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Original Article

Effect of bifid-triple viable capsule combined with reduced glutathione injection on liver function and intestinal flora in patients with primary hepatocellular carcinoma after transcatheter hepatic arterial chemoembolization

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Abstract: Transcatheter hepatic arterial chemoembolization (TACE) could improve the prognosis of patients with primary hepatocellular carcinoma and reduce tumor recurrence. However, it can cause intestinal flora disorders. Our study aimed to assess the effects of bifid-triple viable capsule combined with reduced glutathione injection on liver function, endotoxin, and intestinal flora in patients with primary liver cancer after TACE therapy. Ninety patients with primary liver cancer underwent TACE therapy. The control group (n = 45) was given intravenous infusion of reduced glutathione, 1800 mg once/d, after TACE treatment; the treatment group (n = 45) was given bifid-triple viable capsule (420 mg orally 3 times/d) in addition to the treatment applied in Control group after TACE treatment. Both groups were treated for two weeks. The levels of liver function, endotoxin, and intestinal flora before and after TACE operation and the adverse drug reactions were compared between the two groups. The liver function indices (ALT, AST, TBIL, and DBIL), escherichia coli and endotoxin in the two groups were significantly higher after treatment than those before treatment ($P < 0.05$); the bacillus bifidus, and lactobacillus in the two groups were significantly lower after treatment than those before treatment($P < 0.05$). More importantly, after treatment, the liver function indices (ALT, AST, TBIL, and DBIL), escherichia coli and endotoxin in the treatment arm were significantly lower than those in the control arm and the differences were statistically significant ($P < 0.05$); after treatment, the bacillus bifidus and lactobacillus in the treatment arm were significantly higher than those in the control arm and the differences were statistically significant ($P < 0.05$). After treatment, the treatment group had a significantly higher Quality of life-Liver cancer (QOL-LC) score compared with control group ($P < 0.05$). Some side effects were more common in the treatment group. Bifid-triple viable capsule combined with reduced glutathione injection improved the liver function of patients with primary liver cancer after TACE therapy. Abnormal increases in endotoxin were avoided and intestinal flora was effectively regulated.

Keywords: Hepatocellular carcinoma, transcatheter arterial chemoembolization, bifid-triple viable capsule, reduced glutathione, liver function

Introduction

Primary hepatocellular carcinoma (HCC) is a common malignant tumor of the digestive system, which has high morbidity and mortality, and seriously threatens the health and life of afflicted patients [1-4]. In China, more than 50% patients are diagnosed with HCC annually, with the prevalence of chronic viral hepatitis B [5, 6] being very high in this population [7]. For HCC patients, curative treatments were traditionally only surgical resection and liver transplantation. However, liver cancer is usually highly malignant and most HCC patients are generally not considered suitable for curative treatment since they are often at an advanced stage

Table 1. Demographic and baseline characteristics of patients with primary hepatocellular carcinoma after TACE treatment

Parameters	Treatment group (n = 45)	Control group (n = 45)	*P* value
Age (years)	54.3 ± 7.0	54.4 ± 7.0	0.793
Sex			0.490
Male	33	30	
Female	12	15	
Child-Pugh classification			0.815
A	32	33	
B	13	12	
C	0	0	
BCLC classification			
A	8	9	0.992
B	31	29	
C	6	7	
AFP (μg/L)			0.649
≤ 400	30	32	
> 400	15	13	
Tumor size (cm)			0.484
< 5	4	3	
5-10	26	24	
> 10	15	18	

[8]. Consequently, less than 20% of patients are indicated for these treatments [9, 10]. Currently, transcatheter hepatic arterial chemoembolization (TACE) therapy is considered to be the gold standard of palliative treatment for HCC patients who are not eligible for surgery [11-14]. Indeed, several studies have reported that TACE therapy could reduce the rate of HCC recurrence and prolong the survive time of HCC pateints as a postoperative adjuvant therapy [15-17]. However, TACE therapy inevitably damages normal liver cells and thus can also lead to abnormal liver function [18, 19], resulting in abnormal secretion of endotoxin, which is not conducive to postoperative recovery [20, 21]. Therefore, the protection of liver function of liver cancer patients after TACE therapy is paramount.

In recent years, microecological preparations have been gradually applied to primary liver cancer after TACE therapy but few studies have been performed on the application of bifid-triple viable capsule in patients with primary liver cancer after TACE therapy. The aim of this study was to investigate the effect of bifid-triple viable capsule combined with reduced glutathione injection on liver function, endotoxin, and intestinal flora in patients with primary liver cancer after TACE therapy.

Materials and methods

Ethics statement

This study was approved by the Medical Ethics Committee of Nanjing Jiangbei People's Hospital Affiliated to Nantong University, China. All patients included in the study signed informed consent. Lastly, the study was carried out in accordance with the Helsinki declaration.

Patients

From April 2015 to July 2016, a total of ninety patients in Nanjing Jiangbei People's Hospital Affiliated to Nantong University were analyzed in this study (**Figure 3**). The ninety patients enrolled in this study were all TACE patients. They were randomly divided into the control group and the treatment group, with forty-five people assigned to each group. The treatment group received bifid-triple viable capsule combined with reduced glutathione injection and the control group received reduced glutathione injection only. Age, sex, tumor size, the contents of alpha-fetoprotein (AFP), Child-Pugh classification or BCLC classification were compared between the control arm and the treatment arm (P > 0.05) (**Table 1**).

Treatment protocol

The control group was given intravenous infusion of reduced glutathione (Kunming Jida Pharmaceutical Co. Ltd., China; National Medicine Permission Number H20080353), 1800 mg once/d after TACE treatment. In addition to the treatment mentioned in Control group, the treatment group was given bifid-triple viable capsule (Product Name: Baifei; Jincheng Haisi pharmaceutical Co. Ltd., China; Specification: 210 mg*12 Granules, Batch Number 111023), 420 mg orally 3 times/d after TACE treatment. The two groups were treated for two weeks.

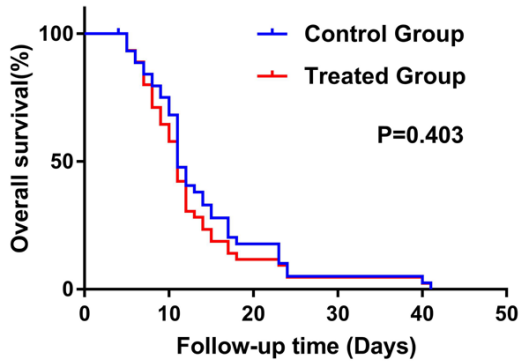

Figure 1. Kaplan-Meier curves comparing overall survival in patients who received bifid-triple viable capsule combined with reduced glutathione injection (treatment group), and patients treated by reduced glutathione injection (control group).

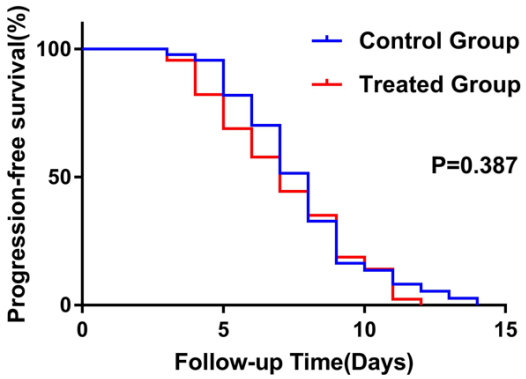

Figure 2. Kaplan-Meier curves comparing progression-free survival in patients who received bifid-triple viable capsule combined with reduced glutathione injection (treatment group), and patients treated by reduced glutathione injection (control group).

Eligibility criteria

Patients with primary HCC were eligible for study inclusion if they met the following criteria: (1) in accordance with the criteria for clinical diagnosis and staging of primary liver cancer [22], at the same time, primary liver cancer was diagnosed by pathological biopsy; (2) evidence of hard liver or liver lumps (AFP > 400 ng/L); (3) single imaging examination revealing features of hepatocellular carcinoma occupying lesions (AFP > 400 ng/L); (4) two imaging examinations revealing features of hepatocellular carcinoma occupying lesions (AFP ≤ 400 ng/L); (5) more than two liver cancer markers were positive and one imaging examination revealed features of hepatocellular carcinoma occupying lesions (AFP ≤ 400 ng/L); (6) TACE postoperative patients; and (7) no extrahepatic metastasis and large vascular infiltration.

Exclusion criteria: (1) autoimmune diseases; (2) patients with severe infectious diseases; (3) people suffering from poor mental health where they would be unable to take medicine or treatment according to a regimen; (4) severe hepatic and renal dysfunction; (5) metastatic liver cancer; (6) gestation; (7) coagulation dysfunction; (8) fulminant ascites.

Assessment

(1) Definition of Efficiency: the clinical symptoms disappeared or markedly improved and the indices of liver function returned to normal; definition of valid: the clinical symptoms improved and the indices of liver function decreased by more than 50% before treatment; definition of invalid: the clinical symptoms did not improve and the decrease in liver function indices was not obvious or the condition was aggravated. (2) In the preoperative and postoperative two-week periods, 5 mL of blood from the elbow vein was centrifuged for 10 min at a speed of 3000 r/min, and then the serum was used. The liver function indices, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and direct bilirubin (DBIL) were detected by an automatic biochemical detector. (3) In the preoperative and postoperative two-week period, the level of endotoxin in plasma was detected by the limulus test and a chromogenic method according to the kit instructions. (4) Fecal samples were collected and the contents of intestinal microflora were measured (isolation and enumeration of 24 h *Escherichia coli*; isolation and enumeration of 24 h Bifidobacterium; isolation and enumeration of 24 h Lactobacillus). (5) On admission and after treatment, the quality of life of the two groups was assessed by the quality of life scale for patients with primary liver cancer. (6) National Cancer Institute Common Toxicity Criteria (version 3.0) was used to evaluated toxicity.

Statistical analysis

Survival curves were analyzed using the Kaplan-Meier method and the differences between the two groups were analyzed by the log-rank test. All statistical analysis was per-

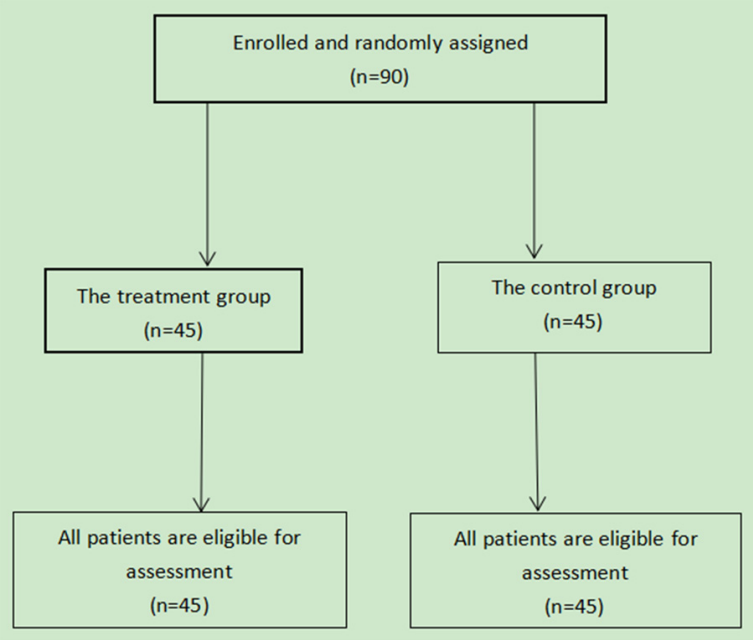

Figure 3. Study flowchart.

formed using SPSS software, version 21.0 (IBM, USA). Measurement data are expressed as mean ± standard deviation and evaluated using the t-test. Categorical data were evaluated using the Chi-square test or Fisher exact test. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

All patients in the study were followed up until death or after 41-months follow-up assessment. Forty people died of upper gastrointestinal bleeding, twenty people died of kidney failure, eleven died of liver rupture, and seventeen died of liver failure. The median overall survival time was 11 months and ranged from 3 to 42 months in the treatment group, while it was 10 months in the control group and ranged from 3 to 40 months. However, the difference was not significant ($P = 0.403$). The Kaplan-Meier curve for overall survival is shown in **Figure 1**. Median progression-free survival (PFS) in the treatment group was 7 months with a range of 3 to 15 months and in the control group it was 8 months with a range of 2 to 14 months. However, the difference was not significant ($P = 0.387$). The Kaplan-Meier curve for PFS is shown in **Figure 2**.

The demographic and baseline characteristics of the ninety patients are summarized in **Table 1**. Ninety patients were randomized to receive either triple viable capsule or its combination with reduced glutathione injection (the treatment group) or reduced glutathione injection only (the control group). All ninety patients were evaluated (**Figure 3**). There were no significant differences in general clinical parameters such as age, sex, tumor size, AFP contents, Child-Pugh classification or BCLC classification between the control and the treatment groups (**Table 1**).

Assessment

Before treatment, there were no significant differences in liver function indices such as ALT, AST, TBIL, and DBIL between the control and the treatment groups ($P > 0.05$); no differences were found in intestinal flora such as bacillus bifidus, escherichia coli or lactobacillus between the control and the treatment groups; the difference in endotoxin was also not significant ($P > 0.05$) (**Table 2**). The liver function indices (ALT, AST, TBIL, and DBIL), escherichia coli and endotoxin in the control and the treatment groups were significantly higher after treatment than those before treatment and the differences were statistically significant ($P < 0.05$); the bacillus bifidus and lactobacillus in the control and the treatment groups were significantly lower after treatment than those before treatment and the differences were statistically significant ($P < 0.05$). More importantly, after treatment, the liver function indices (ALT, AST, TBIL, and DBIL), *escherichia coli* and endotoxin in the treatment group were significantly lower than those in the control group and the differences were statistically significant ($P < 0.05$); after treatment, the bacillus bifidus and lactobacillus in the treatment group were significantly higher than those in the control group and the differences were statistically significant ($P < 0.05$) (**Table 2**).

The clinical efficacy is summarized in **Table 3**. The rate of efficiency, valid and invalid seen in

Table 2. Comparison of liver function, endotoxin, and intestinal flora between the treatment group and the control group

Item	Treatment group (n = 45)		Control group (n = 45)	
	Before treatment	After treatment	Before treatment	After treatment
Liver function index				
ALT ($U.L^{-1}$)	56.8 ± 6.4	97.3 ± 7.5*,▲	56.4 ± 6.3	148.3 ± 7.6*
AST ($U.L^{-1}$)	45.5 ± 4.3	92.1 ± 8.6*,▲	46.5 ± 4.9	164.9 ± 10.0*
TBIL ($\mu mol.L^{-1}$)	21.9 ± 5.1	24.0 ± 3.9*,▲	22.4 ± 5.7	27.9 ± 4.8*
DBIL/(μmol/L)	6.8 ± 3.2	7.5 ± 3.4*,▲	7.3 ± 3.5	8.9 ± 3.8*
Intestinal flora				
Bacillus bifidus ($Lg.g^{-1}$)	8.0 ± 0.5	7.1 ± 0.4*,▲	7.8 ± 0.5	6.4 ± 0.5*
Escherichia coli ($Lg.g^{-1}$)	7.2 ± 1.2	7.9 ± 1.1*,▲	7.3 ± 1.2	8.4 ± 1.4*
Lactobacillus ($Lg.g^{-1}$)	7.4 ± 0.4	7.1 ± 0.3*,▲	7.3 ± 0.5	6.2 ± 0.3*
Endotoxin ($ng.L^{-1}$)	96.3 ± 7.5	97.4 ± 8.3*,▲	95.6 ± 7.2	164.5 ± 10.7*

*P < 0.05 compared with before treatment in the same group, ▲P < 0.05 compared with control group for the same time. ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBIL = total bilirubin, DBIL = direct bilirubin.

Table 3. Comparison of efficacy between the treatment group and the control group

Efficacy	Treatment group (n = 45)	Control group (n = 45)	*P* value
Efficient	17 (37.8)	8 (17.8)	0.034
Valid	24 (53.3)	21 (46.7)	0.527
Invalid	4 (8.9)	16 (35.6)	0.002
Total efficiency	41 (91.1)	29 (64.5)	0.002

Table 4. Comparison of QOL-LC score between the treatment group and the control group

	Treatment group (n = 45)	Control group (n = 45)
Before treatment	121.3 ± 10.5	123.1 ± 9.2
After treatment	189.1 ± 7.5*,▲	157.7 ± 8.7*

*P < 0.05 compared with before treatment in the same group, ▲P < 0.05 compared with control group for the same time.

the treatment group was 37.8% (17), 53.3% (24), and 8.9% (4), respectively; and the rate of *total efficiency* in the treatment groups was 91.1% (41) (**Table 3**). The rate of efficiency, valid and invalid seen in the control group was 17.8% (8), 46.7% (21), and 35.6% (16), respectively, with a rate of *total efficiency* of 64.5% (29) (**Table 3**).

Before treatment, there was no statistically significant difference between the two groups with respect to the QOL-LC score (P > 0.05). Both arms had a significantly higher QOL-LC score after treatment than those before treatment. Notably, after treatment, the treatment group had a significantly higher QOL-LC score compared with the control group (**Table 4**).

The incidences of adverse drug reactions are summarized in **Table 5**. Both treatment regimens displayed expected toxicity. No treatment-related deaths occurred during drug interventions. Adverse drug reactions observed in the treatment arm included gastrointestinal reactions in three patients (6.7%), nervousness and irritability in two patients (4.4%), anxiety and rash in two patients (4.4%), respectively, and autoimmune hepatitis in one patient (2.2%). In the control arm, adverse drug reactions included gastrointestinal reactions in two patients (4.4%), nervousness and irritability in one patient (2.2%), anxiety and rash in one patient (2.2%), respectively (**Table 5**).

Discussion

HCC is one of the most common and malignant tumors in the world, and its 5-year survival rate is not optimistic. Most of liver cancer is caused by hepatitis virus infection [23, 24], especially in China [25]. In recent years, with the rapid development of science and technology, HCC patients in the early stages of disease could be treated by surgery, vascular intervention, or liver transplantation. However, most patients do not benefit from the option of surgery [26]. Currently, TACE is the first choice of treatment for advanced liver cancer but it can lead to liver dysfunction. Our study showed that bid-triple viable capsule was a commonly used microeco-

Table 5. Comparison of adverse drug reactions between the treatment group and the control group

Adverse drug reactions	Treatment group (n=45)	Control group (n=45)	*P* value
Gastrointestinal reactions	3	2	0.645
Anxiety	2	1	0.557
Nervousness and irritability	2	1	0.557
Rash	2	1	0.557
Autoimmune hepatitis	1	0	0.315

logical preparation in clinic, and could effectively regulate the host intestinal flora [27].

Patients with primary liver cancer commonly have disorders of intestinal flora and TACE can aggravate and disturb intestinal flora [28, 29]. The bifid-triple viable capsule, using a unique coating technology, was a triple microecological preparation of bifidobacterium, lactobacillus and *Enterococcus faecalis*, which can not only adjust intestinal flora disturbance and inhibit pathogens in the intestinal tract but can also reconstruct intestinal microecological balance and improve the sensitivity of the intestinal tract. Furthermore, it can also reduce the production of intestinal toxins and promote digestion of nutrients, while also promoting the synthesis of vitamins and stimulating host immunity [30, 31]. Studies by Wang et al [32] and others found that microecological agents could adjust the intensity of intestinal irritation in patients with irritable bowel syndrome, while also inhibiting the growth of normal flora in the small intestine, effectively alleviating the clinical symptoms of patients.

The results of this study showed that after treatment, the indices of liver function (ALT, AST, TBIL, and DBIL) and the level of endotoxin in the treatment arm were significantly lower than those in the control arm. Furthermore, the number of bacillus bifidus and lactobacillus was higher compared with those in the control arm, while the number of escherichia coli was lower than that in the control arm. Simultaneously, the total effective rate of the treatment arm was significantly better than the control arm. It has been suggested that the bifid-triple viable capsule combined with reduced glutathione could not only reduce liver injury, and prevent abnormal elevation of plasma endotoxin level, but it might also break the vicious spiral of liver injury-endo-toxin-liver injury [33]. Furthermore, it could effectively regulate the intestinal flora in patients with primary liver cancer after TACE surgery.

Our results also showed that the QOL-LC score of the treatment group was higher than that of the control group, indicating that the survival quality of the patients was much improved after combined treatment. It was noteworthy that the incidence of adverse drug reactions in the treatment group and the control group were 17.7% and 15.5% respectively, where there was no significant difference between the two groups. Therefore, this indicated that the quality of life of the patients was obviously improved after receiving triple viable capsule combined with reduced glutathione injection.

Our research had some limitations: (1) the sample is small and comes from a single-center study, therefore we should expand the sample size, and larger multicenter randomized-controlled trials are needed to improve the reliability of the experiment; (2) the research was not blind and its design was unreasonable and not as robust as we would wish. Thus, the results may affect the authenticity of our analysis.

In summary, our findings suggested that bifid-triple viable capsule combined with reduced glutathione injection could significantly improve the liver function of patients with primary liver cancer after transcatheter hepatic arterial chemoembolization therapy. Furthermore, this treatment regimen could reduce the levels of endotoxin, and effectively regulate the intestinal flora but reassuringly did not increase the rate of adverse drug reactions.

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Disclosure of conflict of interest

None.

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