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Original Article

Serum VEGF, CTGF and HIF-1α levels in patients with hepatoma following TACE

Dongqi Liang, Nana Li, Hailun Wang, Guiyin Feng, Yan Fan, Geng Zhang

Department of Pain, Cangzhou Central Hospital, Cangzhou 061000, Hebei Province, China

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Abstract: Objective: To evaluate the levels of the hypoxia inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), osteopontin (OPN) and connective tissue growth factor (CTGF) in patients with primary hepatocellular carcinoma (HCC) before and after transcatheter arterial chemoembolization (TACE). Methods: A total of 82 patients with HCC were enrolled as study group, and their serum were collected before and at 1 d, 3 d, 5 d, and 7 d after TACE. Another 20 healthy subjects were included as the control group. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum VEGF, CTGF, OPN, and HIF-1α levels. The relationship between serum fluctuations and tumor diameter, distant metastasis, portal vein tumor thrombus as well as HBsAg and imaging features were compared in both groups. Results: The levels of serum VEGF, CTGF, OPN and HIF-1α in the study group before TACE were significantly higher than those in the control group ($P < 0.05$). Preoperative serum VEGF, CTGF, OPN and HIF-1α levels were significantly correlated with serum fluctuations before and after TACE and preoperative distant metastasis ($P < 0.05$). Significant relationship was also found between preoperative VEGF levels and tumor diameter (>5 cm) ($P < 0.05$) as well as between OPN, CTGF and HBsAg and portal vein tumor thrombus ($P < 0.05$), while a positive correlation was observed between OPN and VEGF ($r = 0.712$, $P < 0.001$), between HIF-1α and VEGF ($r = 0.870$, $P < 0.001$) as well as between HIF-1α and OPN ($r = 0.807$, $P < 0.001$). Conclusion: The levels of VEGF, CTGF, OPN and HIF-1α were related to tumor metastasis, growth and invasion, and the level of HIF-1α was positively correlated with VEGF, OPN and CTGF, indicating that HIF-1α could promote hemangiomas by up-regulating OPN and VEGF, which promoted tumor invasion.

Keywords: Hepatocellular carcinoma, vascular endothelial growth factor, hypoxia-inducible factor-1α, osteopontin, connective tissue growth factor

Introduction

Hepatocellular carcinoma (HCC) is a common tumor in clinical practice, and 810,000 people died of liver cancer globally in 2015, making it the sixth leading cancer worldwide [1]. The primary treatment for early liver cancer is surgical resection. However, the early symptoms of liver cancer are not obvious, and some patients have advanced to mid- or late-state at the time of admission, which reduces the success rate of surgical treatment. Transcatheter arterial chemoembolization (TACE) is suitable for mid-stage HCC. High relapse rate makes it to be cured completely. Therefore, tumor metastasis and recurrence are currently focuses of many scholars [2].

HCC is categorized as hepatocellular carcinoma, cholangiocarcinoma and mixed hepatocellular carcinoma, and can be divided into nodular, massive and diffuse types according to tumor shape [3]. For patients with diffusion-limited growth, surgical treatment is the only way to cure HCC and the most effective treatment. With the continuous improvement of the three-level disease prevention system, the situation of early diagnosis and treatment of the disease has been greatly improved compared with that of the last century, but due to the insipid onset of HCC and atypical early symptoms, about 90% of patients are still diagnosed with middle and late stages thus losing the optimal chance for surgery [4].

According to incomplete statistics, only 15-25% of patients with HCC have the opportunity to undergo surgical treatment, while only 5-17% of patients were eligible for curative hepa-

tectomy, and more than 70% of them still experienced postoperative recurrence [5]. In patients unsuitable for hepatectomy or reoperation, 90% of patients die from liver failure caused by liver tumors rather than distant metastasis [6]. VEGF and bFGF can promote angiogenesis, provide support for tumor growth and promote local tumor recurrence. HIF-1 is the main response factor of adaptive regulation under anoxic environment, and HIF-1 expression is only increased in most tumor patients. A study has shown that vascular endothelial growth factor (VEGF) level after TACE indicates tumor cell death, and the chemokines and growth hormones produced can promote the formation of local blood vessels and prolong the survival time of the remaining tumor cells [7]. This study included 82 patients with HCC who were treated with TACE in our hospital to observe the changes of serum VEGF, connective tissue growth factor (CTGF), osteopontin (OPN) and hypoxia inducible factor-1α (HIF-1α) levels after TACE, and explored the correlation between various serum factors and tumor metastasis and invasion.

Materials and methods

Materials

A total of 82 HCC patients admitted to our hospital from November 2018 to November 2019 were included in the study group, including 42 males and 40 females, aged 25-86 years, with an average age of 48.3 ± 5.6 years. All patients were diagnosed as HCC by clinical and pathological features. The patients were all treated with radiotherapy and chemotherapy and surgical treatment. The indications of TACE for HCC patients were: tumor size < 5 cm with poor hepatic functional reserve; tumor size >5 cm with tumors located in the hilar area around the large blood vessels.

Exclusion criteria: patients with liver and kidney dysfunction, heart disease and diabetes, severe ascites and bleeding tendencies were excluded.

During the same period, 20 healthy subjects were selected as the control group, including 12 males and 8 females, aged 32-86 years, with an average age of 57.4 ± 10.6 years. There was no significant difference in baseline data such as gender and age between the two groups (P>0.05), which were comparable. All patients or their family members have signed informed consent. This study has been approved by the Ethics Committee of Cangzhou Central Hospital.

Treatment methods

The study group underwent abdominal MR, ultrasound, CT, blood routine, liver and kidney function, coagulation, AFP, and hepatitis B tests before TACE. The iodine allergy test was performed 1 d before surgery. During the surgery, the patient was placed in the supine position and punctured 2 cm below the inguinal ligament on the right side. After conventional disinfection, toweling, and anesthesia with 2% lidocaine, the right femoral artery was punctured and 5F sheath was inserted into the hepatic duct along the guide wire. DSA was used to observe the number, size and blood supply of the tumor. Microcatheter was used to superselect the blood supply artery of the tumor, while mitomycin and iodized oil were applied to embolize the blood vessel. The dosage of the drug was determined according to the tumor diameter and body weight. The diluted chemotherapy drug was injected into the abdominal cavity, and adverse reactions such as vomiting, abdominal pain and nausea were monitored. If no adverse reaction occurred, the guide wire, catheter and 5F sheath were withdrawn. Routine hemostasis and pressure bandaging were performed on the puncture site. Postoperative ECG monitoring was performed to observe the patient's vital signs, and hepatoprotection and nutritional support were given.

Outcome measurement

3-5 ml of venous blood samples were obtained from the study group before and 1 d, 3 d, 5 d and 7 d after surgery, and the control group was collected once.

The blood was placed at room temperature for 2 h and centrifuged at 2000 r/min for 10 min. The supernatant was collected in an EP tube and stored at -80°C. ELISA was used to detect the levels of OPN, VEGF, CTGF and HIF-1α.

Statistical analysis

SPSS17.0 was used for statistical analysis. Continuous variables were expressed as mean

Table 1. The serum VEGF, CTGF, OPN and HIF-1α levels of the two groups

Grouping	n	VEGF (pg/ml)	CTGF (pg/ml)	HIF-1α (pg/ml)	OPN (ug/l)
Study group	82	629.54 ± 53.44	1313.21 ± 223.77	53.11 ± 2.87	22.43 ± 2.76
Control group	20	524.31 ± 7.35	904.32 ± 88.51	34.29 ± 4.22	17.81 ± 1.78
P		< 0.001	< 0.001	< 0.001	< 0.001

Table 2. Changes of serum indicators before and after TACE

Timing	VEGF (pg/ml)	CTGF (pg/ml)	HIF-1α (pg/ml)	OPN (ug/l)
Before surgery	629.54 ± 53.44	1313.21 ± 223.77	53.11 ± 2.87	22.43 ± 2.76
1 d	749.59 ± 63.69	1581.25 ± 223.13	64.02 ± 3.56	34.00 ± 3.18
3 d	723.04 ± 56.61	1603.58 ± 269.14	61.29 ± 3.12	30.37 ± 3.16
5 d	683.81 ± 43.29	1484.78 ± 317.08	58.13 ± 3.56	26.71 ± 5.78
7 d	649.0 ± 55.37	1406.69 ± 288.67	55.13 ± 3.48	24.94 ± 3.58

± standard deviation (mean ± SD) and tested by t test, and correlation of variables was analyzed by Spearman analysis. $P < 0.05$ indicated significant difference.

Results

Baseline data

There were 68 patients (82.92%) with AFP < 400 ng/ml, 14 patients (17.07%) with AFP ≥ 400 ng/ml; 28 patients (34.14%) with tumor diameter ≥ 5 cm, 54 patients (65.85%) with tumor diameter < 5 cm; 20 patients with single tumor (24.39%), 62 patients (75.60%) with multiple tumors; 22 patients (26.82%) with I-II stages, and 60 patients (73.17%) with III-IV stages. Imaging examination found that rate of lymph node metastasis and intrahepatic metastasis was 26.82% (22/82).

The preoperative levels of VEGF, CTGF, OPN and HIF-1α between the two groups

The preoperative serum VEGF, CTGF, OPN and HIF-1α levels in the study group were significantly higher than those in the control group ($P < 0.05$, **Table 1**).

Changes of serum indicators in the study group before and after TACE

The serum VEGF and CTGF levels at 1 d, 3 d and 5 d after surgery were significantly higher than those before surgery ($P < 0.05$). The serum VEGF and CTGF levels at 7 d after surgery were not statistically different from the preoperative levels ($P>0.05$). The levels of serum OPN and HIF-1α at 1 d, 3 d and 7 d after surgery were significantly lower than those before surgery ($P < 0.05$, **Table 2**).

The correlation between serum indicators with baseline data and imaging characteristics

The fluctuations in VEGF, CTGF, OPN and HIF-1α levels before and after TACE were significantly correlated with lymph node metastasis and intrahepatic metastasis ($P < 0.05$). There was a significant correlation between preoperative VEGF levels and tumors >5 cm ($P < 0.05$). OPN and CTGF were significantly correlated with portal tumor thrombus and HBsAg positive levels ($P < 0.05$, **Table 3**).

Correlation of VEGF, CTGF, HIF-1α and OPN in HCC

There was a positive correlation between OPN, VEGF and HIF-1α levels in patients with HCC ($r = 0.711, 0.806$, $P < 0.001$). VEGF and HIF-1α levels were positively correlated ($r = 0.869$, $P < 0.001$). CTGF and VEGF, OPN and CTGF, CTGF and HIF-1α were negatively correlated ($P>0.05$ **Figures 1**-**6**).

Discussion

Studies have found that the survival time of untreated HCC patients is only 2-6 months, and radiofrequency ablation, local or systemic chemotherapy can effectively prolong the survival time of patients, but each treatment method has its own shortcomings and complications [8]. Some HCC patients died from local tumors, and chemotherapy can delay the progression of

Table 3. Relationship between serum factors and baseline data and imaging characteristics

Indicators		Preoperative levels			
		VEGF (pg/ml)	CTGF (pg/ml)	HIF-1α (pg/ml)	OPN (ug/l)
Tumor size	< 5 cm	662.63 ± 52.11	1311.06 ± 223.87	52.45 ± 3.67	24.10 ± 3.89
	≥ 5 cm	614.22 ± 54.67	1306.00 ± 245.16	54.63 ± 2.34	22.52 ± 2.53
P		0.036	0.811	0.414	0.215
Distant metastasis	Yes	681.73 ± 51.37	1537.19 ± 304.7	56.41 ± 4.78	26.78 ± 4.66
	No	603.69 ± 55.23	1199.68 ± 218.5	49.52 ± 3.11	22.34 ± 3.41
P		0.002	0.037	0.023	0.027
Portal tumor thrombus	Yes	644.02 ± 59.33	1511.08 ± 299.17	56.37 ± 3.00	24.55 ± 4.7
	No	611.26 ± 57.12	1299.01 ± 278.36	52.78 ± 3.08	21.78 ± 3.42
P		0.074	0.158	0.082	0.071
HBsAg positive	Yes	646.28 ± 57.39	1299.77 ± 214.39	55.79 ± 3.04	24.77 ± 387
	No	629.00 ± 59.22	1325.58 ± 256.03	52.11 ± 6.88	22.03 ± 5.29
P		0.115	0.704	0.078	0.336
		Fluctuations before and after surgery			
		VEGF (pg/ml)	CTGF (pg/ml)	HIF-1α (pg/ml)	OPN (ug/l)
Tumor size	< 5 cm	155.51 ± 66.00	316.23 ± 47.74	13.21 ± 4.62	10.55 ± 3.21
	≥ 5 cm	113.21 ± 55.61	269.78 ± 41.12	10.88 ± 4.16	13.76 ± 3.08
P		0.151	0.066	0.236	0.647
Distant metastasis	Yes	168.74 ± 62.8	329.06 ± 44.63	15.63 ± 4.01	14.65 ± 3.65
	No	120.77 ± 78.21	268.03 ± 58.85	9.85 ± 4.85	10.55 ± 3.01
P		0.011	0.002	0.006	0.031
Portal tumor thrombus	Yes	138.84 ± 51.82	322.58 ± 42.65	13.55 ± 2.78	15.01 ± 3.05
	No	118.36 ± 73.81	269.62 ± 47.82	9.58 ± 3.05	10.02 ± 3.54
P		0.254	0.031	0.066	0.023
HBsAg positive	Yes	129.33 ± 72.47	326.54 ± 34.65	12.86 ± 2.4	14.86 ± 2.87
	No	108.62 ± 98.12	279.32 ± 66.33	10.52 ± 4.82	9.86 ± 3.85
P		0.072	0.035	0.201	0.038

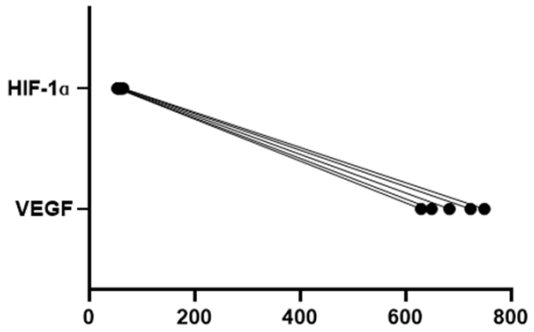

Figure 1. VEGF and HIF-1α. The level of serum VEGF showed the same trend of fluctuations with HIF-1α level ($P < 0.001$).

liver tumors and improve the prognosis. Therefore, the prognosis and quality of life of patients should be improved through local control of cancer [9, 10]. Under the guidance of imaging, TACE can destroy the liver tumors by chemical and physical methods and prolong the natural course of patients with unresectable liver cancer [11, 12].

TACE has the advantages of small trauma and faster recovery, and is widely used in the treatment of HCC. It can effectively eliminate tumors and can also avoid interference with the regulation of body function [13]. Therefore, we should clarify the indications, contraindications, complications, efficacy and costs of each treatment, so as to improve the overall effectiveness of treatments and prolong survival time [14, 15]. VEGFs regulate blood vessels and promote angiogenesis, and VEGF-B has anti-angiogenic activity, while VEGF-C promotes metastasis via distal lymph nodes [13, 16]. Studies have found that VEGF levels are high in HCC patients, and there is a significant correlation between CTGF and VEGF [17, 18]. In

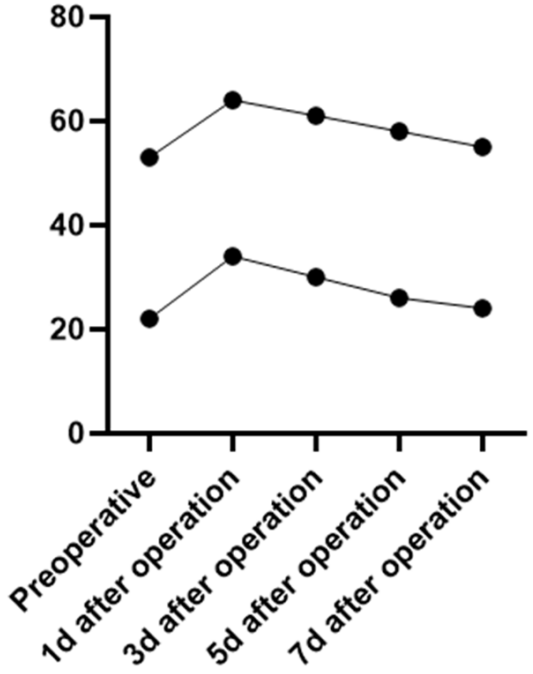

Figure 2. OPN and HIF-1α. The change in OPN level was the same as that of HIF-1α before and at 1 d, 3 d, 5 d and 7 d after surgery ($P < 0.001$).

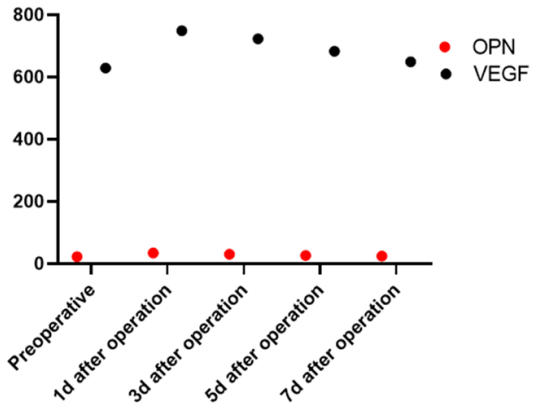

Figure 3. OPN and VEGF. The levels of the two indicators were significantly correlated at 1 d, 3 d, 5 d, and 7 d ($P < 0.001$).

this study, the levels of CTGF and VEGF were negatively correlated, which may be related to the sample size and detection methods. Serum VEGF level of HCC patients in the study group before surgery was significantly higher than that in the control group, and it was positively correlated with HIF-1α level.

Before TACE, the VEGF level was significantly correlated with intrahepatic metastasis, lymph

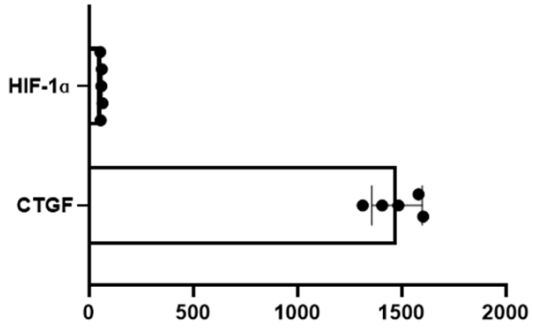

Figure 4. HIF-1α and CTGF. CTGF was negatively correlated with HIF-1α ($P>0.05$).

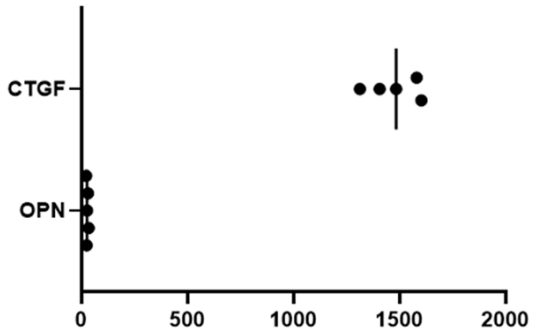

Figure 5. CTGF and OPN. OPN and CTGF levels were negatively correlated ($P>0.05$).

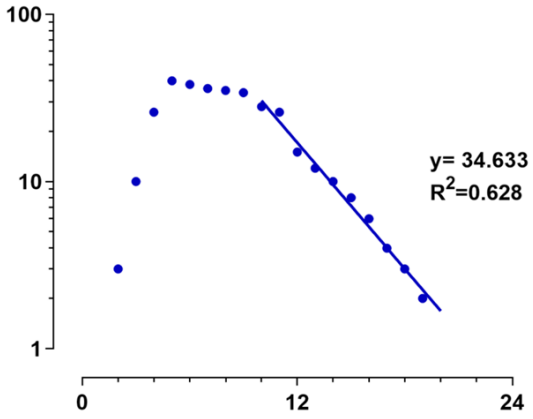

Figure 6. Observation of the correlation between VEGF, HIF-1α, OPN, and CTGF indicators.

node metastasis and tumor diameter >5 cm ($P < 0.05$), indicating that VEGF can promote tumor growth and metastasis. Some studies have found that the VEGF level of HCC patients reached its peak from the 1st day to the 2nd day after TACE, and the increased percentage was significantly correlated with the patient's progression-free survival [12, 19].

In this study, it was found that the VEGF level rose to the highest at the 1st day of TACE, and was higher at 1 d, 3 d and 7 d than that before surgery ($P < 0.05$), which is similar to the results obtained by studies mentioned above. CTGF is expressed in breast cancer, liver cancer, and pancreatic cancer, and CTGF levels in liver cancer tissues were significantly higher than those in surrounding normal tissues. This study showed that the CTGE level of the study group before surgery was significantly higher than that of the control group ($P < 0.05$), and it was significantly associated with tumor metastasis and invasion. The CTGF level rose to the highest at 3 d after TACE, but was lower at 7 d than at 1 d ($P < 0.05$). This study also found that changes in CTGF levels were positively correlated with tumor metastasis, intrahepatic metastasis, and portal vein tumor thrombus ($P < 0.05$).

Studies have shown that HIF-1α levels in HCC patients were significantly higher than those in the healthy controls, and there was a significant correlation between HIF-1α and tumor metastasis [20-22]. This study found that the preoperative HIF-1α level in the study group was significantly higher than that in the control group, and it was significantly associated with midcranial metastasis ($P < 0.05$), and was positively correlated with tumor diameter and HBsAg levels. Studies have found that OPN levels in the peripheral blood of HCC patients were significantly higher than those of the healthy controls. This study found that the OPN level in the study group before TACE was significantly higher than that in the control group ($P < 0.05$), and it was positively correlated with HIF-1α and VEGF levels, indicating that OPN was significantly associated with tumor metastasis and involved in the regulation of tumor metastasis and invasion. Studies have analyzed the relationship between HIF-1, VEGF and bFGF expression and clinicopathological characteristics in patients with pancreatic cancer, and found that high expression of HIF-1, VEGF and bFGF can increase the risk of lymph node metastasis, which is consistent with the results of this study [23]. The reasons could be as follows: (1) After tumor recurrence, the oxygen consumption of tumor cells increases, which may increase HIF-1Q expression, thereby inducing the secretion of VEGF and bFGF. (2) Tumor cells can secrete VEGF and bFGF, resulting in elevated serum VEGF and bFGF levels. (3) Elevated VEGF, bFGF and HIF-1 may promote angiogenesis and tumor cell metastasis.

However, in this study, there may be statistical inaccuracy due to the small sample size included. Therefore, the sample size of the trial and the follow-up time should be increased in the future.

In summary, HIF-1α can promote the formation of tumor blood vessels by increasing VEGF and OPN levels, and increase the tumor cell invasiveness. The study found that the fluctuations of VEGF, CTGF, HIF-1α, and OPN levels are related to distant metastasis.

Disclosure of conflict of interest

None.

Address correspondence to: Geng Zhang, Department of Pain, Cangzhou Central Hospital, No. 16, Xinhua West Road, Cangzhou 061000, Hebei Province, China. Tel: +86-13011989999; E-mail: gengzhang0606@163.com

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