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ORIGINAL ARTICLE

Evaluation of the safety and efficacy of glucocorticoid therapy for hyperbilirubinemia in patients with hepatocellular carcinoma who have undergone transcatheter arterial chemoembolization

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Abstract

Objective The aim of this study was to analyze the safety and efficacy of glucocorticoid treatment for hyperbilirubinemia in patients with hepatocellular carcinoma (HCC) who have undergone transcatheter arterial chemoembolization (TACE).

Methods We conducted a retrospective analysis of the clinical data of 198 patients with HCC who were admitted to The Fifth Medical Center of PLA General Hospital from June 2014 to August 2019 and underwent TACE therapy. The patients were divided into glucocorticoid (GCC) treatment group and control group. Standard liver-protecting procedures were used in both groups. The treatment group also received intravenous injections of methylprednisolone sodium succinate for 3–5 days. Reduction in bilirubin concentration, mean duration of hospitalization, and complications were compared between the two groups to investigate the safety and efficacy of GCCs for treatment of hyperbilirubinemia after TACE treatment.

Results Bilirubin concentrations were significantly lower in the treatment group than in control group on days 3 and 5 after GCC/conventional liver-protecting treatment ($P < 0.05$). The treatment group had significantly shorter durations of total post-surgery hospitalization, and recovery time than the control group (14.5 ± 4.6 days vs. 17.5 ± 6.6 days, $P < 0.001$; 9.2 ± 3.3 days *vs*. 11.8 ± 5.4 days, $P = 0.001$; 7.0 ± 3.3 days vs. 9.3 ± 4.6 days, $P < 0.001$). No GCC-associated complications were detected in the treatment group.

Conclusion Short-term use of GCCs to treat hyperbilirubinemia in patients with HCC who have undergone TACE is safe and associated with rapid decline in bilirubin concentration and shorter hospital stay compared with patients who did not receive GCCs.

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Key words: glucocorticoid; primary liver cancer; hyperbilirubinemia;transcatheter arterial chemoembolization (TACE)

Primary liver cancer (PLC) is the fifth most common cancer worldwide and the third leading cause of cancer deaths [1]. About 90% of PLC are hepatocellular carcinoma (HCC) [2–3]. Transcatheter arterial chemoembolization (TACE) is currently one of the most used methods of treating intermediate- or advanced-stage HCC [1–4]. TACE has been shown to slow tumor growth and vascular invasion and increase the life expectancy of individuals with HCC. Because most of these patients also have hepatic cirrhosis, their liver function is often severely compromised after a TACE procedure. The main manifestations include increased serum aminotransferase and bilirubin, decreased albumin and cholinesterase, and impaired blood coagulation, all of which can slow recovery and prolong hospital stay [5–6].

Glucocorticoids (GCCs) are widely used to treat chronic hepatitis and liver failure [7–9]. However, such treatment may induce adverse reactions such as infection, gastrointestinal tract (GIT) bleeding, and viral replication. Therefore, administration of GCCs to patients with liver disease remains controversial [10–11]. Recent findings show that GCCs could protect against chemotherapy-induced

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apoptosis and improve adverse reactions to tumor necrosis such as edema, inflammation, pain, and electrolyte disturbances [12–13]. Additionally, GCCs can inhibit adverse reactions to chemotherapy-induced cytotoxicity such as nausea and vomiting. We hypothesized that GCCs would rapidly alleviate the inflammatory response resulting from tumor necrosis after TACE, facilitating improved liver function and reduced bilirubin concentrations. We also hypothesized that early, low dose, and short-term administration of GCCs would alleviate its adverse effects. In the present study, we retrospectively analyzed clinical data of 198 patients with HCC who were admitted to The Fifth Medical Center of PLA General Hospital from June 2014 to August 2019 and developed hyperbilirubinemia (HBR) after TACE operation, to investigate the safety and efficacy of administering GCCs to treat post-TACE HBR.

Materials and methods

Patients

Data of 5124 patients with HCC who were admitted to The Fifth Medical Center of PLA General Hospital from June 2014 to August 2019 and treated with TACE were retrospectively analyzed. All patients had liver function tests on days 2 to 5 after TACE procedure. Bilirubin concentrations were mildly increased (17.1–51.3 μmol/L) in 937 patients, and 198 patients had HBR (≥ 51.3 μmol/L). Only the latter were included in our study. All patients had been diagnosed with HCC based on imaging examinations or pathology findings in accordance with the Barcelona clinic liver cancer (BCLC) staging criteria [14]. Among them, 13, 93, and 92 patients were classified as stage A, stage B, and stage C HCC, respectively. All underwent TACE. These patients' baseline characteristics are as shown in Table 1. There was no statistical difference between the two groups ($P > 0.05$).

Table 1 The baseline characteristics of 198 patients with HCC

Items	Treatment (n = 102)	Control (n = 96)	P
Age (year)	54.5 ± 8.7 (Range: 35–72)	56.8±8.9 (Range: 34–83)	0.074
Gender			0.291
Male	93	83	
Female	9	13	
Tumor Size (cm)	7.0 ± 3.3 (Range: 1.0–18.5)	6.4 ± 3.3 (Range: 0.9–18.2)	0.209
< 5	24	33	
≥ 5, < 8	41	36	
≥ 8	37	27	
Etiology			0.607
HBsAg Positive	90	84	
Anti-HCV Positive	8	10	
Alcohol	3	2	
Unknown	1	0	
Child-Pugh			0.343
Class A	61	51	
Class B	41	45	
PVTT			0.309
Absence	72	58	
Branch PVTT	23	28	
Main PVTT	7	10	
EHS			0.120
Presence	25	15	
Absence	77	81	
BCLC			0.982
Stage A	7	6	
Stage B	48	45	
Stage C	47	45	

Note: HBsAg:hepatitis B surface antigen; HCV:hepatitis C virus; PVTT:portal vein tumor thrombus; BCLC:barcelona clinic liver cancer

Treatment protocols

TACE treatment: Standard preoperative preparation was performed. The Seldinger technique was used for femoral arterial catheterization, followed by angiography of the common hepatic and superior mesenteric arteries to investigate tumor staining and portal vein filling. Fluorouracil (0.5–1.0 g), epirubicin (20–40 mg), and super-lipiodol (5–25 mL) were slowly injected after super-selective catheterization of the tumor-feeding arteries, with the volume of lipiodol depending on the tumor size. Gelatin sponge particles were then administered to embolize these arteries.

TACE can be performed in the following [3]: (i) Patients with intermediate- or advanced-stage PLC who cannot be managed surgically, but do not have severe liver or kidney dysfunction. Those patients may have large tumor masses (occupying < 70% of the liver), multiple nodular lesions, partial obstruction of the main portal vein, or complete obstruction of the main portal vein with a compensatory collateral vascular network connecting to the hepatic arteries. Their liver function must be Grade A or B according to the Child–Pugh system and ECOG scores 0–2. (ii) Patients with small lesions, who do not qualify for or are unwilling to undergo surgery or ablation procedures.

Contraindications to TACE include [3]: (i) Severe irreversible coagulation dysfunction; (ii) Complete obstruction of the main portal vein by tumor thrombus with little collateral vascular network development; (iii) Active infection that cannot be treated simultaneously; (iv) Extensive metastases with expected survival time less than 3 months; (v) Severe complications resulting from decompensated cirrhosis, such as GIT bleeding, hepatic encephalopathy, massive ascites, or hepatorenal syndrome; (vi) Cachexia or multi-organ failure; (vii) Tumor occupying ≥ 70% of the

liver; and (viii) Severely decreased numbers of peripheral leukocytes and platelets, with leukocytes < 2.0×10^9/L and platelets < 50×10^9/L.

Liver-protecting procedures: The 198 patients were retrospectively allocated to GCC treatment (n = 102) and control groups (n = 96) according to whether they had received GCCs. Both groups received conventional liver-protecting treatment (*i.e.*, glycyrrhizic acid, glutathione, polyene phosphatidylcholine, and ademetionine) to treat their post-surgery liver injury. The treatment group also received methylprednisolone sodium succinate (MSS, 40–80 mg i.v., q.d., for the first three days, followed by gradual reduction of dosages until discontinuation, which occurred within 7 days).

Follow-up and outcomes

Both groups were followed up with liver function tests on days 0, 3, 5, and 30 after GCC/conventional liver-protecting treatment. Changes in total bilirubin (TBIL), direct bilirubin (DBIL), alanine transaminase (ALT), and aspartate aminotransferase (AST) concentrations, and duration of hospitalization and healing were recorded. Adverse effects of the procedure were classified on a scale of 0–4 in accordance with the CTCAE v3.0 guidelines [15].

Statistical analysis

SPSS 19.0 was used for statistical analysis. Quantitative data are expressed as mean ± standard deviation . Discrete variables are expressed as the number of cases and percentages, and between-group comparisons were performed using the χ^2 test. P < 0.05 was considered to denote statistical significance.

Results

Comparison of major biochemical indexes

Concentrations of TBIL, DBIL, ALT, and AST on admission did not differ significantly between the treatment and control groups (P < 0.05, Table 2). Concentrations of all four of these biochemical variables gradually increased after TACE, but still did not differ significantly between the two groups (P > 0.05, Table 2). These liver function indexes improved in both groups after introduction of GCC/conventional liver-protecting treatment. Three days after commencing these treatments, the treatment group had significantly lower concentrations of TBIL, DBIL, ALT, and AST than the control group (P < 0.05, Fig. 1). Five days later, the treatment group had significantly lower concentrations of TBIL and DBIL than the control group (Fig. 1). On day 30, there were no differences in the

Table 2 Comparison of major liver function indicators before and after TACE treatment between the two groups (mean ± standard)

Group	Cases	Pre-TACE				Post-TACE			
		TBII (μmol/L)	DBII (μmol/L)	ALT (U/L)	AST (U/L)	TBII (μmol/L)	DBII (μmol/L)	ALT (U/L)	AST (U/L)
Treatment	102	24.7 ± 9.9	12.8 ± 7.1	41.3 ± 27.2	55.5 ± 35.5	68.9 ± 17.3	40.8 ± 19.6	335.9 ± 254.3	344.5 ± 267.60
Control	96	27.4 ± 10.5	15.0 ± 8.6	41.9 ± 21.8	57.1 ± 34.7	66.6 ± 18.8	37.6 ± 17.1	314.1 ± 243.4	331.7 ± 317.5
P value		0.069	0.111	0.826	0.390	0.145	0.376	0.489	0.652

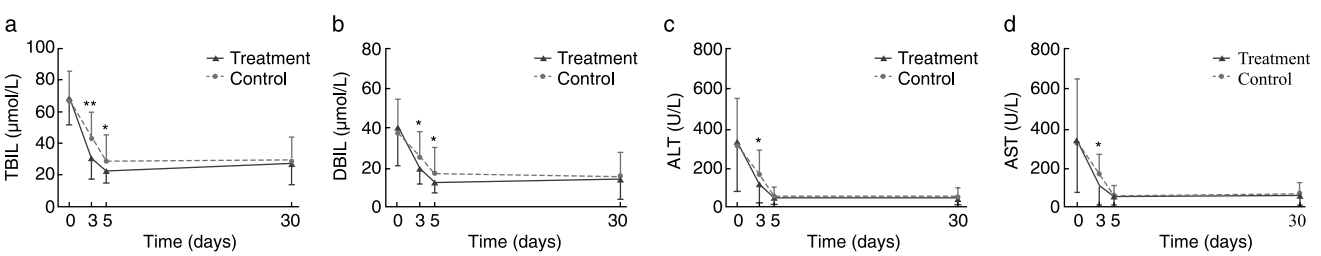

Fig. 1 Comparisons of major liver function indexes between the two groups after administration of GCC/conventional liver protecting procedures on day 0, 3, 5, and 30.

(a, b) Patients in both groups had significantly decreased TBIL and DBIL concentrations compared with pretreatment concentrations. On days 3 and 5, the treatment group had significantly lower TBIL and DBIL concentrations than the control group. (c, d) Both groups had significantly decreased ALT and AST concentrations compared with pretreatment concentrations. On days 3 and 5, the treatment group had significantly lower ALT and AST concentrations than the control group.

**P < 0.01; *P < 0.05

Table 3 Comparison of total duration of hospitalization and post-surgery recovery time between the two groups (mean ± standard)

Group	Cases	Time		
		Total hospitalization duration (day)	Post-surgery hospitalization duration (day)	Symptom improvement time (day)
Treatment	102	14.5 ± 4.6	9.2 ± 3.3	7.0 ± 3.3
Control	96	17.5 ± 6.6	11.8 ± 5.4	9.3 ± 4.6
P value		0.000	0.001	0.000

concentrations of TBIL, DBIL, ALT, and AST between the two groups ($P > 0.05$, Fig. 1).

Comparison of symptom improvement and mean duration of hospitalization between groups

All 198 patients had varying levels of fever, pain, nausea, and vomiting after undergoing TACE. Symptom improvement was defined as follows: body temperature lower than 37.5°C, pain score reduced to less than three points on the visual analog scale [16], and nausea/vomiting lower than Grade 2. Improvement time was defined as the time needed to resolve fever, pain, nausea, or vomiting. The improvement time in the treatment and control groups was 7.0 ± 3.3 days and 9.3 ± 4.6 days, respectively; this difference was significant ($P = 0.000$, Table 3). The duration of hospitalization was 14.5 ± 4.6 days and 17.5 ± 6.6 days, respectively ($P = 0.000$), whereas the duration of post-surgery hospitalization was 9.2 ± 3.3 days and 11.8 ± 5.4 days, respectively ($P = 0.001$). That is, all these variables differed significantly between the two groups (Table 3).

GCC-related complications and adverse effects

Of the 102 patients in the treatment group, 4 developed hyponatremia/hypochloremia and 1 developed temporary hyperglycemia during a fast. These adverse effects resolved completely on taking appropriate steps to correct the electrolyte disturbance and discontinuing GCCs. No hypertension, infection, bleeding, osteoporosis, endocrine disorder, or other corticosteroid-related symptoms occurred.

Discussion

TACE is currently accepted as the most commonly used treatment for patients with unresectable HCC [2–4]. TACE can provide high concentrations of chemotherapy drugs localized at tumor areas, simultaneously reducing the tumor blood supply by artery embolization. The increased duration of drug exposure increases the anti-tumor effects, resulting in ischemia, hypoxia, and apoptosis in tumor cells [17]. However, more than 90% of the patients with HCC have pre-existing cirrhosis, and chemotherapeutic drugs and lipiodol-based embolization agents will damage the remaining normal liver tissue, and further reduce the already impaired hepatic functional reserve. These patients have raised transaminase and bilirubin concentrations and may present evidence of decompensation of liver function such as ascites and GI hemorrhage [17–18]. The main mechanism underlying these beneficial effects is the stabilization of lysosome membranes which inhibits the release of mediators of liver cell necrosis or inflammation, reduces damage to vascular endothelial cells, and promotes bile excretion from biliary capillaries [19–21]. Grieco *et al* [22] followed up patients who underwent TACE for 12 months and reported that the mortality rates were 16/17 and 47/81, respectively, in the patients who did and did not develop liver failure post-procedure. It has been proposed that post-TACE increases in bilirubin and transaminase are mainly attributable to embolization agents causing cellular ischemia, hypoxia, and death, chemotherapy drug toxicities, release of inflammatory factors, and stress responses. GCCs, a broad-spectrum steroid immunosuppressant, is synthesized in and released from the adrenocortical fascicular zone and has anti-inflammatory, anti-shock, anti-allergic, and immunosuppressive effects. GCC is widely used to treat severe liver diseases and liver failure [7–9]. Studies have found that GCCs can accelerate recovery of liver function after TACE, shorten hospitalization, and reduce fatal complications [22–24]. However, in all of these studies preventive GCCs were administered before TACE, which potentially increases GCC-associated adverse effects and risk of infection.

In the present study we retrospectively analyzed the safety and efficacy of administration of GCCs to treat HBR in 198 patients with HCC treated with TACE. The treatment and control groups did not differ significantly in pre-TACE tumor size, tumor number, portal vein tumor thrombus status, extrahepatic metastasis status, Child–Pugh classification of liver function, bilirubin concentration, or transaminase concentration. After TACE, the treatment group had higher bilirubin concentrations than the control group. In both groups, bilirubin and transaminase concentrations decreased after GCC/conventional liver-protecting treatment; however, the treatment group had significantly lower bilirubin concentrations on days 3 and 5, and significantly shorter time to symptom improvement and shorter mean duration of hospitalization than the control group. Four patients in the treatment group developed hyponatremia/hypochloremia, one patient developed hyperglycemia, and none developed hypertension, infection, bleeding, osteoporosis, endocrine disorder, or other corticosteroid-

related symptoms, indicating that GCC treatment of post-TACE HBR in patients with HCC is safe and effective.

Ogasawara *et al* [23] administered dexamethasone (DMS) to prevent postembolization syndrome after TACE in patients with HCC. The treatment group received 20 mg DMS and 3 mg granisetron (GT) intravenously immediately prior to undergoing TACE and continued to receive 8 mg DMS daily for two days thereafter. The control group received saline and 3 mg GT immediately prior to undergoing TACE and continued with saline for two days thereafter. These researchers found that DMS was significantly effective in preventing fever, anorexia, nausea, and vomiting. However, DMS did not significantly prevent increased ALT, AST, or BIL levels. In a prospective, random, double-blind, controlled study of 88 patients, Yang *et al* [24] found that preventive administration of DMS was independently associated with the alleviation of postembolization syndrome. Feng *et al* [19] administered DMS plus ginsenoside to prevent postembolization syndrome. The treatment group received 2.25 mg DMS orally plus 200 mg ginsenosides orally, b.i.d., from 3 days before TACE and continued these medications for an additional 4 days after undergoing TACE. These researchers reported that the treatment group not only had significantly less nausea, vomiting, and fever after TACE surgery than the control group, but also had satisfactory reduction in ALT, AST, and BIL concentrations. However, whether GCCs should be administered preventively to all patients about to undergo TACE is still unclear, particularly for those who do not have severely impaired liver function. In our large study, only 3.86% (198/5124) of patients had bilirubin concentrations greater than 50.1 μmol/L after TACE. Most patients recovered normal liver function with conservative liver-protecting treatment; thus only a few patients required GCC treatment. We therefore did not administer GCCs preventively but prescribed it only after bilirubin concentrations had increased, to minimize blindness and other adverse effects.

The GCCs used in the present study was MSS. Compared with DMS, MSS has a rapid effect, is an active form of corticosteroid and can play a pharmacological role without being transformed by the liver. MSS has twice the binding affinity for GCC receptor and a five times stronger anti-inflammatory effect than DMS. Therefore, it relieves fever and liver function impairment more rapidly, and stresses the liver less in patients with postembolization syndrome after TACE. Additionally, MSS has lesser mineralocorticoid activity, such as water and sodium retention, than DMS. Therefore, we used MSS for short-term, pulse treatment and achieved favorable outcomes. No water or sodium retention, osteoporosis, peptic ulcer, or abnormal glucose tolerance occurred.

In the present study, we administered early, small-dose, short-term MSS treatment to patients with HCC who had significantly increased bilirubin concentrations after TACE. The treatment group attained decreased bilirubin levels in a significantly shorter time and had a significantly higher rate of effectiveness than the control group. No secondary infection, GIT bleeding, or increase in glucose concentration occurred. Compared with conventional liver-protecting treatment, treatment with GCC was associated with quicker recovery from postembolization syndrome and shorter total duration of hospitalization, which reduced the psychological and economic pressure on patients. Compared with the existing prophylactic application of glucocorticoid [19, 23–24] in the treatment of TACE postoperative embolism syndrome, it reduced blindness and side effects. However, the sample size of the present study was relatively small, and GCC efficacy, safety, and long-term effects on prognosis in patients with HCC need to be further confirmed by a large, prospective, randomized, controlled study to provide stronger evidence for its future promotion in clinical practice.

In conclusion, short-term administration of GCCs to treat HBR in patients with HCC who have undergone TACE is safe and is associated with rapid decline in bilirubin concentration and shorter hospital stay compared with patients who did not receive GCCs.

Ethics approval and consent to participate

Patient data were used after obtaining approval from the ethics committee of The Fifth Medical Center of PLA General Hospital, and the study was performed with the written consent of the patients included, in compliance with the Helsinki Declaration.

Conflicts of interest

The authors declare no potential conflicts of interest.

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