ORIGINAL ARTICLE

Transcatheter Arterial Chemoembolisation Combined with Radiofrequency Ablation on Hepatocellular Carcinoma and Levels of Relevant Markers

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ABSTRACT

Objective: To investigate the ablative effect and safety of trans-catheter arterial chemoembolisation (TACE) combined with radiofrequency ablation (RFA), and TACE alone for the treatment of hepatocellular carcinoma and compare the changes in the level of relevant serum inflammatory and tumor markers.

Study Design: Descriptive comparative study.

Place and Duration of Study: Department of Hepatobiliary Surgery, Affiliated Hospital of Hebei University, from January 2016 to June 2018.

Methodology: Patients with hepatocellular carcinoma were randomly chosen and classified into combination group and TACE group, according to the treatment method. The 106 patients in the combination group were given RFA combined with TACE for treatment. The 112 patients in TACE group were given only TACE treatment. The objective response rate (ORR) and disease control rate (DCR) of short-term ablative effect, and adverse effect, serum inflammatory, and tumor markers' levels were compared for both groups before and one month after treatment.

Results: ORR and DCR of combination group were significantly higher than those of TACE group: 84 *vs*. 58%, and 99 *vs*. 80%, respectively (p=0.013). The differences in the frequency of adverse effects were statistically significant (p<0.05). After treatment, vascular endothelial growth factor (VEGF), alpha fetoprotein (AFP), and matrix metalloproteinase (MMP) of both groups declined significantly (p<0.05), that of the combination group significantly lower than those of TACE group (p<0.05). After treatment, tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), and hypersensitivity C reactive protein (hsCRP) of both groups declined significantly (p<0.05), that of combination group significantly lower than those of TACE group (p<0.05).

Conclusion: TACE combined with RFA has better ablative effect than pure TACE in the treatment of hepatocellular carcinoma. It can effectively reduce the level of tumor active factor and improve microinflammed state of the body.

Key Words: *Trans-catheter arterial chemoembolization (TACE), Radiofrequency ablation (RFA), Hepatocellular carcinoma, Vascular endothelial growth factor (VEGF), Alpha fetoprotein (AFP), Matrix metalloproteinase (MMP), Tumor necrosis factor-a (TNF-a), Interleukin-6 (IL-6), Hypersensitivity creative protein (hsCRP).*

How to cite this article: Feng J, Yang J, Li J, Jin X, Sun Q. Transcatheter arterial chemoembolisation combined with radiofrequency ablation on hepatocellular carcinoma and levels of relevant markers. *J Coll Physicians Surg Pak* 2020; **30(3)**:259-262.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of common malignant tumors. Its onset is hidden, and there is no typical symptom in the early stage. Most patients lose the best treatment opportunity by the time they receive diagnosis.[1] Trans-catheter arterial chemoembolisation (TACE) is an important method to treat non-hepatocellular carcinoma in middle and advanced phases. Its ablative effect is obvious, but it also has problems such as relapse, poor long-term effect and liver function decline.[2,3] RFA can enhance immune response capacity of the body to tumors and thus give play to the treatment effect on hepatic carcinoma.[4] In clinical work, the effect of pure TACE or RFA in treatment of hepatocellular carcinoma with diameter greater than 5cm or more than one mass is not good.[5,6] TACE combined with RFA has obvious curative and synergistic effect on hepatocellular carcinoma.[7,8] Some studies have shown that the combination therapy has a high response to advanced HCC, which is expected to achieve better clinical efficacy.[9,10]

Since the research results are uncertain, large sample size is needed to evaluate the overall therapeutic effect.

The objective of this study was to investigate the ablative effect and safety of TACE combined with RFA, and TACE alone for the treatment of HCC in the advanced stages, and compare the changes in the level of relevant serum inflammatory and tumor markers.

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Received: June 01, 2019; Revised: January 03, 2020; Accepted: February 03, 2020

METHODOLOGY

The study was approved by the Institutional Ethics Committee of Affiliated Hospital of Hebei University, and written informed consents were obtained from all participants. Patients' compling with relevant standards of diagnosis and treatment standards of hepatocellular carcinoma (2011), who were treated in Department of Hepatobiliary Surgery, Affiliated Hospital of Hebei University from January 2016 to June 2018 were chosen. According to the treatment given, 218 patients were randomised into a combination group and TACE group. One hundred and six patients in the combination group were given RFA combined with TACE for treatment. One hundred and twelve patients in TACE group were given pure TACE treatment.

Inclusion criteria accorded with manifestations of hepatocellular carcinoma through CT and/or MRI or serum AFP, surgically contraindicated; TNM staging II~IV Phase; and complied with TACE and RFA operation indications. Exclusion criteria were obvious hepatic arteriovenous fistula; coexistent other malignant tumors, and patients with chemotherapy contraindication such as those with uncontrolled infection, and diabetes.

For TACE, selective hepatic arterial angiography was performed using Seldinger technique to confirm tumor blood supply, size and localisation of tumor. Non-ionic contrast media iodinated oil (5ml) mixed with 5-fluorouracil (2g) and oxaliplatin (200mg) was injected followed by gelatin sponge and polyvinyl alcohol particles until the feeding artery was completely occluded. Then, the catheter was withdrawn and pressure dressing was applied to the punctured part.

In the combination group, after two weeks of the final TACE treatment, ultrasonic examination was conducted to localise the puncture site, depth and direction. After local anesthesia, 700-101320 disposable radio-frequency electrode was advanced into the tumor centre according to the size, form and number of nidius. Appropriate ablation power was chosen. 1500 RF ablation therapeutic instrument was used for RFA single-point or multi-point treatment. Each point was ablated for 10 to 15 minutes. Ablation power was set as 60W. After the needle was withdrawn, electrocoagulation and needle channel ablation were carried out simultaneously.

Contrast enhanced CT or MRI scanning was conducted before treatment and one month after treatment. The maximum diameter of intrahepatic typical target nidi ($\leq$5) was recorded, and the sum of diameters was calculated. According to the responses of target nidi before and after treatment, short-term ablative effect was divided into complete remission (CR), partial remission (PR), stability (SD) and progress (PD). The evaluation criteria were Cr, PR, SD and PD. CR lasted for more than four weeks. PR was more than 50% reduction of the mass, maintained for 4 weeks, SD was less than 50% reduction or less than 25% increase of the mass. PR was one or more lesions increased by more than 25% or new lesions appear once. Overall response rate (ORR) was calculated as (CR+PR) number/total number x 100%; DCR) was calculated as (CR + PR + SD) number/total number x 100%.

Adverse events were described as hepatalgia, abnormal liver function, gastrointestinal reaction and bone marrow suppression. VEGF, AFP MMP TNF-a, IL-6 and hsCRP levels of both groups were estimated before treatment and one month after treatment by enzyme-linked immunosorbent assay (ELISA).

SPSS 22.0 statistical software was applied for data analysis. Enumeration data were expressed with rate (%), and tested with x^2. Measurement data were expressed with mean value and standard deviation. Independent sample t test was applied for intergroup comparison. Paired t-test was used for intra-group comparison; $p<0.05$ was statistical significance.

RESULTS

The combined group had 59 male and 53 female patients, with mean age of 56.47 ±5.93 years, mean tumor diameter 3.91 ±1.38cm, mean number of 3.68 ±0.79 lesions, child-pugh grading A in 84 and B in 28, with 89 having tumor in middle stage and 23 in advanced stage. TACE group had 56 male and 50 female patients, with mean age of 57.12 ±6.32 years, mean diameter of tumor as 3.86 ±1.32 cm, mean of 3.51 ±0.68 lesions, child-pugh grading A in 80 and B in 26, tumor staging 85 in middle stage and 21 in advanced stage.

The differences in the gender (p=0.982), age (p=0.432), tumor size (p=0.785), tumor number (p=0.091), liver function grading (p=0.936), and tumor staging (p=0.894) of both groups had no statistical significance. DCR and DCR of combination group were higher than those of TACE group, and the differences had statistical significance (p=0.009), as shown in Table I. The comparison differences in the occurrence rate of abnormal liver function (p=0.049), gastrointestinal reaction (p=0.006) and bone marrow suppression (p=0.035) of both groups had statistical significance.

After treatment, VEGF, AFP and MMP of both groups declined obviously ($p<0.001$). Serum VEGF, AFP and MMP of combination group were lower than those of TACE group, and the differences had statistical significance ($p<0.001$), as shown in Table II. After treatment, TNF-a, IL-6 and hsCRP of both groups reduced obviously, and the differences had statistical significance ($p<0.001$). After treatment, IL-6, TNF-α and hsCRP of combination group were lower than those of TACE group, and the differences had statistical significance ($p<0.001$), as shown in Table III.

Table I: Comparison of short-term ablative effect (n/%).

Group	No.	CR	PR	SD	PD	ORR	DCR
Combination group	112	40 (35.71)	44 (39.29)	15 (13.39)	7 (6.25)	84 (75.00)	99 (88.39)
TACE group	106	21 (19.81)	37 (34.91)	22 (20.75)	32 (30.19)	58 (54.72)	80 (75.47)
X^2		6.835	0.447	2.095	21.245	9.866	6.190
P		0.009	0.504	0.148	<0.001	0.002	0.013

Table II: Tumor and inflammatory markers before and after treatment (x±s).

Group	No.	VEGF (pg/mL)		AFP (μg/mL)		MMP (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	112	359.10 ±102.13	181.59 ±110.84*	472.75 ±75.36	155.25 ±32.72*	125.32 ±22.37	55.72 ±13.64*
TACE group	106	358.72 ±101.22	243.71 ±105.62*	485.25 ±72.55	182.37 ±33.15*	127.16 ±26.17	68.44 ±14.16*
t		0.028	-4.232	-1.246	-6.078	-0.559	-6.756
P		0.978	<0.001	0.214	<0.001	0.577	<0.001

*Inter-group comparison, *p <0.05*

Table III: Comparison of serum inflammatory factor before and after treatment.

Group	No.	TNF-a (pg/mL)		IL-6 (pg/mL)		hsCRP (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	112	66.71 ±16.98	34.76 ±7.21*	82.32 ±29.75	65.32 ±5.08*	12.85 ±3.34	6.62 ±0.85*
TACE group	106	67.75 ±18.63	50.34 ±7.80*	83.45 ±31.36	70.29 ±5.21*	13.65 ±3.63	8.89 ±0.78*
t		-0.431	-15.325	-0.273	-7.131	-1.695	-20.511
P		0.667	<0.001	0.785	<0.001	0.092	<0.001

*Inter-group comparison,*p <0.05*

DISCUSSION

TACE injects antineoplastic drugs and iodipin in the tumor blood supply artery through the catheter to induce tumor nidus necrosis and shrinkage, preserve liver function, reduce postoperative complications and lengthen patients' survival time to the largest extent.[11] Under the image, RFA inserts the ablation needle into the tumor, and high-frequency current is applied to generate heat so that albuminous degeneration, coagulative necrosis and even carbonisation happen to partial tissues so as to reach the purpose of treating the tumor.[12] The research shows that liver cancer effect of RFA is basically similar to surgical operation.[13] In recent years, TACE+RFA treatment scheme has better short-term curative effect than pure TACE. This may be because RFA can reduce or block blood supply artery of tumor through TACE, relieve thermal ablation and cooling effect of blood in the hepatic artery and enhance tumor necrosis degree. In addition, thermal effect reaction during thermal ablation can enhance chemo-therapy drug intake and sensitivity.[14] Perez *et al.* applied embolism and ablation to treat liver tumor, which is consistent with the result in this study.[15] Yagi *et al*. found that the occurrence rate of adverse effects of combination group was significantly higher than that of the independent group.[16]

VEGF and MMP as serum markers of cancer cell activity or malignant behaviour capacity play an important role in cancer cell invasion and metastasis.[17] AFP has high sensitivity to disease recovery and relapse,[18,19] and it is often used as a reference basis to evaluate curative effect and relapse risk.[20] VEGF, AFP and MMP are important tumor activity factors. The higher their level, the stronger tumor invasion.[20] This study found that the descend range of tumor activity factor was higher than that of pure TACE treatment method. Primary hepatic carcinoma can make the body in the micro-inflammation state, and make the level of serum inflammatory factors (hs-CRP, IL-6 and TNF-a) rise.[21,22] This study held that the two treatment methods could suppress micro-inflammation state caused by the tumor, but the combined treatment had the better effect on improving inflammation state.[23] At present, domestic and overseas scholars combine TACE and RFA as the optimal combination method to treat liver cancer in the middle and advanced phases.[23]

CONCLUSION

TACE combined with RFA has better ablative effect than pure TACE in the treatment of hepatocellular carcinoma. It can effectively reduce the level of tumor active factor and improve micro-inflammation state of the body.

ETHICAL APPROVAL:
The study was approved by the Institutional Ethics Committee of Affiliated Hospital of Hebei University, and ethical approvals were obtained prior to initiation of the research work.

PATIENTS' CONSENT:
The informed consents were obtained from all patients to publish the data concerning this case.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

FJ,SQ: Designed this study and prepared this manuscript.

YJH, LJH, JXS: Collected and analysed clinical data.

BBB, LM, HZ: Significantly revised this manuscript.

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