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Original Article

Bear bile powder suppresses the increase of IL-8 and improves liver function post transcatheter arterial chemoembolization in hepatocellular carcinoma patients

Cheng Wu[1,2*], Shufang Liang[1*], Qun Liu[1*], Shasha Yu[1], Yuyu Guo[1], Xiaolin Liu[1], Yicheng Yan[1], Man Yao[1], Yongbin Meng[1], Xiaofeng Zhai[1], Zhe Chen[1], Shu Li[3], Binbin Cheng[1], Changquan Ling[1,4]

[1]Department of Traditional Chinese Medicine, Changhai Hospital, Second Military Medical University, Shanghai, China; [2]Department of Infectious Disease, No. 456 Hospital of PLA, Jinan, Shandong Province, China; [3]Department of Gastroenterology, Baoshan Branch, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China; [4]E-Institute of TCM Internal Medicine, Shanghai Municipal Education Commission, Shanghai, China. [*]Equal contributors and co-first authors.

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Abstract: Transcatheter arterial chemoembolization (TACE), the main therapeutic method for unresectable hepatocellular carcinoma (HCC), may induce the release of a large number of proinflammatory cytokines, which may promote tumor recurrence and metastasis and angiogenesis. We therefore investigated the effect of bear bile powder (BBP) on TACE-induced proinflammatory cytokines in HCC patient. A total of 107 cases aged from 18 to 80 years were enrolled, and were randomly assigned into control or BBP groups, with 56 cases in control group and 51 cases in BBP group. Drugs were initially administered 1 day before TACE and were withdrawn on the 5th day after TACE. CRP, IL-6, and IL-8 levels significantly increased on the 3rd and 5th days post TACE. BBP treatment significantly reduced the IL-8 level on the 5th day post TACE, but showed little effect on the elevation of CRP and IL-6. TNFα levels were not significantly increased in the two groups on the 3rd and 5th days after TACE. However, BBP significantly decreased the TNFα level compared with control. BBP also significantly improved the AST level and AST/ALT ratio post TACE. In conclusion, our study suggests that BBP is able to decrease elevation of IL-8 and improve liver function post TACE in HCC patients. Therefore, the results indicate that BBP may probably improve the prognosis of HCC patient undergoing TACE.

Keywords: Bear bile powder, hepatocellular carcinoma, hypoxia, inflammatory cytokines, transcatheter arterial chemoembolization

Introduction

Hepatocellular Carcinoma (HCC), the most common primary malignant tumor of the liver, is considered to be the third leading cause of all cancer-related deaths and fifth common cancer worldwide [1]. Despite recent advances in the treatment of HCC, the prognosis of HCC patients is still poor [2, 3]. Only a few patients are eligible for curative treatments such as resection or liver transplantation.

Transcatheter arterial chemoembolization (TACE) is the main therapeutic method for the treatment of unresectable and recurrent HCC [4]. Although many studies showed that TACE is able to improve survival and suppress tumor progression, other studies showed that TACE increases the recurrence rate and aggravates the prognosis in HCC patients [5-8]. Ideally, iodine oil should achieve complete embolization and thus lead to the complete tumor necrosis. However, TACE treatment usually does not reach complete embolization in the majority of HCC patients. It is widely reported that TACE-induced tissue ischemia and hypoxia may lead to the release of a large number of proinflammatory cytokines, such as interleukin (IL)-6 and IL-22, which are able to aggravate liver injury, and even increase the risk of death [9, 10]. In

Table 1. Clinicopathological characteristics of HCC patients

Characteristics		Cases		Total
		Control	BBP	
Gender	Male	44	38	82
	Female	12	13	25
Age (years)		55.7 ± 8.5	54.1 ± 8.1	54.9 ± 8.3
BCLC stage	0	2	1	3
	A	12	10	22
	B	42	40	82
Child-Pugh classification	A	55	50	105
	B	1	1	2

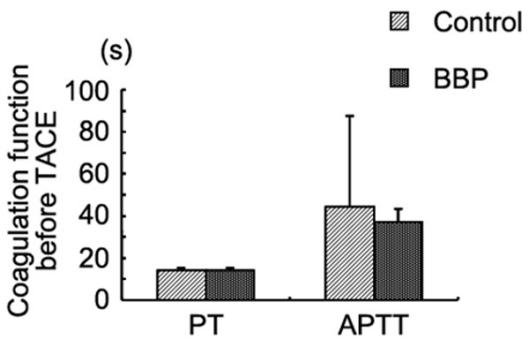

Figure 1. Coagulation function of patients before TACE.

addition, increased proinflammatory cytokines in the tumor microenvironment may enhance migration and invasion of HCC cells, and thereby facilitate the metastasis of tumor [11-14]. Therefore, effective prevention and management of the inflammation are crucial to fast patient recovery and improve patient satisfaction and quality of life.

Bear bile powder (BBP) is the dried bile from black or brown bear, possessing many pharmacological activities, including antipyretic analgesic and anti-inflammatory effects [15]. It has been reported that ursodeoxycholic acid, the main active component of BBP, is able to activate the PI3K/Akt signaling pathway to promote the synthesis of glutathione by liver cells and thereby prevent oxidative damage [16, 17]. Treatment with cytoxan in combination with BBP could not only protect the liver functions, but also reduce the recruitment of monocytes and macrophages through the regulation of tumor microenvironment and thus plays anti-inflammatory and anti-metastasis effects [18]. Therefore, we investigated the effect of BBP on the inflammatory reaction of HCC patients after TACE.

Materials and methods

Patients

Diagnosis of HCC was achieved according to the standards for the diagnosis and treatment of primary liver cancer (2011) issued by the Ministry of health of People's Republic of China [19]. Male or female patients aged from 18 to 80 years with recurrent or unresectable tumors were admitted to Department of Traditional Chinese Medicine, Changhai Hospital from June 2015 to July 2016. The patients met the following criteria were enrolled in this study.

Inclusion criteria: (1) Child-Pugh A or B stage of liver function; (2) 0, A or B stage of the tumor according to the BCLC criteria; (3) No upper gastrointestinal bleeding in the past 1 month; (4) The patient agreed to participant in the clinical trial and signed the informed consent document.

Exclusion criteria: (1) Participating in other clinical trial; (2) Platelet count < 30 × 10^9/L; (3) Use of glucocorticoids in the past 1 month; (4) In combination with severe heart, brain, liver, kidney, or hematopoietic system diseases or mental disease; (5) Patients who were not treated according to regulations in the setting of informed consent so that efficacy was difficult to assess or patients who withdraw from the clinical trial regardless of the reason.

Treatment procedure

Randomization and masking: The randomization code was prepared using computer-generated random numbers. Every eligible participant obtained a code before admission to the treatment groups. The details of the assignment and administration were unknown to any of the investigators including the coordinator. All study personnel and participants were blinded to the treatment assignment for the duration of the study.

Administration: The patients enrolled were assigned into two groups, the placebo control group and the BBP group. Drugs were initially administered 1 day before TACE and were withdrawn on the 5th day post TACE. The course of treatment was 6 days. Patients in the placebo

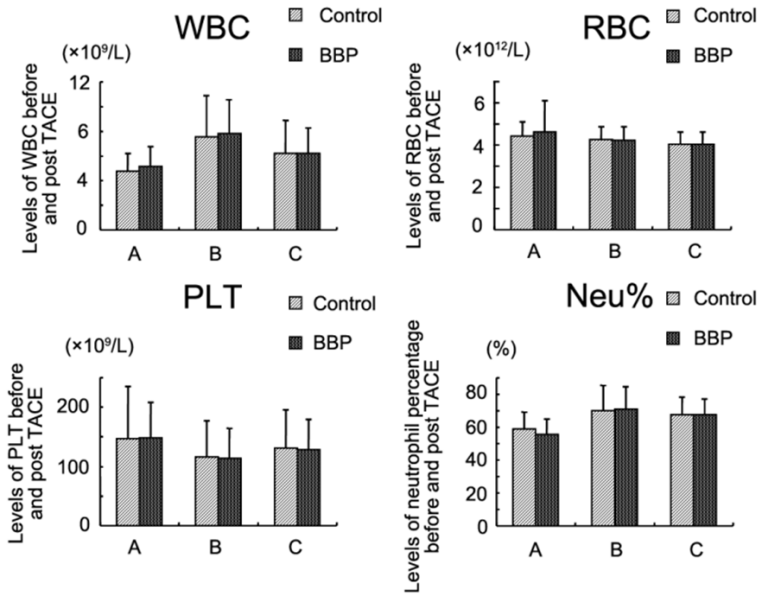

Figure 2. Routine blood parameters of patients before and post TACE. A. Before TACE; B. The 3rd day post TACE; C. The 5th day post TACE.

control group were treated with oral placebo capsule (essential component was corn starch), 2 capsules 2 times daily. Patients in the BBP group were treated with 2 BBP capsules (250 mg BBP per capsule), 2 times daily. The drugs were given half an hour after breakfast and supper, respectively. The BBP capsule and the placebo capsule were provided by the Fujian Greetown Medicine Industry CO., LTD (Quanzhou, Fujian, China).

Ethics: This study was approved by the Ethics Committee of Changhai Hospital, Second Military Medical University (No. CHEC2015-070). Informed consent documents were signed by the patients or the assigned relatives. All work reported herein was conducted in China.

TACE: TACE procedures on all patients were performed as described previously by one group of doctors in the Department of Radiology, Changhai Hospital [20].

Clinical assessment

Routine blood parameters, coagulation function, liver function parameters including total bilirubin (TB) level, direct bilirubin (DB), alanine aminotransferase (ALT), aspertate aminotransferase (AST), and albumin (ALB) were measured by the Clinical Laboratory Center, Changhai Hospital.

Enzyme linked immunosorbent assay

The C reaction protein (CRP), tumor necrosis factor (TNF) α, IL-6, and IL-8 were determined by enzyme linked immunosorbent assay (ELISA) as described previously [21].

Statistical analysis

All data are presented as the mean ± standard deviation (S.D). Statistical significance was determined using SPSS 18.0 for Windows. Data analysis was performed by one-way analysis of variance (ANOVA), followed by Fisher's LSD. Differences with P values < 0.05 were considered to be statistically significant.

Results

Baseline of the patients

From June 2015 to July 2016, a total of 107 cases diagnosed with HCC were recruited in this study, with 82 cases of male and 25 cases of female, and an average age of 54.9 ± 8.3 years. Fifty-six patients (44 cases of male and 12 cases of female, average age 55.7 ± 8.5 years) were designated into the control group and 51 cases (38 cases of male and 13 cases of female, average age 54.1 ± 8.1 years) were designed into the BBP group (**Table 1**). There were no significantly differences in the gender, age, BCLC stage, and Child-Pugh stage in the two groups before TACE (**Table 1**). The differences in the WBC, RBC, HGB, PT, APTT, TB, DB, ALT, AST, ALB, AST/ALT, CRP, TNFα, IL-6, and IL-8 levels before TACE between the two groups were all not significant (**Figures 1**-**4**).

BBP reduced the IL-8 and TNFα levels post TACE

In accordance with previous reports, CRP and many proinflammatory cytokines, including IL-6 and IL-8, were significantly increased on the 3rd and the 5th days post TACE compared with those before TACE in the control group (**Figure 3**). The levels of TNFα in the control group were also increased on the 3rd and the 5th days post

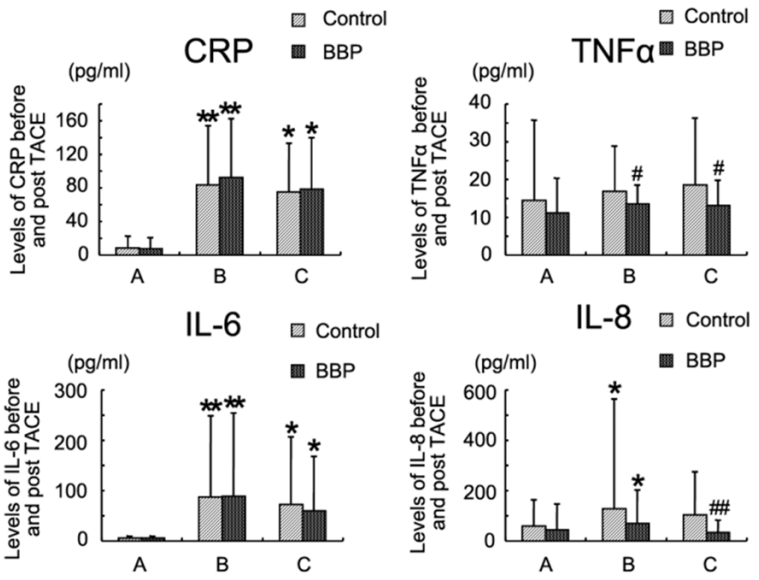

Figure 3. Inflammatory cytokines of patients before and post TACE. A. Before TACE; B. The 3rd day post TACE; C. The 5th day post TACE. *P < 0.05, **P < 0.01, compared with before TACE; #P < 0.05, ##P < 0.01, compared with control group at the same time point.

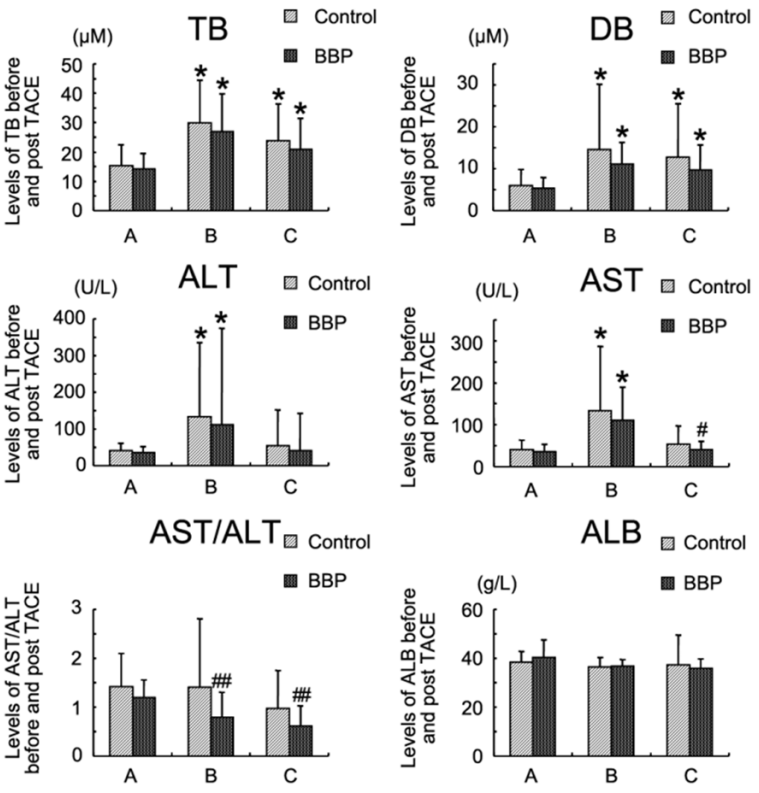

Figure 4. Liver function parameters of patients before and post TACE. A. Before TACE; B. The 3rd day post TACE; C. The 5th day post TACE. *P < 0.05, **P < 0.01, compared with before TACE; #P < 0.05, ##P < 0.01, compared with control group at the same time point.

TACE compared with that before operation, but the differences were not significant. BBP significantly reduced the IL-8 level on the 5th day post TACE compared with control, but showed little effects on the CRP and IL-6 levels compared with control. On the 3rd and 5th days post TACE, the TNFα levels in BBP group were significantly lower than those in control group.

BBP improved the liver function post TACE

To observe whether BBP could improve the liver function, the TB, DB, ALT, AST, ALB, AST/ALT levels were determined on the 3rd and 5th days post TACE. As shown in **Figure 4**, there were no significant differences in the TB, DB, ALT, AST and ALB levels on the 3rd day post TACE. The AST/ALT value was lower in the BBP group than that in the control group. On the 5th day post TACE, the AST level and AST/ALT ratio in the BBP group were significantly decreased compared with those in the control group. However, there were no significant differences in the TB, DB, ALT, and ALB levels on the 5th day post TACE.

Discussion

TACE-induced hypoxia induces the accumulation of HIF-1α inside tumor cells and nuclear translocation, and subsequently it promotes expression of proinflammatory cytokines, which may promote the metastasis and drug resistance of cancer cells [10, 22]. In the present study, our study showed that BBP administration suppressed the expres-

sion of IL-8 level after TACE. Furthermore, BBP also promotes the retrieve of liver function.

TACE is the common treatment method for the unresectable and recurrent HCC. TACE blocks blood vessels branching to the liver from arteries with lipiodol and/or chemoagents such as epirubicin, leading to hypoxic tumor necrosis. One of the main limitations of TACE is to cause an increased expression of angiogenic factor and thereafter an increase in angiogenesis by inducing hypoxia [23]. Therefore, TACE in combination with antiangiogenic therapeutics such as sorafenib has been considered a promising strategy to improve clinical outcomes of HCC and several clinical trials including the SPACE study have been conducted [24-27]. HIF-1α and VEGF are the key factors that are responsible for the regulation of angiogenesis during hypoxia [28]. However, angiogenesis is still induced even after HIF-1α knockdown in the hypoxic microenvironment [29]. These findings suggest that tumor angiogenesis is also partially influenced by various other factors, such as IL-8 [30]. IL-8, a key factor of endothelial cell survival and angiogenesis, is also regulated by HIF-1α [31]. HIF-1α promotes migration and invasion of HCC cells by upregulating IL-8 expression [32]. In human umbilical vein endothelial cells (*HUVEC*), inhibition of IL-8 results in angiogenic inhibition [33]. Combined knockdown of HIF-1α and IL-8 inhibits HCC cell-conditioned media induced-tube formation and invasion of endothelial cells, up-regulates the expression of apoptotic factors while down-regulates anti-apoptotic factors simultaneously [29]. In the current study, our results show that BBP administration suppresses TACE-induced IL-8 upregulation on day 5 post TACE, indicating that BBP may be an effective agent in regulating the hypoxic tumor microenvironment after TACE to hinder hypoxia-induced angiogenesis.

TACE also induces an increase of many other cytokines, such as IL-6 [10]. In accordance with previous study [10], our study also showed an early-phase increase in IL-6 levels after TACE which reflects acute-phase responses, whereas the levels of TNFα did not show a significant increase after TACE. Although the IL-6 levels in the BBP group 5 days after TACE were lower than in the control group, no significant difference was determined between control group and BBP group. Hypoxia has been shown to result in the activation of NF-κB which directly regulates the expression of many proinflammatory cytokines, including IL-6 and IL-8. Therefore, we conclude that the different effects of BBP on IL-6 and IL-8 expression shown in our study may be due to the relatively small sample size. In addition, the initial administration time and drug dose may also affect the result. In conclusion, our study showed that BBP could decrease TACE-induced elevation of IL-8 in HCC patients. BBP also promotes the decrease of AST level post TACE. However, there are also some limitations in the current study. First, our study only observed the effect of BBP on TACE-induced cytokines. Whether BBP could suppress TACE-related tumor recurrence or metastasis and thereby improve the prognosis of HCC patients should be further investigated. Second, the cytokines we determined were from the peripheral blood, and thus whether BBP could improve hypoxia-related inflammatory tumor microenvironment post TACE should be further confirmed in an animal model. Third, the sample size was relatively small. Fourth, the application of BBP has attracted substantial concerns and controversy from worldwide, because extensive use of BBP has made bears become endangered species and the extraction of bile from living bears is widely considered cruel [34]. Therefore, further study should be performed to verify the clinical value of BBP in the treatment of HCC in combination with TACE, and the effective components should be identified which may reduce the application of BBP in future.

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Disclosure of conflict of interest

None.

Abbreviations

BBP, Bear bile powder; HCC, Hepatocellular carcinoma; TACE, Transcatheter arterial chemoembolization; IL, Interleukin; TB, Total bilirubin; DB, Direct bilirubin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase;

ALB, Albumin; CRP, C reaction protein; TNF, Tumor necrosis factor; PT, Prothrombin time; APTT, Activated partial thromboplastin time; WBC, White blood cell; RBC, Red blood cell; HGB, Hemoglobin; PLT, Platelet.

Address correspondence to: Binbin Cheng and Changquan Ling, Department of Traditional Chinese Medicine, Changhai Hospital, Second Military Medical University, 168 Changhai Road, Shanghai 200433, China. Tel: +86 21 31161966; E-mail: cbb8202@126.com (BBC); Tel: +86 21 81871559; Fax: +86 21 81871559; E-mail: changquanling@smmu.edu.cn (CQL)

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