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Research Article

Low-Dose and Short-Course Dexamethasone Treatment as a New Therapy against the Post-Embolization Syndrome after Transcatheter Arterial Chemoembolization in Primary Liver Cancer: A Retrospective Case-Control Study

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Abstract

Objective: Dexamethasone (DEX) is considered an effective treatment for Post-Embolization Syndrome (PES). However, the current commonly used DEX treatment course is long and involves a large amount of DEX and thus causes substantial side effects. This study aimed to evaluate the efficacy and safety of low-dose short-course DEX treatment in the prevention of PES to establish a new treatment course.

Methods: A retrospective cohort study was conducted to observe the efficacy of DEX in treating PES on patients with primary liver cancer who underwent Transcatheter Arterial Chemoembolization (TACE). DEX was selected according to the wishes of the patients, who were subsequently divided into two groups. In the experimental group, 52 patients daily received an intravenous injection of 5 mg DEX and 5 mg tropisetron, starting on the day of TACE. The remaining 52 patients (control group) were treated with only 5 mg tropisetron daily. Incidence and degree of vomiting, abdominal pain, and fever were recorded. Routine blood tests and the C-Reactive Protein (CRP) test were performed, liver and kidney functions were evaluated, and the coagulation index and Eastern Cooperative Oncology Group (ECOG) performance status were assessed before and after TACE.

Results: Severity scores of adverse reactions, such as vomiting, fever, and abdominal pain; incidence of grade 2 and 3 adverse reactions; and CRP and ECOG scores were significantly lower in the experimental group than in the control group ($P < 0.05$). There was no significant difference in routine blood parameters, liver and kidney functions, or coagulation between the two groups before or after TACE ($P > 0.05$).

Conclusion: Low-dose and short-course DEX treatment after TACE can effectively reduce the severity of PES without side effects.

Keywords: Post-embolization syndrome; TACE; Dexamethasone; Liver cancer

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Introduction

Liver cancer is the second leading cause of cancer-related deaths in China and worldwide [1]. Hepatocellular Carcinoma (HCC) accounts for 85–90% of patients with liver cancer. By the time of definitive diagnosis, most patients are already advanced and have lost the opportunity for surgical resection [2]. In addition to surgical resection, liver transplantation, Transcatheter Arterial Chemoembolization (TACE), and ablation are also strategies used for the treatment of liver cancer. TACE is the most commonly used treatment for most patients with multinodular HCC [3]. However, the side effects after TACE are substantial and include persistent high fever, vomiting, and severe abdominal pain, collectively referred to as Post-Embolization Syndrome (PES) [4]. PES lowers the life quality of patients, reduces treatment tolerance, and delays post-operative recovery. Studies have shown that the occurrence of PES is closely related to embolic ischemia and embolic inflammatory response [5]. Dexamethasone (DEX) has been shown to be effective in preventing PES [6-8]. However, long-term and high-dose use of glucocorticoids causes other side effects [9]. Effective suppression of the embolic reaction after interventional surgery and minimization of the side effects caused by glucocorticoids are essential for the earliest post-operative recovery with the maximum curative effect and minimum impact on the life quality of patients. This retrospective cohort study was conducted to assess for the therapeutic effect of daily low-dose DEX administration on the PES after TACE in 104 patients with liver cancer in Shanghai Changhai Hospital, so as to provide a reference for future clinical studies.

Methods

This retrospective cohort study was conducted in Shanghai Changhai Hospital between October 2019 and October 2020. Primary liver cancer was diagnosed via histological or imaging evaluation according to the guidelines of the Chinese Society of Clinical Oncology [10]. The enrolled patients met the requirements for TACE indications and did not use glucocorticoids for the 3 months preceding TACE.

Patients who had any of the following were excluded [11]: (1) an organ disease, such as one involving the heart, brain, kidney, or lung; (2) portal vein tumor thrombosis, cholangiocarcinoma thrombosis, or collateral vessel formation; (3) severe esophageal varices in the fundus of the stomach, severe portal hypertension, or a risk of rupture and bleeding; (4) systemic infection with sepsis or liver abscess; (5) Child-Pugh C liver function; (6) severe liver cirrhosis; (7) tumors accounting for ≥ 70% of the whole liver; and (8) allergic constitution or allergic to the study drugs.

The study was approved by the Institutional Review Board of Changhai Hospital (CHEC2010112) and adhered to the tenets of the Declaration of Helsinki.

Results

Patient Characteristics

This clinical study included 104 patients with primary liver cancer who received liver TACE treatment in the Traditional Chinese Medicine (TCM) oncology department of Changhai Hospital between October 2019 and October 2020. These patients were divided into the following two groups based on their willingness to be treated with DEX: the experimental group consisted of 52 patients daily intravenously injected with both 5 mg DEX and 5 mg tropisetron after TACE, and the remaining 52

Table 1: Baseline of Demographic Data and Patient Characteristics.

	Experimental group	Control group	P
	(N=52)	(N=62)	
Gender, n%			0.304
Male	45(86.5)	49(76.5)	
Female	7 (13.4)	13 (20.3)	
Age			0.095
<65	31(59.6)	45 (72.6)	
≥65	21(40.4)	17 (27.4)	
HBV,* n (%)			1.000
Absent	0	0	
Present	52 (100)	62 (100)	
ECOG-PS>0, n (%)			0.570
Absent	40(76.9)	49 (79.0)	
Present	12 (23.1)	13 (21.0)	
Child-Pugh			0.570
A	25(48.1)	31(50.0)	
B	27(51.9)	31(50.0)	
BCLC, n (%)			0.654
A	7(13.4)	9 (14.5)	
B	31(59.6)	39 (62.9)	
C	14(26.9)	14(22.6)	
Tumor number, n (%)			0.506
Single	19(36.5)	18 (29.0)	
Multiple	27(51.9)	36 (58.0)	
Megablock type	6 (11.5)	8(13.0)	
Tumor location			0.062
Right lobe	29(55.7)	26(41.9)	
Left lobe	4(7.6)	13(20.9)	
Left and right lobe	19(36.5)	23(37.0)	
Number of tumors			0.169
1	22(42.3)	19(30.6)	
2	12(23.0)	13(20.9)	
Multiple	18(34.6)	30(48.3)	
Tumor size			0.057
<3cm	5(9.6)	4(6.5)	
≥3cm, <5cm	6(11.6)	14(22.6)	
≥5cm	41(78.8)	44(70.9)	
Tumor thrombus			0.589
Absent	47(90.4)	57(91.9)	
Present	5(9.6)	5(8.1)	
Lymphnodemetastasis			0.847
Absent	42(80.8)	50(80.6)	
Present	10(19.2)	12(19.4)	
Distant metastasis			0.382
lung	3(5.8)	7(11.3)	
bone	3(5.8)	0	

patients (control group) were injected only with 5 mg tropisetron. At the baseline, there was no significant difference in gender, age, liver function grade, or tumor stage between the two groups (Table 1), *P*> 0.05.

Comparison of the Two Groups for PES Incidence and Severity

(Table 2) shows the incidence of PES in the control versus experimental group. Incidence of abdominal pain (8 [12.9%] vs. 0[0%] patients, *P*< 0.05) or grade-3 fever (6[9.68%] vs. 2[3.58%] patients, *P*< 0.05) was significantly higher in the control group than in the experimental group. Patients who did not experience vomiting (15[28.58%] vs. 7[11.29%] patients, *P*< 0.05) or abdominal pain (22[42.31%] vs. 9[14.52%] patients, *P*< 0.05) were significantly more in the experimental group than in the control group. Between the two groups, no significant difference was found in the number of patients who experienced fever (9[14.52%] vs. 8[15.38%] patients, *P*> 0.05).

Related Indices Before and After TACE Treatment

Between the two groups, there was no significant difference in the changes in routine blood parameters, liver and kidney functions, or coagulation before and after TACE treatment (*P*> 0.05). However, the C-Reactive Protein (CRP) and Eastern Cooperative Oncology Group (ECOG) scores in the experimental group were significantly lower than those in the control group on the 3rdand5thdaysof the treatment *P*< 0.05, (Table 3 and Figure 1).

Table 2: Incidence of postoperative adverse reactions in two groups.

PES Classification	Control group (n = 62)		Experimental group (n = 52)	
	N	Percentage (%)	N	Percentage (%)
Vomit				
0	7	11.29	15	28.85
1	38	61.29	29	55.77
2	17	27.42	8	15.38
3	0	0	0	0
Abdominal pain				
0	9	14.52	22	42.31
1	30	48.39	21	40.38
2	15	24.19	9	17.31
3	8	12.90	0	0.00
Fever				
0	9	14.52	8	15.38
1	21	33.87	36	69.23
2	26	41.94	6	11.54
3	6	9.68	2	3.85

Table 3: The changes of ECOG score, blood routine, liver and kidney function and coagulation function between the two groups before and after operation.

	Control group (n = 62)			Experimental group (n = 52)		
	Before operation	3 days after operation	5 days after operation	Before operation	3 days after operation	5 days after operation
ECOG	0.24±0.5	1.82±0.66	1.41±0.58	0.25±0.47	1.25±0.55	1.05±0.46
CRP	11.3±24.55	91.56±59.78	78.24±53.98	14.22±27.05	69.37±55.45	65.16±57.81
TB	16.75±8.8	25.52±16.91	23.24±15.5	17.25±7.25	24.68±11.04	22.67±10.72
DB	6.55±5.65	12.4±12.27	11.6±11.2	6.01±2.98	11.43±8.27	10.27±6.96
ALB	40.06±4.27	36.33±6	35.35±3.26	41.28±3.25	37.1±3.59	36.27±3.26
ALT	35.9±23.92	144.67±149.73	83.98±65.42	35.26±34.52	168.92±171.84	91.21±69.85
AST	36.59±25.15	90.93±82.26	44.59±29.29	35.82±22.46	103.07±118.19	46.23±27.23
BUN	5.13±1.49	4.29±1.52	4.21±1.25	5.26±1.83	4.44±2.22	4.42±1.96
Cr	66.3±17.27	65.7±16.68	65.38±17.32	66.09±19.66	70.96±25.05	64.59±18.95
WBC	5.02±1.78	6.65±2.89	6.12±2.61	4.96±1.61	6.74±2.49	6.39±2.24
GRAN%	59.56±13.26	72.67±8.35	68.01±9.45	60.03±10.41	73.21±8.71	67.36±8.66
RBC	4.54±0.61	4.46±1.35	4.19±0.57	4.63±0.54	4.43±0.55	4.26±0.56
HGB	137.96±26.36	130.91±21.12	126.82±17.89	142.11±15.58	136±15.89	129.73±15.1
PLT	153.56±75.35	116.3±63.66	134.79±70.03	144.13±54.63	102.34±37.82	115.53±48.14
PT	13.62±1.2	17.25±18.33	14.61±1.13	12.54±0.98	13.93±1.21	16.71±21.83

*#P<0.05(Ctl.VSExp.)

Table 4: Dexamethasone dosage form, dosage, course of treatment and mode of administration in different research protocols.

Research programme	Dexamethasone dosage form	Total dose of dexamethasone (mg)	Course of treatment (d)	Route of administration
Sadahisa	injection	20+8+8=36	3	iv.
Feng	capsule	2.25x2x7=31.5	7	po.
YANG	injection	12	1	iv.
Low-dose and short-course dexamethasone	injection	5	1	iv.

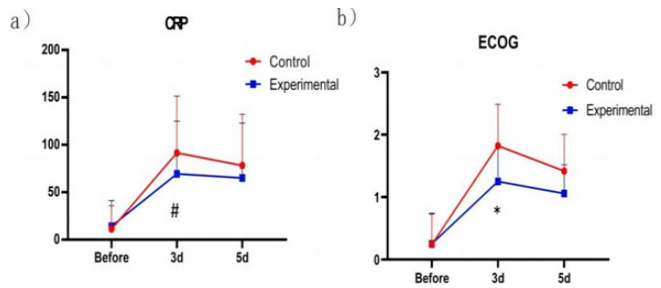

Figure 1: The changes of CRP and ECOG score between the two groups before and after operation a) CRP b) ECOG *#P<0.05(Ctl. VS Exp.).

Discussion

The main reason for the PES after TACE is the systemic stress response after the local embolization of tumor vessels, which induces the adrenal cortex to secrete a large amount of glucocorticoid, thus reducing the number and affinity of the glucocorticoid receptor through the negative feedback regulation of the hypothalamus pituitary adrenal axis [12]. This process can lead to the release of inflammatory factors and the pathogenesis of PES. Therefore, DEX is currently used to reduce the side effects after TACE, but there is no consensus on the optimum treatment course [13].

In a prospective study by Sadahisa Ogasawara [14] from Japan, the DEX regimen was more effective than the control regimen in preventing the TACE-induced fever, anorexia, and nausea/vomiting in patients with HCC. In the study, 120 patients who underwent TACE were randomly assigned to two groups in a1:1 ratio via a minimization method. One group was administered a DEX regimen for 3d, from the day before TACE until day 2 post-surgery. The complete response rate was higher in the DEX-treated group than in the control group. Additionally, the cumulative incidence of fever, anorexia, and nausea/vomiting was higher in the control group than in the DEX-treated group.

Feng et al. [15-16] have reported that DEX combined with ginsenoside scan effectively prevent and treat the PES following TACE. In their trial, 120 patients with primary liver cancer were divided into four groups, with 30 patients per group. Their results indicated that this combinatorial therapy not only markedly decreased the PES incidence (evidenced by the decreased incidence of nausea, vomiting, and fever) and duration but also significantly improved liver function, compared with those observed in the individual use of DEX or ginsenosides. It should be noted that DEX was administered orally, not intravenously, in the study of Feng et al. They started the drug administration 3 days pre-TACE and stopped on day 4 post-TACE in all the groups. Thetreatmentdurationwas6d. In addition, Yang et al. [17] have demonstrated that prophylactic administration of DEX before chemoembolization is an effective way to reduce PES. In their prospective, randomized, double-blinded, place bo-controlled trial, a total of 88 patients with intermediate-stage HCC were enrolled. After randomization, 44 patients were assigned to DEX group, and then 10 ml of normal saline containing 12 mg DEX was injected intravenously before chemoembolization, while the other 44 patients were only injected 10 ml of normal saline intravenously as controls. PES incidence was lower in the DEX group than in the control group (78.0% vs. 97.5%). Similar results were found in our study. Moreover, DEX was used at a lower dosage and for a shorter period, thus causing fewer side effects, in our study than in the study by Yang et al., who used daily intravenous injections of 12 mg DEX. Feng Yinglu orally administered 31.5 mg DEX for 7 d in the peri-TACE period, and Sadahisa Ogasawara intravenously injected 36 mg DEX for 3 d post-TACE. All these dosages are relatively high (12–36 mg), and the treatment duration was 1–7 d. In fact, high-dose DEX increases the risk of gastrointestinal bleeding after TACE for liver cancer, causes metabolic disorders, and increases the probability of infection. Additionally, the effect of long-term DEX use on tumor growth is elusive. Several studies have shown that hormones can promote the apoptosis of liver cancer cells [18-20] but also have an anti-angiogenesis effect on liver cancer [21]. The effects of DEX on tumors in different micro-environments are uncertain. However, it is certain that high-dose and long-term DEX treatments increase the incidence of adverse reactions and can seriously interfere with the treatment of tumors. Therefore, in DEX treatment, optimum efficacy with minimum adverse reactions should be aimed. In our study, DEX was administered at only 5 mg per day and was used only on the first day after TACE. This treatment strategy proved effective. Because the dosage was much lower and the treatment duration was much shorter, the side effects were relatively fewer, compared with those in the previous studies. Therefore, the lower the dose and the shorter the duration of DEX, the less effect it has on the tumor.

The symptoms of PES generally appear in the post-operative 6-LOH and last for 3–20 d, among which nausea and vomiting can last for 3-LOD, and liver pain and fever generally last slightly longer. The most obvious period was 72 h after surgery [22]. As a long-acting preparation of glucocorticoids, DEX has a half-life of 36–72 h and is characterized by a long duration of action and a strong anti-inflammatory effect [23].

Theoretically, low-dose and short-term DEX treatment can effectively cover 72 hours after surgery. Thus, long and strong DEX regimes are likely unnecessary. Notably, we observed that ECOG scores were significantly lower in the experimental group than in the control group 3 d after TACE. It can be concluded that in practice, a single daily course of low-dose dexamethasone DEX can significantly reduce the side effects of TACE and improve the life quality of patients, especially for the acute reaction after 72 h of surgery after embolization. In both the experimental and control groups, CRP scores increased in the first 3 days post-TACE and then decreased, consistent with the trends in inflammation levels. Between the two groups, there was no significant difference in the changes in routine blood parameters, liver and kidney functions, and coagulation on the 3rd and 5th days post-TACE. Thus, it can be concluded that low dose and short-term administration of DEX has no adverse effects.

In conclusion, a single course of daily administration of DEX at a low dose (5 mg) effectively reduces the PES post-TACE in PLC patients. Low-dose and short-term DEX treatment can be used as a new preventive strategy against the PES post-TACE.

Authorship Contribution Statement

Yong-Bin Meng: Case collection, Datacuration, Writing-original draft.

Si-Mo Cheng: Experimental design, Methodology, Writing-original draft.

Man Yao: Formal analysis, Language arrangement, Writing-original draft.

Juan Du: Conceptualization, Funding acquisition, Supervision, Writing-review & editing.

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Ethical Approval

The study has been approved by the Institutional Review Board of Changhai Hospital (CHEC2010-112) and follows the tenants of the Declaration of Helsinki.

Competing Interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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