,有关研究报道[6]肿瘤的发展程度和癌痛程度有一定关系。

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血管内皮生长因子(VEGF)能够参与血管形成,和肿瘤转移、复发有关,近年来研究显示[7]VEGF 和多种疼痛模型的疼痛有关,可能为参与疼痛的致痛物质之一。脑源性神经营养因子(BDNF)可在多种恶性肿瘤中表达,与肿瘤的恶性生物学行为有关,研究显示[8]BDNF 能够参与脊髓水平伤害感受器的调节。纤维细胞生长因子 -2(FGF-2)在诱导肿瘤血管生成、肿瘤发生发展中有重要作用,和肿瘤的预后高度相关[9]。最新研究显示[10]FGF-2 对星形胶质细胞有活化作用,从而参与疼痛调节。但目前缺乏血浆 VEGF、BDNF、FGF-2 水平和肝癌疼痛的相关研究报道。本研究主要探讨了肝癌疼痛与血浆 VEGF、BDNF、FGF-2 水平的相关性,旨在为肝癌疼痛的治疗提供参考依据。

1 资料与方法

1.1 一般资料

选择我院收治的 30 例肝癌疼痛患者作为研究对象，入选标准[11,12]:有原发性肝癌的细胞学诊断依据;卡氏评分(KPS)≥ 50 分;TNM 分期≥ Ⅲ期;数字疼痛量表(NRS)评分≥ 4 分。排除标准:患者神志不清,无正常表达能力;严重心肺功能异常;其他病因所致的肝区疼痛；阿片类药物过敏史；预计生存期≤ 3 个月;病例资料不完整。30 例肝癌患者中年龄 30~72 岁,平均(52.19±6.84)岁;男 17 例,女 13 例;TNM 分期:Ⅲ期 8 例、Ⅳ期 22 例,依据疼痛程度分为 4 例轻度疼痛组(NRS 为 1~3 分,对睡眠无影响)、19 例中度疼痛组(NRS 为 4~6 分)、7 例重度疼痛组(NRS 为 7~9 分,睡眠中可痛醒或无法入睡)[13]。同期纳入 30 例肝癌无痛组(符合原发性肝癌诊断标准,NRS 评分为 0 分)和 30 例健康对照组。肝癌无痛组年龄 29~70 岁,平均(51.73±7.21)岁;男 14 例,女 16 例。对照组年龄 28~73 岁,平均(52.01±6.42)岁;男 14 例,女 16 例。三组性别、年龄比较无统计学差异(P>0.05),具有可比性。

1.2 治疗方法

所有肝癌患者均进行系统、正规的抗癌治疗,肝癌疼痛患者均进行疼痛宣教,并依据三阶梯止痛法进行镇痛干预。于治疗前及治疗结束时采集肝癌疼痛患者外周静脉血,常规抗凝后分离血浆。采用酶联免疫法测定患者血浆 VEGF、BNDF 水平。

1.3 统计学分析

数据处理选用 SPSS18.0 软件包,计量资料用($\bar{x}\pm s$)表示,两组间同时点数据比较选用独立 t 检验，两组间治疗前后比较选用配对 t 检验,多组间比较选用方差分析,计数资料用[例(%)]表示,组间比较采用 x^2 检验,以 P<0.05 表示差异有统计学意义。

2 结果

2.1 各组血浆 VEGF、BDNF、FGF-2 水平的比较

肝癌疼痛组血浆 VEGF、BDNF、FGF-2 水平依次高于肝癌无痛组及对照组(P<0.05),见表 1。

表 1 各组血浆 VEGF、BDNF、FGF-2 水平的比较($\bar{x}\pm s$)

Table 1 Comparison the plasma levels of VEGF, BDNF and FGF-2 between different groups($\bar{x}\pm s$)

Groups	n	VEGF(ng/L)	BDNF(ng/mL)	FGF-2(ng/L)
Control group	30	103.85±12.91	5.79±0.61	254.11±30.42
Painless liver cancer group	30	341.27±45.28#	11.64±1.28#	381.05±45.07#
Liver cancer pain group	30	420.96±61.33#*	19.33±2.65#*	473.86±69.75#*

Note: Compared with control group, #P<0.05; Compared with Painless liver cancer group, *P<0.05.

2.2 不同程度肝癌疼痛组血浆 VEGF、BDNF、FGF-2 水平的比较

重度疼痛组血浆 VEGF、BDNF、FGF-2 水平显著高于中度疼痛组及轻度疼痛组，中度疼痛组血浆 VEGF、BDNF、FGF-2 水平显著高于轻度疼痛组，差异有统计学意义(P<0.05),见表 2。

表 2 不同程度肝癌疼痛组血浆 VEGF、BDNF、FGF-2 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the plasma VEGF, BDNF and FGF-2 levels in patients with different degree of liver cancer pain($\bar{x}\pm s$)

Groups	n	VEGF(ng/L)	BDNF(ng/mL)	FGF-2(ng/L)
Mild pain	4	367.29±44.02	13.28±1.39	421.08±65.14
Moderate pain	19	417.85±62.17a	19.20±2.57a	479.89±69.24a
Severe pain	7	460.07±68.93ab	23.12±3.58ab	512.07±73.77ab

Note: Compared with mild pain, aP<0.05; Compared with moderate pain, bP<0.05.

2.3 肝癌疼痛患者治疗前后血浆 VEGF、BDNF、FGF-2 水平的比较

治疗后，肝癌疼痛患者血浆 VEGF、BDNF、FGF-2 水平均显著低于治疗前(P<0.05),见表 3。

2.4 肝癌疼痛患者血浆 VEGF、BDNF、FGF-2 水平和 NRS 的相关性分析

肝癌疼痛患者血浆 VEGF、BDNF、FGF-2 水平均和 NRS 呈显著正相关,见表 4。

3 讨论

肝癌为临床常见的恶性肿瘤之一,其发病隐匿,早期无特异性症状,有较高的恶性程度,发展快速,能够经淋巴、血液等方式转移。临床研究报道[14]手术切除治疗早期肝癌能够获得较好的临床效果,但中晚期肝癌的临床疗效尚无法令人满意。大

表 3 肝癌疼痛患者治疗前后血浆 VEGF、BDNF、FGF-2 水平的比较($\bar{x}\pm s$)

Table 3 Comparison of the plasma VEGF, BDNF and FGF-2 levels in patients with liver cancer pain before and after treatment($\bar{x}\pm s$)

Time	VEGF(ng/L)	BDNF(ng/mL)	FGF-2(ng/L)
Before treatment	420.96±61.33	19.33±2.65	473.86±69.75
After treatment	321.07±40.25c	9.85±1.37c	352.17±40.39c

Note: VS after treatment, $^cP<0.05$.

表 4 肝癌疼痛患者血浆 VEGF、BDNF、FGF-2 水平和 NRS 的相关性分析

Table 4 Correlative analysis of plasma VEGF, BDNF, FGF-2 levels and NRS in patients with liver cancer pain

	VEGF		BDNF		FGF-2	
NRS	r	*P*	r	*P*	r	*P*
	0.619	<0.001	0.571	<0.001	0.563	<0.001

部分中晚期肝癌患者肝区可产生持续性或间歇性的剧烈疼痛，且疼痛可牵涉至右肩背部，严重降低患者的生活质量[15]。既往研究表明[16]癌痛对于患者工作能力、行走能力、睡眠、活动水平及情绪能够产生严重的消极影响。Glithero C 通过研究也发现[17]癌痛能够直接影响患者焦虑、抑郁等情绪反应。大部分癌痛患者经有效的镇痛干预能够得到明显缓解，从而改善患者的生活质量。

癌痛的发生机制较复杂，国外研究报道[18]肿瘤侵袭和癌痛的发生有关。肿瘤细胞具有生长快速、浸润、转移等特点，实体肿瘤的生长与血管新生有重要作用，新生血管网可为肿瘤生长提供有利条件，且可经旁分泌形成促进肿瘤生长，诱导肿瘤细胞进入血液循环，发生浸润、转移。机体血管新生由抑制因子及刺激因子控制，与内皮细胞受体结合具有调控作用。抑制肿瘤血管新生对肿瘤治疗有积极作用，VEGF 是促进血管新生的主要因子，能够增加微血管的通透性，为毛细血管网形成及肿瘤细胞生长创造微环境，导致细胞入侵周围基质，产生迁移、增殖反应[19]。近年来有研究表明[20]VEGF 具有类似炎症介质作用，其可通过促进外周感觉神经的炎症损伤作用增强机体机械及热痛敏，研究显示[21]VEGF 能够参与机体病理性疼痛，抑制祖细胞的分化，发挥免疫抑制作用。临床研究显示[22]转移性肝癌患者血浆 VEGF 水平显著上升，是影响肝癌不良预后的独立危险因素。肺癌转移患者疼痛程度和自身 VEGF 浓度也有一定相关性。动物癌痛模型研究也显示[23]VEGF 可参与小鼠肿瘤与外周神经的相互作用，注射 VEGF 能够增加正常鼠及癌痛模型鼠的痛敏行为。本研究结果显示肝癌疼痛患者血浆 VEGF 水平显著高于肝癌无痛组及对照组，且随着肝癌疼痛程度增加上升，推测 VEGF 浓度较高能够影响机体癌症疼痛。疼痛后患者 VEGF 浓度较治疗前低，提示疼痛得到有效控制后可下调 VEGF 的表达。NRS 评分为疼痛评估的常用量表之一，能够客观反映机体疼痛程度。相关性分析显示 NRS 评分和 VEGF 呈正相关，进一步提示血浆 VEGF 水平和肝癌癌痛的发生有关。

BDNF 主要在大脑外周神经系统、中枢神经系统及内分泌系统等表达，能够调节神经元的生长及分化，且可调节突触功能。临床研究报道[24]BNDF 和特异性受体结合后能够抑制或促进凋亡发生，导致肿瘤细胞增殖及迁移。近年来研究显示[25]肝癌的复发、侵袭及转移可能和 BDNF 异常表达有关，能够反映肝癌恶性生物学行为等。此外，BDNF 可参与恶性肿瘤的浸润性生长及自分泌生长，在多种肿瘤中呈高表达，血清 BDNF 水平和肿瘤分化程度、大小有关。BDNF 在疼痛调节中有重要作用，其主要通过 B 型 Trk 受体参与机体病理性疼痛的发生、发展，可作为疼痛传递的重要神经递质[26]。正常状态下，BNDF 对伤害性信息无影响，炎症情况下，BNDF 浓度明显上调，可调节伤害性神经元的兴奋性，引起细胞内信号的级联反应，从而导致中枢敏感性，引起疼痛发生[27]。Sikandar S 等[28]研究表明慢性神经病理性疼痛的发生和维持可能和 BDNF 有关，鞘内注射 rhBNDF 能够直接激活星形胶质细胞，引起持续的痛经过敏，阻断 BDNF 作用或下调 BDNF 表达能够减轻疼痛程度。本研究结果显示肝癌疼痛组血浆 BDNF 水平相对较高，肝癌重度疼痛组血浆 BDNF 水平明显高于中度疼痛及轻度疼痛组，提示血浆 BDNF 水平可能和肝癌疼痛相关。进一步研究显示肝癌疼痛患者镇痛干预后血浆 BDNF 水平有所下降，且和 NRS 评分呈正相关，提示 BDNF 浓度较高可能引发肝癌疼痛。

FGF-2 是广谱靶细胞的细胞因子，通过调控多种基因的转录及翻译，具有促进胚胎发育、促血管生成、细胞分化和迁移等作用[29]。Miura K 等[30]研究指出肺癌患者血浆 FGF-2 表达水平显著上升，和患者淋巴结转移、TNM 分期有关。文献报道[31] FGF-2 作为血管生长因子，还可直接促进肿瘤血管形成，增加肿瘤血管供应，导致肿瘤毛细血管内皮增殖，引起肿瘤细胞分裂，和肿瘤细胞的恶性表型形成有关。Kim SS 等[32]研究发现 FGF-2 可抑制细胞凋亡、诱导化疗耐药。临床研究也报道[33]，FGF-2 表达和肿瘤的紫杉醇抵抗有关。最新研究则报道[34]，FGF-2 通过激活星形胶质细胞、神经生长发育等反应影响神经元的刺激反应，和星形胶质细胞参与维持疼痛。FGF-2 上调能够导致和星形胶质细胞有关的机械痛觉过敏。动物模型显示[35]在小鼠鞘内注射抗 FGF-2 抗体可减轻触摸痛，并降低脊髓星形胶质细胞活化程度。本研究数据显示肝癌无痛组及肝癌疼痛组 FGF-2 水平均高于健康对照组，提示 FGF-2 表达和肝癌有关，且肝癌疼痛组 FGF-2 水平较肝癌无痛组高，表明 FGF-2 表达和肝癌疼痛有关。随着肝癌疼痛程度的加重，FGF-2 水平相应上升，且和 NRS 评分呈正相关，提示 FGF-2 浓度越高机体疼痛程度越明显。

综上所述，肝癌疼痛患者血浆 VEGF、BDNF 和 FGF-2 水

平较肝癌无痛者明显上升,且和疼痛程度显著相关。但本研究样本量较少,需进一步增加样本量,减少随机误差,增加结论的可靠性。

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