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FULL PAPER

Angiographic evaluation of hepatic arterial injury after cisplatin and Gelfoam-based transcatheter arterial chemoembolization for hepatocellular carcinoma in a 205 patient cohort during a 6-year follow-up

C H SUH, MD, J H SHIN, MD, H M YOON, MD, H-K YOON, MD, G-Y KO, MD, D-I GWON, MD, J-H KIM, MD and K-B SUNG, MD

Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Seoul, Republic of Korea

Address correspondence to: Dr Ji Hoon Shin

E-mail: jhshin@amc.seoul.kr

Objective: To evaluate the overall and cumulative incidence, degree, interval change and predictors of hepatic arterial injury (HAI) after cisplatin and Gelfoam® (Upjohn, Kalamazoo, MI)-based transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).

Methods: A total of 205 patients with HCC who underwent three or more sessions of TACE without additional surgical or local treatment were included. HAI was evaluated at each segment of the hepatic artery using a three-grade scale: 1 (slight wall irregularity), 2 (overt stenosis) and 3 (occlusion). HAI interval change was categorized into three groups: progression, stable state and improvement. Cumulative incidence of HAI was analysed using Kaplan-Meier method, and predictors of HAI (patient age, sex, portal vein thrombosis and Child-Pugh classification) were analysed by univariate logistic regression.

Results: HAI occurred in 50 of the 205 study patients (24.4%). The cumulative incidence of HAI was 16.0% [95% confidence interval (CI), 10.21–21.77] during 5 sessions of

TACE, 52.1% (95% CI, 37.83–66.29) during 10 sessions and 68.0% (95% CI, 67.62–88.46) during 15 sessions. Initial HAI was interpreted as grades 1, 2 and 3 in 11 (22.0%), 17 (34.0%) and 22 (44.0%) patients, respectively. When the interval change was assessed in 48 patients with available follow-up TACE, 40 (83.3%) were included in the progression, 2 (4.2%) in the stable state and 6 (12.5%) in the improvement groups. The univariate analysis used to determine the predictors of HAI revealed no significant predictors.

Conclusion: In three or more sessions of TACE, the incidence of HAI was 24%. Increasing TACE causes increased incidence of HAI. The initial presentation was most commonly grade 3, and 12.5% of the patients with HAI showed improvement of the HAI grade during follow-up TACE.

Advances in knowledge: In patients who underwent three or more sessions of cisplatin and Gelfoam-based TACE, the overall incidence of HAI was 24.4%, and increasing TACE causes increased incidence of HAI.

Transcatheter arterial chemoembolization (TACE) is an effective method for the palliative treatment of hepatocellular carcinoma (HCC).¹ Patients with HCC frequently require repeated TACE for the treatment of residual viable tumour or local recurrence. However, TACE for HCC may cause damage to the hepatic arteries, which leads to hepatic artery spasm and inflammatory constriction, and severe cases may lead to occlusion, dissection, intrahepatic and extrahepatic collateralization and aneurysm formation in the hepatic artery.^{2–4} A direct result of irreversible occlusion is the difficulty in selecting the artery for the next TACE procedure.⁵

Maeda et al³ reported that the incidence of significant hepatic artery damage after TACE for HCC based on 33 patients and using epirubicin as a chemotherapeutic agent

was 16% per artery and 48% per patient (mean follow-up period of 497 days). Geschwind et al⁶ also reported that subsequent arterial patency seen on follow-up angiography after TACE performed for liver cancer and based on 160 patients was 54.6–80.6% depending on the embolization protocol using oil, polyvinyl alcohol particles or Gelfoam pledgets. However, both of these previous reports had a limited number of study patients. To our knowledge, published reports regarding the incidence or predictors of hepatic arterial injury (HAI) in a large series of cisplatin and Gelfoam-based TACE treatments have been limited, although cisplatin is one of the widely used chemotherapeutic regimens for HCC. Gaba⁷ reported the results of an online survey replied to by 268 Society of Interventional Radiology members, regarding iodized oil chemoembolization for

HCC. The preferred chemotherapeutic regimen consisted of 100 mg of cisplatin (44%), 50 mg of doxorubicin (58%) and 10 mg of mitomycin (59%) emulsified in 10 ml of iodized oil (71%).⁷ Moreover, follow-up changes in the hepatic artery after HAI have not yet been reported. Therefore, the purpose of this study was to evaluate the incidence, degree, interval change and predictors of HAI after cisplatin and Gelfoam-based TACE for HCC in a 205 patient cohort during a 6-year follow-up.

METHODS AND MATERIALS

Study subjects

Our institutional review board (University of Ulsan College of Medicine, Seoul, Republic of Korea) approved this study, and informed consent was waived owing to the retrospective nature of the study. Between January 2006 and December 2006, we searched our institution's electronic database and identified 1302 consecutive patients who had undergone initial TACE for HCC. Among these patients, a total of 205 patients were included in this study according to the following criteria: (a) they were confirmed to have HCC by imaging and laboratory findings obtained before TACE; (b) they underwent three or more sessions of TACE because of imaging evidence of residual/recurrent HCC; (c) they did not have any other subsequent treatment, such as surgery, radiofrequency ablation or percutaneous ethanol injection. There were 171 male and 34 female patients with an average age of 55.5 years (range, 23–81 years). The presence of portal vein thrombosis seen on the initial CT scans was detected in 78 (38.0%) patients. The Child–Pugh classification was Class A in 154 (75.1%) patients, Class B in 44 (21.5%) patients and Class C in 7 (3.4%) patients at the time of the initial TACE.

In all 205 patients, the diagnosis of HCC was based on a combination of the imaging findings and the increased serum level of α -fetoprotein and/or protein-induced vitamin K antagonist-II (PIVKA II). In all 205 study patients, contrast-enhanced CT was performed before TACE in order to evaluate the tumour characteristics and the possible presence of extrahepatic metastasis.

Transcatheter arterial chemoembolization

Arteriography of the superior mesenteric and common hepatic arteries was initially performed to assess the vascular anatomy, tumour location and tumour vascularity and to confirm the portal vein patency. After selective catheterization of the feeding artery with the use of a microcatheter, cisplatin (Cisplan; Dong-A, Seosan, Republic of Korea) and an emulsion of iodized oil (Lipiodol®; Laboratoire Guerbet, Aulnay-sous-Bois, France) were infused into the feeding arteries.

The administered dose of cisplatin was 2 mg per kilogram of body weight, which was infused over 15 min without embolic particle administration. Embolization of the feeding arteries was then performed using 1-mm diameter absorbable gelatin sponge particles (Gelfoam) until arterial flow stasis was achieved.

Hepatic arterial injury assessment

The angiographic findings were assessed by two interventional radiologists (JHS and CHS, with 15 and 3 years' clinical experience, respectively), and a consensus interpretation was made.

HAI was evaluated at each segmental hepatic artery using a three-grade scale: 1 = slight wall irregularity; 2 = overt stenosis; and 3 = occlusion (Figure 1). Distal hepatic arteries directly supplying a tumour were not evaluated because the configuration of the arteries could be changed without HAI as a tumour shrinks or enlarges and could thus be confused with true HAI. The four, segmental, hepatic arteries were evaluated, that is, the right anterior segmental hepatic artery, right posterior segmental hepatic artery, left lateral segmental artery and the left medial segmental hepatic artery. When the first HAI occurs, the highest HAI grade among the segments of the hepatic arteries was defined as the HAI grade for that patient. The HAI interval change was categorized into three groups: progression, stable state and improvement. Progression was defined as aggravation of the HAI degree seen on the follow-up of two subsequent angiographies compared with the previous angiography. Stable state was defined as no definite interval change of the HAI degree, and improvement was defined as improvement of the HAI degree seen on the follow-up angiography compared with the previous angiography. To prevent misinterpreting arterial spasm as a genuine HAI, at least two angiography sessions before improvement were required in order to claim consistent findings of HAI.

Statistical analyses

The cumulative incidence of HAI was analysed using the Kaplan–Meier method. Predictors of HAI, such as patient age, sex, portal vein thrombosis and Child–Pugh classification, were analysed using univariate logistic regression. Statistical analyses were performed using computer statistical software (SPSS® v. 19.0; SPSS Inc., Chicago, IL), and $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

In the 205 study patients, a total of 1372 TACE sessions were evaluated (range, 3–18 sessions per patient). There were no technical failures seen during hepatic angiography in TACE procedure. The follow-up period between the initial TACE and the last follow-up TACE ranged from 63 to 2420 days (median, 492 days). The mean interval of the TACE procedures was 91 days. There were no recognized iatrogenic catheter-related dissection flaps in TACE procedure or follow-up TACE.

HAI was observed in 50 of the 205 patients (24.4%) during the follow-up period. The cumulative incidence of HAI was 16.0% [95% confidence interval (CI), 10.21–21.77] during 5 sessions of TACE, 52.1% (95% CI, 37.83–66.29) during 10 sessions of TACE and 68.0% (95% CI, 67.62–88.46) during 15 sessions of TACE (Table 1, Figure 2). The initial HAI was interpreted as grades 1, 2, and 3 in 11 (22.0%), 17 (34.0%) and 22 (44.0%) patients, respectively. HAI occurred in the right anterior segmental hepatic artery in 24 of the 50 patients (48.0%) followed by the right posterior segmental hepatic artery in 11 patients (22.0%).

When the interval change was assessed in 48 patients with available follow-up TACE, 40 patients (83.3%) showed progression of the HAI during the interval change, 2 patients (4.2%) showed stable state, and 6 patients (12.5%) showed improvement (Figure 3). In six patients with improvement during the interval change,

Figure 1. Sequential change of the hepatic arterial injury (HAI), as seen in the common hepatic arteriograms of a 65-year-old male who underwent transcatheter arterial chemoembolization. Normal hepatic arterial configuration and patency were seen at the initial session (a). At the second session (b), slight wall irregularity (HAI grade 1) of both the right hepatic artery (arrow) and the middle hepatic artery (arrowhead) was observed. At the fourth session (c), overt stenosis (grade 2) of the right hepatic artery (arrow) and the middle hepatic artery (arrowhead) was observed. At the sixth session (d), occlusion (grade 3) of the middle hepatic artery (arrowhead) and more overt stenosis (grade 2) of the right hepatic artery were observed.

the grades before improvement were 2 and 3 in four and two patients, respectively.

The univariate analysis for predictors of HAI revealed no significant predictors such as patient age, sex, portal vein thrombosis or Child–Pugh classification (Table 2).

DISCUSSION

It is suggested that hepatic artery interruption caused by repeated TACEs or arterial dissection is the primary cause of extrahepatic collateral vessel development.^{8–10} Extrahepatic collateral vessel formation and irreversible occlusion of hepatic arteries cause difficulty when selecting the artery for the next TACE procedure.⁵ Since recanalization of the tumour vasculature is a pre-requisite to a subsequent TACE procedure, it is of critical importance to be aware of the HAI following the TACE procedures. In our study, in patients who underwent three or more sessions of cisplatin and Gelfoam-based TACE, the overall incidence of HAI was 24.4%, whereas the cumulative incidence of HAI was 16%, 52.1% and 68.0% during 5, 10 and 15 sessions of TACEs, respectively.

The cumulative HAI incidence of 16% during five sessions of TACE in our study is similar to the arterial patency rate of 80.6%

following TACE using chemotherapy, oil and Gelfoam pledgets in a study by Geschwind et al,⁶ although the follow-up period length and the session numbers analysed were not specified in their study. In our study, when the follow-up period was extended to 10 or 15 sessions of TACE procedures, the HAI incidence increased to >50% (52.1% and 68.0%, respectively), and thus indicating that the more often patients undergo TACE, the more HAI occurs. This cumulative incidence of HAI seen after TACE is very important because it can predict the incidence of HAI based on the number of TACE sessions, which may affect the type of patient care.

The overall HAI incidence of 24.4% in our study patients is much lower than that of 48% seen in the 33 patients in the previous study.³ In their study, they used epirubicin, and as they assessed the HAI at the level of the subsegmental hepatic artery, the configuration change in the hepatic arteries, according to tumour shrinkage or enlargement, might have been included as part of the HAI. However, our study used cisplatin as a chemotherapeutic agent in a large number of study patients.

In our study, 22 patients (44.0%) presented with grade 3 (occlusion) HAI at their initial manifestation of HAI, which was relatively higher than the incidence of 15% (5/33) seen in the

Table 1. The incidence rate and cumulative incidence of hepatic arterial injury occurring after transcatheter arterial chemoembolization (TACE)

TACE sessions	Total number of patients	Number of injuries	Incidence rate (%)	Cumulative number of injuries	Cumulative incidence (%)	95% confidence interval	
2	205	8	3.90	8	3.90	1.25	6.55
3	197	9	4.57	17	8.29	4.52	12.07
4	136	6	4.41	23	12.34	7.54	17.14
5	96	4	4.17	27	15.99	10.21	21.77
6	65	5	7.69	32	22.45	14.83	30.08
7	47	3	6.38	35	27.40	18.44	36.36
8	36	4	11.11	39	35.47	24.56	46.38
9	25	5	20.00	44	48.38	35.01	61.74
10	14	1	7.14	45	52.06	37.83	66.29
11	8	0	0.00	45	52.06	37.83	66.29
12	7	0	0.00	45	52.06	37.83	66.29
13	6	1	16.67	46	60.05	41.48	78.62
14	5	1	20.00	47	68.04	47.62	88.46
15	3	0	0.00	47	68.04	47.62	88.46
16	3	1	33.33	48	78.69	56.88	100.00
17	2	1	50.00	49	89.35	70.99	100.00
18	1	1	100.00	50	100.00	100.00	100.00
Total	205	50	24.39				

Using the Kaplan-Meier method.

previous study.³ One of the possible explanations is that we might have a shorter interval of TACE procedures, with the mean interval being 91 days and ranging between 29 days and

1087 days. If TACE procedures are carried out more frequently during a certain amount of time, they can result in continuous hepatic arterial damage caused by chemotherapeutic agent-induced

Figure 2. The cumulative incidence of hepatic arterial injury after transcatheter arterial chemoembolization (TACE).

Figure 3. Improvement of the hepatic arterial injury (HAI) as seen in common hepatic arteriograms in a 76-year-old male who underwent transcatheter arterial chemoembolization. Normal hepatic arterial configuration and patency were seen at the initial session (a). At the second session (b), overt stenosis (HAI grade 2) of the right hepatic artery (arrow) was observed. After the fifth session, the HAI of the right hepatic artery showed gradual improvement. At the tenth session (c), normal configuration and patency of the right hepatic artery (arrow) were observed.

inflammation or hypoxia caused by the embolic effect.^{2,11,12} If the level of damage exceeds a certain point, morphologic change could happen suddenly and/or severely.

The Gelfoam used in our study seems to be advantageous for keeping the hepatic artery patent. In another study, arterial patency was higher when Gelfoam was used than polyvinyl alcohol particles.⁶ Because Gelfoam is an absorbable gelatin sponge particle, it induces hypoxic damage to the tumour while minimizing the HAI owing to its transient nature. However, according to the TACE survey, the overall use of Gelfoam as an embolic material is not very popular as only 17% of 268 the Society of Interventional Radiology members used Gelfoam as a particle embolic agent.⁷

It is noteworthy that, when the interval change of HAI was assessed, six patients (12.5%) showed interval improvement during follow-up from grade 2 or 3 to grade 1 or 2 in our study. Hepatic artery spasm is usually reversible, although hepatic artery attenuation, stenosis, occlusion and aneurysmal change have been seen to be irreversible.⁵ To our knowledge, there has been no report showing interval change of the HAI following TACE or interval improvement of HAI following TACE. Although the possible causes of improvement of HAI after angiographic injury are unclear, they may result from prolonged vasospasm or a reversible inflammatory component in the

presumed HAI site. Although it would seem to be impossible to distinguish the superimposed reversible component from irreversible morphological change in injured arteries, we suggest that the subsequent TACE procedures should not be abandoned owing to verified HAI as HAI may be reversible.

In this study, univariate analysis of the predictors of HAI revealed no significant correlation between the HAI and the Child–Pugh classification unlike the previous study. TACE is more likely to induce HAI in patients with cirrhosis with impaired liver function.³ One possible explanation is that HAI might be influenced by chemotherapeutic agents or embolic materials rather than by a patient's liver function. The other theory is that as patients with B or C Child–Pugh classification tend to have fewer numbers of TACE sessions, the incidence of HAI could be unclear.

Our study has several limitations, the first of which is its retrospective design. Owing to the retrospective nature of this study, the follow-up interval between angiographic procedures was not uniform and was quite variable. Second, outcomes of the TACE procedures were not analysed according to the HAI. Third, comparison of various chemotherapeutic agents or embolic materials and protocols was not made. Comparison between studies is very difficult, because different embolization protocols and materials are being used. Finally, hepatic artery segments targeted for each procedure could be variable during TACE procedures.

Table 2. Univariate logistic regression used to determine the risk factors for hepatic arterial injury

Parameter	Odds ratio	95% confidence interval	<i>p</i> -value
Age	1.007	0.978–1.038	0.635
Sex			
Male	1.583	0.656–4.433	0.338
Portal vein thrombosis			
Present	0.794	0.400–1.533	0.498
Child–Pugh score			
A	2.158	0.354–41.384	0.483
B	1.333	0.188–26.990	0.802
C	1		

In conclusion, in three or more sessions of TACE, the incidence of HAI is 24%. Increasing TACE causes increased incidence of HAI. The initial presentation of HAI was most commonly

grade 3 (arterial occlusion), and 12.5% of the patients with HAI showed improvement of their HAI grade during follow-up TACE procedures.

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