Oncology and Translational Medicine
DOI 10.1007/s10330-014-1416-y

April 2015, Vol. 1, No. 2, P87–P91

ORIGINAL ARTICLE

Jinlong capsule decreases adverse reactions after transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma*

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Abstract

Objective The aim of this study was to analyze whether Jinlong capsule could decrease adverse reactions after transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma.

Methods Eighty-two patients with hepatocellular carcinoma were randomly divided into the control group and experimental group. On the first day after TACE, the experimental group started receiving four Jinlong capsules orally three times daily, whereas the control group did not receive the treatment.

Results The incidences of erythropenia and thrombocytopenia in the experimental group was lower than those in the control group (P = 0.040 and 0.033, respectively). The differences in serum levels of aminotransferase, albumin, potassium, and sodium between the two groups were significant (P = 0.034, 0.034, 0.013, and 0.044, respectively). The mean durations of stomachache and abdominal distension in the experimental group was significantly shorter than those in the control group (P = 0.004 and 0.021, respectively). However, there were no significant differences in the incidences of nausea, fever, and vomiting between the two groups (P = 0.490, 0.495, and 0.585, respectively).

Conclusion The reduction in the incidence rate and duration of partial adverse reactions after TACE was observed in hepatocellular carcinoma patients treated with Jinlong capsule compared to untreated patients, suggesting possible beneficial effects exerted by Jinlong capsule on the reduction of TACE-induced liver damage, thereby improving liver function and, consequently, the quality of life.

Received: 20 October 2014
Revised: 7 January 2015
Accepted: 5 March 2015

Key words: Jinlong capsule; primary hepatocellular carcinoma (PHC); transcatheter arterial chemoembolization (TACE); adverse reaction

Primary hepatocellular carcinoma (PHC) is one of the common malignant tumors of digestive system with high annual morbidity and mortality, which ranks the sixth most common cancer and the third leading cause of cancer-related death worldwide. In China, the latest numbers of new PHC cases and deaths per year account for more than 50% of those worldwide, ranking the second and third, respectively [1–2]. As the disease is often advanced at the first manifestation, there is a low rate of surgical resection or liver transplantation. Among the non-operative treatment approaches, transcatheter arterial chemoembolization (TACE) has been widely recommended as main palliative therapy for patients with unresectable PHC, who could not undergo surgical resection or liver transplantation [3]. However, because of high local concentration of chemotherapeutic agents and vascular embolization, TACE inevitably results in postembolization syndrome, manifesting as abdominal pain (mainly liver pain) and distention, temporary fever, poor appetite, insomnia, myelosuppression, decreased liver function, electrolyte disturbances, and other adverse reactions affecting most patients. Conservative treatment of these adverse reactions is mainly based on symptomatic therapy, including use of painkillers, stimulation of gastrointesti-

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* Supported by a grant from the Scientific Innovation Foundation of Xinjiang Medical University (No. XJC2013118).

nal motility, antifebrile medications, activation of bone marrow, and parenteral nutrition. The aim of this study was to investigate the effect of Jinlong capsule, a traditional Chinese medicine with complex composition, on the alleviation of the adverse reactions in PHC patients after TACE.

Patients and methods

Inclusion criteria

Patients with (1) PHC diagnosis according to the diagnostic criteria of modern oncology [4], (2) the Karnofsky performance status (KPS) > 60, (3) life expectancy of more than 3 months, who (4) declined to receive any other anticancer therapies (chemo- or radiotherapy) and (5) signed informed consent form were included in the study.

Exclusion criteria

Patients with (1) KPS < 60, (2) allergy to control medium, (3) severe organ dysfunction, (4) pregnancy and psychopathy, and (5) life expectancy of less than 3 months were excluded from this study.

General information

According to the group standard, 82 patients with PHC were selected for the study. The patients, 74 men and 8 women aged from 24 to 73 years [mean age (48.54 ± 4.16) years] were treated in the Affiliated Tumor Hospital of Xinjiang Medical University (Urumqi, China) between July 2010 and December 2011. Among them, 32 patients had one single nodule and 50 patients had multiple tumor nodules, 48 patients had tumor nodules located in the right lobe of the liver, 18 in the left, and 16 in both, and 4 patients had portal vein tumor thrombosis. We used a random number table to determine the patients' enrollment during the study period. The 82 patients were divided between the experimental group and control group ($n = 41$). There were no significant differences in sex, age, clinical type, histological type, and liver function between the groups ($P > 0.05$). The institutional ethical committee approved the current retrospective study, and written informed consent was obtained from all patients.

The extracted data included complete blood count and biochemical profiles obtained before and after the treatment. The numbers of patients with decreased leukocyte, erythrocyte, and thrombocyte counts, reduced levels of serum albumin, potassium, and sodium, and increased total bilirubin and alanine aminotransferase (ALT) were recorded. Other parameters included the quality of life (QoL) score after TACE and the mean duration of post-treatment adverse reactions.

Treatment

TACE was performed according to the standard protocol by the same intervention radiologist with more than 10 years of experience. Briefly, an arterial catheter was inserted into the femoral artery using the Seldinger method and placed in the hepatic artery. Prior to that, hepatic angiography was conducted to identify all the arteries feeding the tumor. After the arterial supply to the tumor was analyzed, the target vessels were selected. If variation in tumor vascularization occurred, the catheter was placed in the appropriate hepatic arteries.

The solution containing 100 to 200 mg of the chemotherapeutic agent (oxaliplatin, 50 mg/m^2, Hengrui Medicine Co., Ltd., Jiangsu, China) was injected into the hepatic artery through the catheter (5 F) or micro-catheter (2.8 F or 3 F). After that, hepatic artery embolization was performed with pirarubicin (60 mg/m^2; Pfizer, Nerviano, Italy) mixed or not with a maximum of 20 mL iodized oil (Lipiodol Ultra-Fluide; Andre Guerbet Laboratories, France) and control medium. The doses of oxaliplatin, pirarubicin, and iodized oil were individually determined according to the tumor size, tumor extent, and patient's liver function.

After interventional therapy, the patients of the experimental and control groups were provided with conventional therapy and care, including preoperative antiemetic, rehydration, and other symptomatic treatments. The patients in the experimental group were administered four Jinlong capsules (250 mg each) three times a day. Jinlong capsule (Z10980041) was prepared by the Beijing Health Pharmaceutical Co. (China) and provided by our hospital pharmacy.

Statistical analysis

All statistical analyses were performed with SPSS 13.0 statistical package (SPSS, Chicago, IL). Associations between categorical variables were assessed with the Chi-square test or Fisher exact test, and comparison of continuous variables was performed with the Student *t*-test. A *P*-value of less than 0.05 was considered significant.

Results

In this study, the numbers of patients with decreased erythrocyte and thrombocyte counts were notably less in the experimental group than in the control group on the fifth day after TACE, and the differences between the two groups were significant ($\chi^2 = 4.232$, $P = 0.040$, and $\chi^2 = 4.556$, $P = 0.033$, respectively). Moreover, the mean differences in leukocyte, erythrocyte, and thrombocyte counts were also statistically significant between the two groups ($P = 0.043$, 0.021, and 0.005, respectively, experimental versus control groups; Table 1).

With regard to the differences in liver enzymes and electrolytes between the two groups on the fifth day after TACE, the numbers of patients with increased ALT and

Table 1 Comparison of three parameters of blood routine examination in two groups

Groups	Leukocyte		Erythrocyte		Thrombocyte	
	Reduced No.	Reduced mean value (10^9/L)	Reduced No.	Reduced mean value (10^{12}/L)	Reduced No.	Reduced mean value (10^9/L)
Experimental group	16	1.01*	27*	0.44*	29*	10.61*
Control group	20	1.49	35	0.63	35	16.14
χ^2	0.792		4.232		4.556	
t		–2.106		–2.364		–2.927
P	0.373	0.043	0.04	0.021	0.033	0.005

Note: compared with control group, * $P < 0.05$

Table 2 Comparison of liver function and electrolyte in two groups (n)

Groups	No.	No. of raised parameters		No. of reduced parameters		
		Total bilirubin	Glutamic-pyruvic transaminase	Serum albumin	Serum kalium	Serum sodium
Experimental group	41	28	27*	31*	19*	19*
Control group	41	33	36	38	30	28
χ^2		1.600	4.474	4.479	6.136	4.038
P		0.206	0.034	0.034	0.013	0.044

Note: compared with control group, * $P < 0.05$

Table 3 Comparison of appetite, spirit, sleep, and fatigue after operation in two groups

Groups	No.	Average score			
		Appetite	Spirit	Sleep	Fatigue
Experimental group	41	4.51*	4.27*	4.41*	4.32*
Control group	41	4.10	3.78	4.00	3.95
t		2.378	2.712	2.425	2.079
P		0.020	0.008	0.018	0.041

Note: compared with control group, * $P < 0.05$

Table 4 Comparison of stomachache, abdominal distension, nausea, fever, and vomit after operation in two groups

Groups	No.	Stomachache		Abdominal distension		Nausea		Fever		Vomit	
		No.	Average time (d)	No.	Average time (d)	No.	Average time (d)	No.	Average time (d)	No.	Average time (d)
Experimental group	41	36	2.19*	12	1.58*	29	1.31	34	2.24	4	1.75
Control group	41	34	2.94	15	2.53	27	1.41	35	2.09	5	2.20
t			–2.963		–2.470		–0.695		–0.686		–0.574
P			0.004		0.021		0.490		0.495		0.584

Note: compared with control group, * $P < 0.05$

decreased albumin, potassium, and sodium levels in the experimental group were statistically less than those in the control group (P = 0.034, 0.034, 0.013, and 0.044, respectively). However, the difference in bilirubin between the two groups was not statistically significant (P = 0.206, Table 2).

As shown in Table 3, the QoL score in the experimental group was higher than that in the control group, as evidenced by statistically significant differences in appetite, spirit, sleep, and fatigue status between the two groups on the fifth day after TACE (P = 0.020, 0.008, 0.018, and 0.041, respectively).

The mean durations of stomachache and abdominal distension in the experimental group were significantly less than those in the control group (P = 0.004 and 0.021, respectively). However, there were no significant differences in the incidences of nausea, fever, and vomiting between the two groups (P = 0.490, 0.495, and 0.585, respectively; Table 4).

Discussion

According to the theory of traditional Chinese medicine (TCM), the basic pathogenesis of PHC is stagnation of liver Qi and blood, and fever. TCM treatment methods could exert their therapeutic effects by cleaning fire toxins, activating blood flow, and dissolving stasis, and through softening and dissipating stagnation. Jinlong capsule contains fresh extracts of Shougong (gecko), *Bungarus parvus*, and *Agkistrodon*. The active ingredients

are extracted by the process of modern cryogenic and biochemical separation from raw animal material, and hence, they retain maximum activity. Jinlong capsule contains 19 free amino acids, 18 hydrolyzed amino acids, polypeptides, enzymes, nucleosides, and various vitamins and microelements (but not arsenic, cadmium, mercury, bismuth, and antimony, all of which are harmful). Thus, Jinlong capsule can help in breaking blood stasis, dissipating binds, and resolving depression, and can exert attenuating and synergistic effects.

Bao *et al* [5] have reported that Jinlong capsule may enhance tumor response to treatment by inhibiting liver cancer cell proliferation and promoting their differentiation and maturation; they can also induce immune response by activating macrophages and NK cells and stimulating T and B cell proliferation. Another study has demonstrated that the activity of $CD3^+$, $CD4^+$, and NK cells and the ratio of $CD4^+$ to $CD8^+$ lymphocytes significantly increased in patients treated with Jinlong compared to the control group [6]. Furthermore, the study by Li *et al* [7] has confirmed that Jinlong capsule suppressed oncogenic transformation by significantly inhibiting the invasion, adhesion, and migration of MHCC97H liver cancer cells.

Modern studies suggest that cancer is a systemic disorder. Therefore, in cancer treatment, careful consideration should be given not only to local efficacy, but also to patient tolerance, adverse reactions, and quality of life during therapy. Surgical operation and radiofrequency ablation are considered as the treatments of choice in the early stages of cancer. Among non-surgical treatments, TACE is generally believed to be an effective palliative therapy [8–9]. According to the study of Takayasu *et al* [10], the median survival time of 8510 patients who underwent TACE as an initial treatment was 34 months. Moreover, TACE can be combined with radiofrequency ablation, radiation therapy, and targeted therapy. It has been reported that, in massive hepatocellular carcinomas, TACE combined with radiofrequency ablation caused complete necrosis in 43.9% of lesions (18/41), and partial necrosis in 56.1% of lesions (23/41); meanwhile, the levels of alpha-fetoprotein (AFP) decreased in 83.3% (25/30), increased in 10.0% (3/30), and did not change in 6.7% (2/30) of patients [11]. TACE combined with radiotherapy could improve the curative effect, prolong survival, and increase the one-year survival rate and QoL score for PHC patients with portal vein tumor thrombus [12]. However, TACE alone or combined with other treatments cannot completely destroy tumor tissue. In addition, TACE can cause serious side effects such as liver damage, bone marrow suppression, fever, pain, and vomiting.

Therefore, for the maintenance of patients' quality of life and systemic function of the body, clinicians should focus on reducing the adverse reactions after TACE. Recent years have seen the benefit of Jinlong capsule in PHC patients treated with TACE, which can not only improve the efficacy, but also reduce the side effects of chemotherapy and improve the quality of patients' life. In the present study, the number of patients with erythropenia and thrombocytopenia was less in the Jinlong-treated group than in the control group, and the reduction was significant. Moreover, leukopenia decreased in the Jinlong-treated group, although the difference in the number of patients with reduced leukopenia was not statistically significant. Overall, our results suggest that Jinlong capsule alleviates bone marrow suppression. Dong *et al* [13] have found that Jinlong capsule could prolong the overall survival rate of TACE-treated PHC patients and significantly improve neutropenia; compared with the control group, there was a marked decrease in AFP level (84.7%) and improvement in the efficacy (62.7%) and QoL score.

In our study, the patients in the Jinlong group demonstrated a more significant improvement in the Child-Pugh score, used to assess the prognosis of chronic liver disease, compared to the patients in the control group (79.2% versus 48.1%). Meanwhile, the extents of ALT increase and albumin decrease in the Jinlong group were significantly lower than those in the control group ($P < 0.05$). These effects may be attributed to the hepatoprotective effect exerted by Jinlong capsule against TACE-induced liver damage.

However, in our study we did not observe statistically significant difference in the number of patients with leukopenia between the two groups, which suggests that other factors such as postoperative fever and inflammation may be present. We found that the quality of life parameters such as postoperative appetite, mental state, sleep, and lassitude in the experimental group were superior to those in the control group. In addition, the duration of abdominal pain and distension was significantly shorter in the experimental group than in the control group ($P < 0.05$), which is consistent with a previous study [14].

Conclusion

In conclusion, the results of this study demonstrate that Jinlong capsule appears to increase the efficacy of TACE by decreasing the incidence and duration of adverse reactions, increasing tumor response, improving the post-treatment QoL, and reducing TACE toxicity for the patients with unresectable PHC. Although a definitive recommendation is currently premature, these findings suggest that Jinlong capsule could be considered as an adjuvant therapy for patients with unresectable PHC during TACE treatment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-014-1416-y
Cite this article as: Huang WK, Liu DY, You LN. *et al*. Jinlong capsule decreases adverse reactions after transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma. Oncol Transl Med, 2015, 1: 87–91.