RESEARCH ARTICLE

Three Treatment Methods via the Hepatic Artery for Hepatocellular Carcinoma - A Retrospective Study

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Abstract

Background: To evaluate the relative effectiveness of different treatments of hepatocellular carcinoma (HCC) via the hepatic artery. Materials and Methods: The study sample group consisted of 418 patients who were randomly selected from 2008 to 2012 with a first diagnosis of HCC and treated with transcatheter arterial chemoembolization (TACE) or without (TAE) chemotherapy or transcatheter arterial infusion (TAI). We collected data including tumor size preoperative and one month thereafter to compare change in areas across the three groups, along with various laboratory indexes for comparison. Results: The overall average change of areas was 240.8±72.1 mm^2. In the three groups it was 265.0±58.0 mm^2 vs. 250.5±51.9 mm^2 vs. 123.7±26.2 mm^2. In groups TACE and TAE values were larger than in group TAI (p<0.01), but the difference between the two was not statistically significant (p= 0.191). Additionally, U/L change of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in groups TACE and TAE was greater than in the TAI cases (24.0±13.5 vs. 20.9±12.1 vs. 5.47±8.20 and 25.6±13.5 vs.23.2±12.28 vs.5.48±14.3) on the preoperative day and two days thereafter (p<0.01). Between the two groups there was no significant cariation (p= 0.320 and p= 0.609). However, the AST and ALT recovered to normal levels one month later on therapy with liver protecting drugs. Conclusion: The groups TACE and TAE demonstrated more effective reduction of tumor size than group TAI. While lipiodol caused acute liver function damage, this proved reversible.

Keywords: HCC - effect - intervention treatment - hepatic artery - retrospective

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Introduction

Treatment of hepatocellular carcinoma (HCC) via hepatic artery is mainly suitable for the patients who have lost the chance of surgical resection (Lencioni et al., 2012), it also applies to those who have other contraindications of minimally invasive treatment. There are three main methods via the hepatic artery. However, the comparison of relative effectiveness of them for hepatocellular carcinoma (HCC) is scanty.

Morse et al reported that the addition of chemotherapy to TAE prolongs progression-free survival (PFS) and time to progression (TTP). Future efforts should focus on adjunctive therapies after the embolization to increase survival (Morse et al., 2012). However, Llovet et al indicated that chemoembolization improves survival of patients with unresectable HCC (Llovet et al., 2003).

A meta-analysis that compared TACE versus TAE in nine trials with 645 participants claimed that there is no firm evidence to support or refute TACE or TAE for patients with unresectable HCC. More adequately powered and bias-protected trials are needed (Oliveri et al., 2011; Farinati et al., 2012; Forner et al., 2012).

Another meta-analysis indicated that there is no a survival advantage associated with therapeutic embolization versus supportive care alone in patients with unresectable hepatocellular carcinoma. Existing survival data from randomized controlled trials are of poor quality (Geschwind et al., 2003).

At the same time, Bruix et al found that arterial embolization improved 2-year survival versus control and this benefit was significant for TACE but not for TAE (Bruix et al., 2001). Camm'a et al demonstrated that both TACE/TAE significantly reduced overall 2-year mortality, but the magnitude of benefit was relatively low (Cammà et al., 2002).

Takayama et al reported that HAI-TAE-hyperthermia combination therapy was favorable for the treatment of advanced liver cancer (Izumi et al., 1998; Takayama et al., 1998). But there was no clear report to assess the efficacy of TAI and TACE/TAE in patients with HCC. Ikoma'A et al compared three intervention methods in the swine models (Ikoma et al., 2012), it was highly concluded that although the necrosis volume ratio of the liver was tolerable, lipiodol-TACE caused the greatest delay in outflow ratio for each cancer drug and the greatest negative effect to liver in a swine model.

From the above, these investigation teams were

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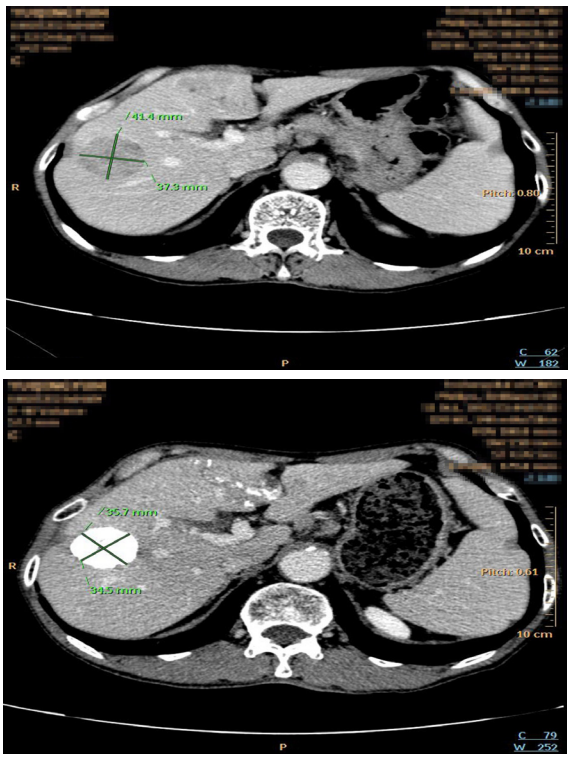

Figure 1. Measurement Method of Change Areas. A: The CT image for hepatocelluar carcinoma patients who was first time to be diagnosed of preoperative, we measure its area by calculating the longest diameter of the image. B: That the CT image for a month after the operation of the patient, the same method was used to evaluate the area of the tumor

conducted in specialized difference centers in selected patients. In our retrospective study we focus on the perspective in change of the tumor sizes and analyzed the preoperative and postoperative changes of various laboratory indexes among three intervention groups.

Materials and Methods

Study Subjects and Endpoint

This study was a retrospective design. All patients first diagnosed with HCC and treated with any intervention therapy via hepatic artery from 2008 to 2012 in the hospital. We had strict inclusion criteria: all the Child-Pugh score C patients were excluded, also including those over the age of 75 and the longest diameter of tumor was more than 10 cm were excluded, as well as the patients with portal vein thrombosis and metastases. A month was selected as the unique endpoint to evaluate the efficacy. The study protocol was approved by the ethic committees of all the participating Institutions.

Variables chosen

All the research parameters were obtained in clinical records, we collected the images of contrast-enhanced CT preoperative and a month after the intervention operation of three groups. We measured the areas by the longest diameter of tumors (Figure 1). For the multiple lesions patients, we selected the maximum level layer to calculate. We also recorded the laboratory indexes which including white blood cells (WBC), hemoglobin (Hb), platelet (Plt), AST, ALT, serum creatinine (Scr) and blood urea nitrogen (BUN) the day before operation and the second day of postoperative.

Table 1. Baseline Characteristics of the Study Patients by Treatment

Variable	Total (N=418)	TACE (N=247)	TAE (N=111)	TAI (N=60)
Yearof diagnosis				
2008	81(19%)	42(17%)	26(23%)	13(22%)
2009	92(22%)	50(20%)	19(17%)	23(38%)
2010	105(25%)	69(28%)	32(29%)	4(7%)
2011	74(18%)	46(19%)	15(14%)	13(22%)
2012	66(16%)	40(16%)	19(17%)	7(12%)
Male gender	309(74%)	189(77%)	94(85%)	26(43%)
Age yrs, mean(SD)	66(7)	62(8)	68(7)	64(8)
Diagnostic assessment				
Histology	211(50%)	126(51%)	52(47%)	33(55%)
CT+AFP>400	88(21%)	53(21%)	25(23%)	10(17%)
CT only	119(29%)	68(28%)	34(30%)	17(28%)
Underlying liver disease				
Liever cirrhosis	411(98%)	244(99%)	108(97%)	59(98%)
Chronic Hepatitis	7(2%)	3(2%)	3(3%)	1(2%)
Etiology				
Viral	359(86%)	217(88%)	92(83%)	50(83%)
Nonviral	42(10%)	25(10%)	14(13%)	3(5%)
Missing	17(4%)	5(2%)	5(5%)	7(12%)
Viral etiology				
HBV	334(81%)	203(82%)	84(76%)	46(92%)
HCV	25(6%)	14(6%)	8(7%)	4(8%)
Child-pugh score				
A	298(71%)	163(66%)	98(88%)	37(62%)
B	120(29%)	84(34%)	13(12%)	23(38%)
Numbers of nodules				
<3	335(80%)	203(82%)	79(71%)	53(88%)
≥3	83(20%)	44(18%)	32(29%)	7(12%)

Data were reported as Absolute Numbers (Percentages), but for Age

Statistical analysis

First we calculated the comparison of difference among three groups by using the data that we collected. After then we conducted every two sets of comparisons in that. All the data including preoperative and postoperative changes in the area and a variety of laboratory indexes were compared with Kruskal-Wallis test. Results were expressed as mean ± standard (S.D). All analyses were conducted via Statistical Package for Social Sciences, version 19.0 (SPSS Inc., Chicago, IL, USA). The difference is considered statistically significant by this study if a p value is less than 0.01.

Results

Over 609 HCC patients were randomly selected from 2008 to 2012, 105 of that was not the first time for intervention treatment were excluded. About 59 patients who had surgical resection or radio frequency ablation (RFA) and 27 patients that did not find preoperative contrast-enhanced CT images were also excluded. Baseline characteristics of 418 patients were reported in Table 1. There was no significant difference among three groups. It was clearly found that TACE was the common method for HCC patients (59%), TAE was mainly suitable

Table 2. The Data were Collected from the Record

Variable	Total (N=418)	TACE (N=247)	TAE (N=111)	TAI (N=60)
Tumor area changes mean (SD) mm^2				
	240.83±72.05	264.98±58.78	250.45±51.90	123.65±26.20
Lab indexes changes mean (SD)				
WBC (~10^9/L)	0.12±0.56	0.15±0.55	0.05±0.55	0.12±0.59
Hb (g/L)	0.33±5.74	0.10±5.80	0.57±5.80	0.85±5.44
Plt (~10^9/L)	3.2±9.83	3.6±10.88	2.8±8.11	2.2±7.89
AST (U/L)	20.48±13.96	23.95±13.49	20.86±12.09	5.47±8.20
ALT (U/L)	22.09±14.33	25.63±13.51	23.19±12.28	5.48±8.60
Scr (μmol/L)	0.66±4.98	0.60±4.93	0.72±4.89	0.78±5.39
BUN (mmol/L)	0.10±0.54	0.14±0.55	0.06±0.53	0.06±0.55

Data were reported as Absolute Numbers

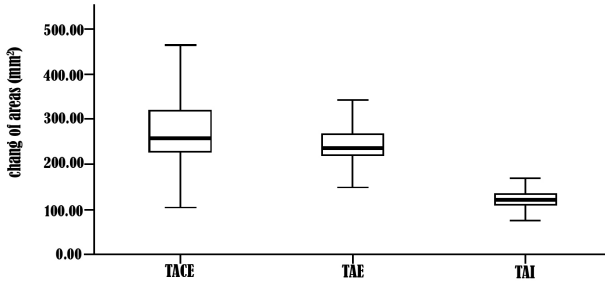

Figure 2. The Comparison of Change Areas in Three Groups. It clearly demonstrated that groups TACE and TAE displayed a significant difference than group TAI (p<0.01), there was no difference between two groups

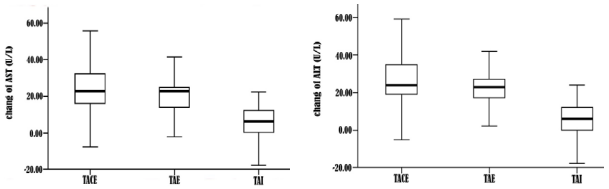

Figure 3. The Comparison of Change AST and ALT in Three Groups. It reported that the value of change AST and ALT in groups TACE and TAE was larger than group TAI (p<0.01), there was no difference between that two groups

for those who did not expect to use chemotherapy drugs (27%). TAI was mainly applied in those tumor vessels were circuity and small that could not be super-selective embolization. The groups of TAI and TACE used the same dosage and type of chemotherapy drugs. The groups of TACE and TAE used the lipiodol for hepatic artery embolization.

The data that we collected were reported in Table 2. After the comparison between preoperative and postoperative contrast-enhanced CT, we calculated the change of areas among three groups, we found changes in group TACE was the largest, representing group TAI with a statistically difference (p<0.01). TAE group also had statistically significant compared with the TAI group (p<0.01). However, there was no significant differences between TACE and TAE in the change of areas (p=0.191) (Figure 2).

In the laboratory indexes, the same method was taken to the comparison of difference. Apparently, we found significantly increased postoperative liver function series in AST and ALT compared with preoperative. The groups TACE and TAE was statistically significant compared with the group TAI (p<0.01). Similarly, the groups TACE and TAE had no statistically difference between them. The p value was 0.320 and 0.609 for change of AST and

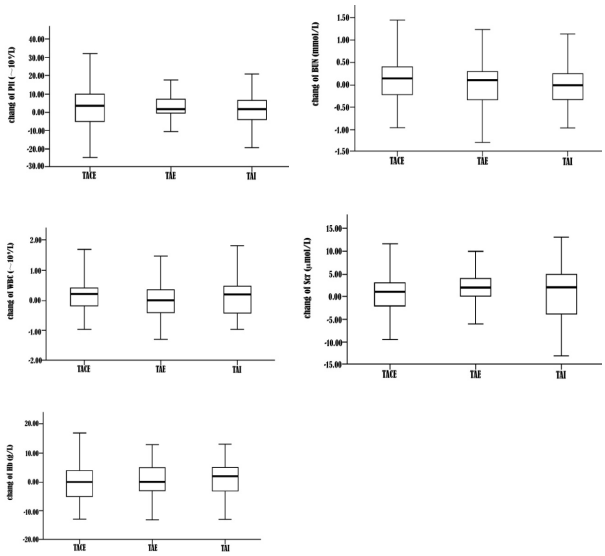

Figure 4. The Comparison of Other Laboratory Indexes Changes in Three Groups. We compared the other parameters of laboratory indexes. It turned out to be no significant difference among three groups

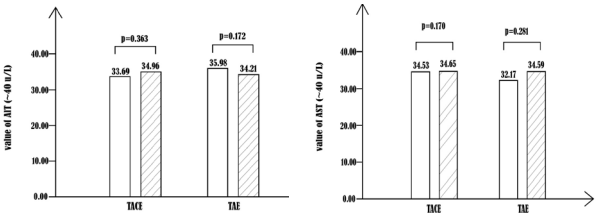

Figure 5. The Comparison of AST and ALT of Preoperative and one Month after the Operation in Groups TACE and TAE. There was no difference between two groups in the value of AST and ALT preoperative and postoperative. The liver function can return to normal level by using appropriate drugs

ALT respectively (Figure 3). It was clear that lipiodol embolization of hepatic artery resulted in an acute damage of liver function. Then by observing other laboratory parameters of the changes between preoperative and postoperative, there was no statistically difference among three groups (Figure 4).

Discussion

In our retrospective study, we found that the difference in the reduction of tumor sizes among three groups. Although powered randomized trials need to verify this conclusion, but our study provides the directions and possibilities. Someone concerned that HCC was very chemoresistant, thus embolization may be more important than chemotherapy (Marelli et al., 2007; Pleguezuelo et al., 2008). Whether use the chemotherapy drugs for unresectable patients with HCC in hepatic artery embolization is becoming a focus of discussion. Further studies should investigate if the new available embolization agents or drug eluting beads may improve the effect on tumor necrosis (Miraglia et al., 2007). Simultaneously, whether some of the different chemotherapy drugs combined can obtain definitely results need more randomized trials.

The most accurate support for our observation was that

we refer to each patient contrast-enhanced CT images of preoperative and postoperative. Careful analysis of images and the calculation of area difference were performed by us, then we inspected the data and carried on the statistical analysis. For the laboratory indexes observation, we compared parameters the day of preoperative and the two days after the operation. it is concluded that lipiodol caused acute liver function damage. However, we also collected the liver function parameters of three groups patients a month later after the operation. The liver function of three groups recovered to normal level. There was no statistically significant among three groups to compare with the data of preoperative in liver function series by using mann-whitney u test (Figure 5). This month follow-up period clearly demonstrated that three groups of patients treated with the same protection liver function drugs. It is described that although lipiodol can cause acute liver function damage, it is reversible by using the protection drugs.

Our study also has some important limitations. First, we randomly selected patients with HCC those were carried on the operation by different persons. The level and habits of different operators may affect the results of embolization and thereby influence the results of the study. Second, we evaluated the change of tumor areas by measuring the longest diameter of contrast-enhanced CT. However, this method can be influenced by many factors that confused the results of the study. Third, patients of three groups in the postoperative had different nutritional status and recovery rata, so the larger deviations may appear in liver function indexes. Fouth, we just analyzed some of the more important parameters and not for others, it produced some bias that we unexpected.

In conclusion, this retrospective study focused on 418 patients with HCC who accepted TACE, TAE and TAI different intervention operation. The groups TACE and TAE gained a greater impact in tumor size changes than group TAI, but there was no difference between the two ones. We found that lipiodol caused acute liver function damage. However, this kind of damage can be restored by the treatment of liver protection drugs.

Acknowledgements

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