Original Article

Balloon Occlusion Decreases Liver Injury Following Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma

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Abstract: Aim: Selective balloon-occluded transcatheter arterial chemoembolization (B-TACE) was performed for hepatocellular carcinoma (HCC). The safety and therapeutic effects of B-TACE were evaluated to clarify its usefulness in patients with HCC.

Methods: Thirty-six patients underwent B-TACE for HCCs. The degree of liver injury, adverse events, damage to liver function, and treatment effects in patients who underwent B-TACE were evaluated and compared with those who underwent conventional superselective TACE (cTACE).

Results: The means of serum alanine aminotransferase levels at 3 days after the treatments were 68.2 IU/l and 111.2 IU/l in the B-TACE and cTACE groups, respectively. Abdominal pain was significantly milder in the B-TACE group. The damage to liver function and treatment effects were equated in the B-TACE and cTACE groups.

Conclusion: Compared with cTACE, B-TACE has an equal effect on HCC, with significantly reduced liver injury. B-TACE is a useful procedure in patients with HCC who have a poor residual liver function.

Key Words: Hepatocellular Carcinoma, Therapeutic Chemoembolization, Balloon Occlusion.

Introduction

Transcatheter arterial chemoembolization (TACE) has been widely performed to treat hepatocellular carcinoma (HCC). In the 1990s, superselective TACE using a microcatheter was developed, which improved the local control rates of HCCs[1)2)]. Selective balloon-occluded TACE (B-TACE) has been recently reported to be a new technique for treating HCC[3)]. Moreover, B-TACE increased the accumulation of lipiodol (Lipiodol Ultrafluid, Guerbet Japan, Tokyo, Japan) in HCCs and improved local controls compared with conventional superselective TACE (cTACE)[4)]. Furthermore,

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the inflow of lipiodol into the liver parenchyma around HCC is considered to reduce under balloon occlusion[5]. This retrospective study evaluated the safety, particularly liver injury following the intervention, and therapeutic effects of B-TACE.

Materials and Methods

Between October 2013 and February 2015, 36 patients who underwent B-TACE for HCC and 41 patients who underwent cTACE at Japanese Red Cross Kyoto Daiichi Hospital were enrolled as subjects. In the first half of the study period, cTACE was mainly performed, whereas in the second half, B-TACE was mainly performed. The indication for cTACE and B-TACE was that patients had no indication for hepatic resection or radiofrequency ablation (RFA) monotherapy. Forty-five HCC nodules that were treated with B-TACE and 45 nodules that were treated with cTACE were evaluated as target nodules. A HCC nodule, which is one of multiple HCC nodules in tumor stage II or III or IV according to the staging of the Live Cancer Study Group of Japan[7], treated with either selective B-TACE or cTACE was included in this study. HCC nodules that required additional treatment, RFA, or percutaneous ethanol injection before assessing the effect of the treatment were excluded.

B-TACE was performed according to the procedure reported by Irie et al[3]. A microballoon catheter (Logos [Piorax, Kanagawa, Japan]) was inserted into the tumor-feeding artery as peripherally as possible at the least segmented branch. A miriplatin-lipiodol suspension (Miripla; Dainippon Sumitomo Pharma, Osaka, Japan) was injected after the balloon was inflated to occlude the tumor-feeding artery. Once the tumor vessels were filled with miriplatin, an embolic agent (Gelpart; Nihonkayaku, Tokyo, Japan) was injected into the artery until a mold-like structure was formed.

Conventional TACE was performed according to a similar procedure as B-TACE, except for the use of a microcatheter [Nadeshiko (JMS, Hiroshima, Japan)] and an emulsion, which was mixed with epirubicin hydrochloride (Mylan, Canonsburg, USA), iodine contrast medium, and lipiodol instead of miriplatin.

Serum alanine aminotransferase (ALT) levels were measured as an index of liver injury before treatment and 3 days and 1 month after treatment. In the case examined more than twice during the admission, maximum value was adopted. Serum albumin and total bilirubin (T-Bil) levels were measured as indexes of liver function before and 1 month after treatment.

The adverse events following the treatments were assessed according to the Common Terminology Criteria for the Adverse Events version 4.0 (Japan Society of Clinical Oncology)[6].

The treatment effects on the target nodules were assessed using computed tomography or magnetic resonance imaging that was performed 2 or 3 months after the treatments, according to the Response Evaluation Criteria in Cancer of the Liver (RECICL 2015 revised version) published by the Liver Cancer Study Group of Japan[7].

The χ^2 test or Mann-Whitney U test was performed for comparisons between the two groups. A P value of <0.05 denoted the presence of statistically significant differences.

All procedures that were followed were performed according to the Declaration of Helsinki (1975), as revised in 2008. Informed consent was obtained from all patients prior to being included in this study. This study was approved by the ethical committee of Japanese Red Cross Kyoto Daiichi Hospital.

Results

The baseline characteristics of the patients who underwent B-TACE and cTACE are listed in Table 1. There were no significant differences in the baseline characteristics, except for the injected dose of lipiodol and number of treated nodules, between the B-TACE and cTACE groups. The injected dose of lipiodol was significantly ($P<0.01$) greater in the B-TACE group than in the cTACE group. In B-TACE group, it was significantly ($P<0.05$) more frequent that multiple nodules were treated simultaneously as compared with cTACE group.

Changes in biochemical tests following B-TACE and cTACE are shown in Fig. 1 and Fig. 2. The means of serum ALT levels before the treatments were not significantly different between the B-TACE group (40.0 IU/l) and cTACE group (34.2 IU/l). The means of serum ALT levels at 3 days after the treatments were 68.2 IU/l and 111.2 IU/l in the B-TACE and cTACE groups, respectively, and were significantly different ($P<0.01$) (Fig. 1). The means of serum albumin and T-Bil levels at 1 month after the treatments were not significantly different (3.3 g/dl and 1.2 mg/dl, in the B-TACE group and 3.4 g/dl and 1.4 mg/dl, in the cTACE group) (Fig. 2).

The adverse events reported for the clinical symptoms observed after TACE are presented in Table 2. Fever, nausea, and ascites were not significantly different between the two groups. However, there was a significant difference ($P<0.05$) with respect to abdominal pain, which was observed in three (8%) patients in the B-TACE group and sixteen (39%) patients in the cTACE group. Grade 2 abdominal pain was found only in the cTACE group. Leukocytopenia and elevated serum creatinine levels were rare. Thrombocytopenia and elevated T-Bil levels were frequently observed, however, these abnormal data were observed before treatment and caused by liver cirrhosis. Elevation in serum ALT levels were significantly more frequent ($P<0.05$) in the cTACE group (83%) than in the B-TACE group (58%). Adverse events related to balloon dilatation, injury or dissection of the hepatic artery did not occur.

The treatment effects of target HCC nodules classified as TE4, TE3, TE2, and TE1 were 55.6%,

Table 1. Characteristics of the patients

		B-TACE, n=36	cTACE, n=41	
age	median (range)	78(53-90)	73(52-84)	n.s.
gender	M/F	28/8	28/13	n.s.
ethiology	HCV/HBV/alcohol/other	16/4/6/10	24/6/5/6	n.s.
onset	initial/recurrence	7/29	10/31	n.s.
pervious TACE	absence/presence	10/26	13/28	n.s.
Child-Pugh grade	A/B/C	21/15/0	27/14/0	n.s.
HCC stage	I/II/III/IV	6/15/14/1	13/17/10/1	n.s.
tumor size (mm)	median (range)	13 (10-40)	14(10-22)	n.s.
AFP (ng/ml)	median (range)	38 (1-4055)	12 (1-4798)	n.s.
DCP (mAU/ml)	median (range)	76 (5-557000)	56 (11-8470)	n.s.
dose of lipiodol (mL)	median (range)	2.45 (1.0-4.0)	1.7 (0.75-4.0)	$P<0.01$
number of treated nodules	1/2/3/4	16/14/4/2	30/6/5/0	$P<0.05$

B-TACE, balloon-occluded transcatheter arterial chemoembolization; cTACE, conventional transcatheter arterial chemoembolization; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; HCV, hepatitis C virus; HBV, hepatitis B virus; n.s., not significant.

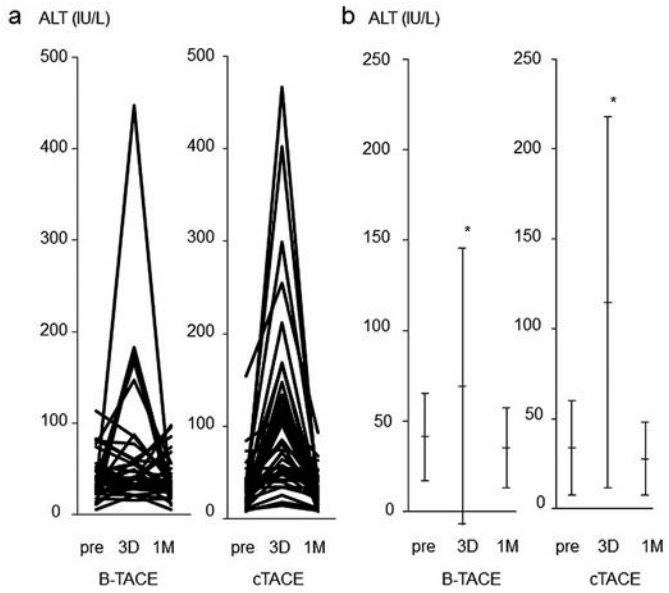

Fig. 1. Changes in alanine transaminase (ALT) levels before treatment and at 3 days (3D) and 1 month (1M) after treatment in the balloon-occluded transcatheter arterial chemoembolization (B-TACE) group and conventional superselective transcatheter arterial chemoembolization (cTACE) group. (a) Changes in each case. (b) Means ± standard error, $^{*}P<0.05$.

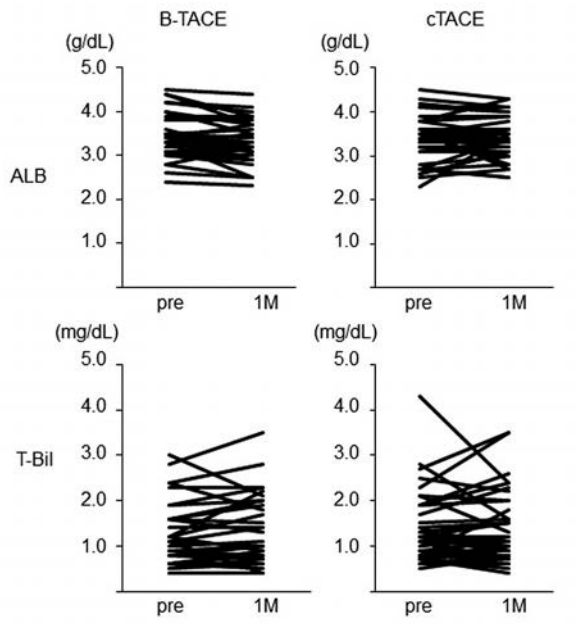

Fig. 2. Changes in albumin (ALB) and total bilirubin (T-Bil) levels before treatment and at 1 month (1M) after treatment in the balloon-occluded transcatheter arterial chemoembolization (B-TACE) group and conventional superselective transcatheter arterial chemoembolization (cTACE) group.

Table 2. Adverse events after TACE

	B-TACE (n=36)			
	Grade 1	Grade 2	Grade 3	Grade 4
Fever	15 (42%)	0	0	0
Abdominal pain*	3 (8%)	0	0	0
Nausea, vomitting	4 (11%)	0	0	0
Ascites	1 (3%)	0	0	0
Leukocytopenia	2 (6%)	1 (3%)	0	0
Thrombocytopenia	15 (42%)	8 (22%)	10 (28%)	0
Elevation of T-Bil	12 (33%)	7 (5%)	1 (3%)	0
Elevation of ALT*	15 (42%)	4 (11%)	2 (6%)	0
Elevation of CRE	2 (6%)	0	0	0

	cTACE (n=41)			
	Grade 1	Grade 2	Grade 3	Grade 4
Fever	13 (32%)	2 (5%)	0	0
Abdominal pain*	13 (32%)	3 (7%)	0	0
Nausea, vomitting	10 (24%)	0	0	0
Ascites	3 (7%)	0	0	0
Leukocytopenia	1 (2%)	2 (5%)	0	0
Thrombocytopenia	17 (41%)	11 (27%)	4 (10%)	1 (2%)
Elevation of T-Bil	11 (27%)	11 (27%)	3 (7%)	0
Elevation of ALT*	18 (44%)	11 (27%)	5 (12%)	0
Elevation of CRE	6 (15%)	0	0	0

The Grade of adverse events were evaluated by CTCAE ver. 4.0.
B-TACE, balloon-occluded transcatheter arterial chemoembolization; cTACE, conventional transcatheter arterial chemoembolization; T-Bil, total bilirubin; ALT, alanine transaminase; CRE, creatinine; *, $P<0.05$.

17.8%, 20.0%, and 6.7%, respectively, in the B-TACE group and 44.4%, 22.2%, 26.7%, and 6.7%, respectively, in the cTACE group (Table 3). There was no significant difference observed between the two groups.

Discussion

In our retrospective study, the injected dose of lipiodol was significantly greater and the simultaneous treatment of multiple nodules was significantly frequent in the B-TACE group. However, injury of the liver parenchyma, which is measured by the elevation of serum ALT level at 3 days after TACE was significantly lower in the B-TACE group than in the cTACE group.

When the balloon on the catheter occludes the hepatic artery, the peripheral blood pressure is reduced. However, blood flow is preserved by the blood supply from the peribiliary vascular plexus[8] or isolated artery[9]. Therefore, when the hepatic artery is occluded by the balloon, the miriplatin-lipiodol suspension has difficulty in flowing into the liver parenchyma. Consequently, it is considered that liver injury is reduced in the B-TACE group.

Many patients with HCC have liver cirrhosis as an underlying disease. Therefore, these patients are more likely to have a poor residual liver function. HCC therapies demand not only a curative effect

Table 3. Treatment effects of target HCC nodules

	B-TACE n=45	cTACE n=45
TE4	25 (55.6%)	20 (44.4%)
TE3	8 (17.8%)	10 (22.2%)
TE2	9 (20.0%)	12 (26.7%)
TE1	3 (6.7%)	3 (6.7%)

B-TACE, balloon-occluded transcatheter arterial chemoembolization; cTACE, conventional transcatheter arterial chemoembolization; TE, treatment effect

on HCCs but also the safe preservation of liver functions. Serum albumin and T-Bil levels at 1 month after TACE were not worse compared with those before treatment for both groups. The degree of liver injury does not appear to have an influence on the liver function. However, HCC is characterized by multicentric genesis and intrahepatic metastasis. Therefore, treatments for HCCs (e.g., TACE) are repeatedly performed for the same patient. There is some possibility of reducing the decline in liver function when B-TACE is performed rather than when repetitive cTACE is performed. Furthermore, with regard to adverse effects, abdominal pain caused by TACE is significantly milder in the B-TACE group than in the cTACE group. Grade 2 fever was found only in the cTACE group.

Because the number of elderly patients with HCC who often have poor residual liver function are increasing, the influence on hepatic function and adverse effects have become more important factors while selecting a treatment for patients with HCC.

TACE is an effective therapy for HCCs[10)11)]. In particular, superselective TACE is useful for improving the patients' prognosis[2)12)]. Superselective TACE aims to obtain a local therapeutic effect via hepatic infarction and requires the selective deep insertion of a microcatheter into a peripheral artery. This functions to wedge the tumor-feeding artery, and thus, the injection of lipiodol under high pressure into the tumor and surrounding liver tissues can be performed[13)]. However, it is difficult to insert a microcatheter far enough to wedge the artery.

In B-TACE, a similar situation with superselective TACE is obtained by a balloon occlusion at a more proximal portion of the tumor-feeding artery. In addition, the inflated balloon prevents the backflow of lipiodol and embolic material. Therefore, B-TACE makes it possible to intensively administer lipiodol and anti-cancer drugs to HCC[3)] and to enhance the therapeutic effects[4)].

In this study, there is no significant difference in the treatment effects between the B-TACE and cTACE groups. Arai et al[4)] and Ogawa et al[5)] reported significantly higher TE values in the B-TACE group than in the cTACE group. This difference may be caused by the smaller tumor size in our study than in previous studies[4)5)]. Consequently, relatively high TE values were obtained in the cTACE group in our study.

The limitation of the current study is the retrospective approach and small number of cases investigated only in single facility. To assure the argument, a multi-institutional randomized control

study is required.

In conclusion, in the B-TACE group, we obtained equal treatment effects and significantly less liver injury compared with the cTACE group. Our findings indicate that B-TACE with miriplatin is a useful procedure for patients with HCC who have a poor residual liver function and require TACE repeatedly.

Acknowledgements

The author declare no potential conflicts of interest.

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〈和文抄録〉

肝細胞癌に対する TACE 後の肝障害はバルーン閉塞下に行うことで軽減される

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市立福知山市民病院消化器内科

肝細胞癌に対するバルーン閉塞下肝動脈化学塞栓療法（B-TACE）の安全性と治療効果を通常の肝動脈化学塞栓療法（cTACE）と比較し，その有用性を検討した．方法：36 症例に B-TACE を行い，術後の肝障害の程度，肝予備能への影響，副作用の頻度，治療効果を cTACE を行った 41 症例と比較検討した．結果：B-TACE 群の術後 3 日目の血清 ALT 値は平均 68.2 IU/l で，cTACE 群の平均 111.2 IU/l に比し，有意に（$P<0.05$）低値であった．また B-TACE 群では術後の腹痛が有意に（$P<0.05$）軽度であった．肝予備能への影響や治療効果には差が見られなかった．結論：B-TACE は cTACE に比し，軽度な肝障害で，同等の治療効果を得ることができた．肝硬変により肝予備能が低下した肝細胞癌患者にとって，B-TACE は有用な治療法である．

キーワード：肝細胞癌，バルーン閉塞下肝動脈化学塞栓療法，肝障害，治療効果．