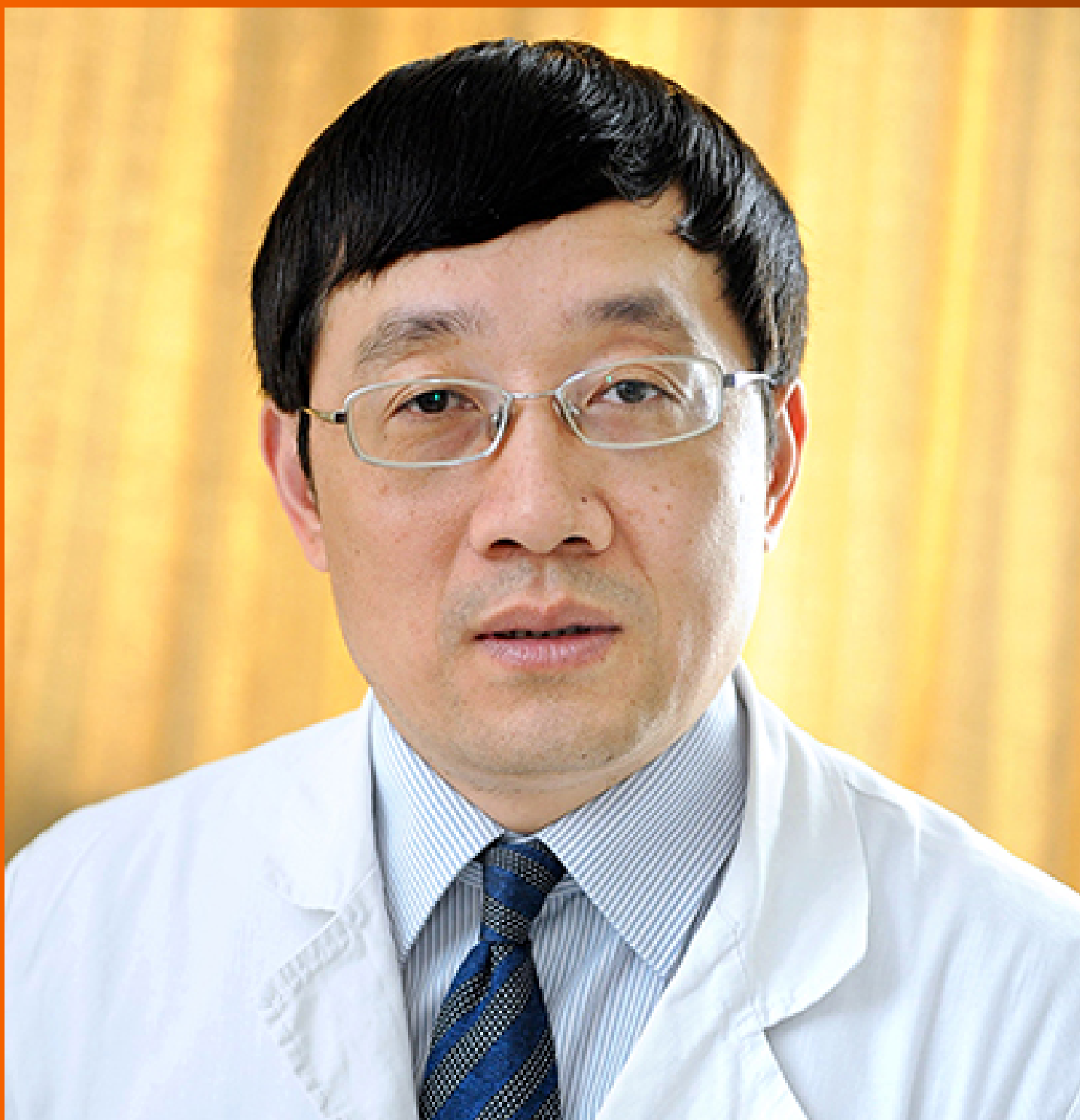


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Clinical Trials Study

Efficacy of dexamethasone and N-acetylcysteine combination in preventing post-embolization syndrome after transarterial chemoembolization in hepatocellular carcinoma

Nitipon Simasingha, Wasu Tanasoontrarat, Torpong Claimon, Supatsri Sethasine

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Abstract

BACKGROUND

Conventional transarterial chemoembolization (cTACE) is the current standard treatment for intermediate-stage hepatocellular carcinoma (HCC). Post-embolization syndrome (PES) is complex clinical syndrome that presents as fever, abdominal pain, nausea, and vomiting. Either dexamethasone (DEXA) or N-acetylcysteine (NAC) is used to prevent PES; however, the synergistic effect of their combined therapy for preventing PES and liver decompensation has not been determined.

AIM

To evaluate the efficacy of DEXA and NAC combination in preventing PES and liver decompensation after cTACE.

METHODS

Patients with Barcelona Clinic Liver Cancer stage A or B HCC who were scheduled for TACE were prospectively enrolled. All patients were randomly stratified to receive NAC and DEXA or placebo. The dual therapy (NAC + DEXA) group received intravenous administration of 10 mg DEXA every 12 h, NAC 24 h prior to cTACE (150 mg/kg/h for 1 h followed by 12.5 mg/kg/h for 4 h), and a continuous infusion of 6.25 mg/h NAC plus 4 mg DEXA every 12 h for 48 h after cTACE. The placebo group received an infusion of 5% glucose solution until 48 h after procedure. PES was defined by South West Oncology Group toxicity code grading of more than 2 that was calculated using incidence of fever, nausea, vomiting, and pain.

RESULTS

One-hundred patients were enrolled with 50 patients in each group. Incidence of PES was significantly lower in the NAC + DEXA group compared with in the placebo group (6% *vs* 80%; $P < 0.001$). Multivariate analysis showed that the dual treatment is a protective strategic therapy against PES development [odds ratio (OR) = 0.04; 95% confidence interval (CI): 0.01-0.20; $P < 0.001$]. Seven (14%) patients in the placebo group, but none in the NAC + DEXA group, developed post-TACE liver decompensation. A dynamic change in Albumin-Bilirubin score of more than 0.5 point was found to be a risk factor for post-TACE liver decompensation (OR = 42.77; 95%CI: 1.01-1810; $P = 0.049$).

CONCLUSION

Intravenous NAC + DEXA administration ameliorated the occurrence of PES event after cTACE in patients with intermediate-stage HCC.

Key Words: Hepatocellular carcinoma; Post-embolization syndrome; Transarterial chemoembolization; Liver decompensation

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Core Tip: Conventional transarterial chemoembolization (TACE) is the current standard treatment for intermediate-stage hepatocellular carcinoma (HCC). A combination of N-acetylcysteine and dexamethasone ameliorated the occurrence of post-embolization syndrome event after TACE in patients with intermediate-stage HCC. A dynamic change in Albumin-Bilirubin score of more than 0.5 point was found to be a risk factor for post-TACE liver decompensation.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major-public health concern and the fourth common cause of cancer-related deaths worldwide[1]. In Thailand, HCC is the second most common tumor type and the most common cause of cancer-related death. Without treatment, patients with HCC have a one-year overall survival rate of less than 20%. Conventional transarterial chemoembolization (cTACE) has been established as a standard treatment for HCC with Barcelona Clinic Liver Cancer (BCLC) stage B. Systemic reviews and meta-analyses have demonstrated that cTACE therapy improved the survival of patient at this stage. HCC patients who underwent super-selective TACE had a 5-year survival rate of 40%-48%. cTACE involves embolization of vessel supply to tumors, causing ischemia in not only tumor cells but also normal hepatocytes, along with targeted chemotherapy; the systemic effects of chemotherapeutic agents result in the occurrence of post-embolization syndrome (PES)[2-5].

PES is a complex clinical syndrome manifested as fever, abdominal pain, nausea, and vomiting[6,7] with a South West Oncology Group (SWOG) score > 2 [7]. PES is self-limited and either resolves within 24 h or exhibits sustained symptoms for up to two weeks based on various factors such as tumor size, tumor numbers, dosage of chemotherapy, and performance status of the patient[6,8,9]. Management of PES mainly includes supportive treatment such as with analgesic, antiemetic, and antipyretic administration[9,10]. Depending on its pathogenesis, PES may be related to systemic inflammation, resulting in toxic and ischemic effects on tumor cells and hepatocytes[9]. Steroids and antioxidants may play an important role in the prevention and treatment of PES. Dexamethasone (DEXA) and prednisolone are recommended by the National Comprehensive Cancer Network as effective medications for preventing chemotherapy-induced nausea/vomiting. Moreover, a few randomized control trials have demonstrated the effect of DEXA in terms of PES prevention[11-14]. N-acetylcysteine (NAC), an established glutathione precursor and a potent antioxidant, was found to ameliorate ischemic liver injury by improving the systemic hemodynamic parameter and tissue oxygen delivery in animal models[14-16]. Further, a pilot study reported that NAC can reduce the incidence of PES after cTACE but cannot reduce that of post-TACE liver decompensation[17]. Currently, there are no standard prevention guidelines for PES. Our study aims to evaluate the dual effect of DEXA and NAC therapy in preventing

PES or liver decompensation after cTACE in patients with HCC.

MATERIALS AND METHODS

Study design

A randomized, double blind, placebo-controlled trial was conducted at the Gastroenterology and Liver Unit, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand from November 2020 to January 2022.

Study population

Eligible patients were those aged 18-80 years with diagnosed early- or intermediate-stage HCC, according to BCLC classification, and had a good performance status, defined by the Eastern Cooperative Oncology Group. Diagnosis of HCC was based on either histological or radiological typical hallmark criteria according to the American Association for the Study of Liver Disease[18] and European Association for the Study of the Liver[19]. The exclusion criteria were as follows: (1) Decompensated liver cirrhosis (Child-Pugh score ≥ 9) or cirrhosis with main portal vein invasion; (2) Congestive heart failure and/or respiratory failure; (3) Severe comorbid illness, such as end-stage renal disease, persistent poorly-controlled diabetes mellitus or hemoglobin A1C ≥ 8.5 , uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 120 mmHg), with a life expectancy of < 6 mo; (4) Severe allergy or anaphylaxis/anaphylactoid to NAC; (5) Pregnancy; and (6) History of non-steroid anti-inflammatory drugs, steroids, or NAC use within 21 d of trial initiation. All enrolled patients agreed on receiving cTACE treatment and provided informed consent before participating in the study.

Sample size calculation

Based on previous results, the incidence of PES among patients with HCC after receiving cTACE was $> 60\%$ [12]. Superiority of the DEXA regimen over the control regimen was defined as a 25% decrease in PES. Intravenous DEXA was hypothesized to reduce the incidence of PES by 20%. This study used a two-tailed test that calculated the requirement of at least 44 patients in each group to obtain a P value < 0.05 with alpha and beta errors of 5% and 20%, respectively.

Ethical approval

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Faculty of Medicine, Vajira Hospital (COA 051/2564).

Randomized strategy and intervention

All patients were admitted at least 24 h before the prescheduled cTACE procedure and were randomly (1:1) assigned to either NAC-DEXA or placebo group. The randomization sequence was computer-generated in blocks of four and stratified according to Child-Pugh classification (class A or B). All patients were blinded to the treatment assignment. Both groups underwent therapy initiation 24 h prior to the procedure. The specific dosage of the NAC-DEXA protocol was based on a previously reported recommended dosage[11,17]. The NAC-DEXA group received intravenous infusion of 5% dextrose with NAC, with an initial loading dose of 150 mg/kg/h over 1 h followed by 12.5 mg/kg/h for 4 h and 10 mg of intravenous DEXA every 12 h; this was followed by continuous intravenous infusion of 6.25 mg/kg/h NAC and 4 mg of intravenous DEXA every 12 h for the remaining 48 h post-TACE. The placebo group received 5% glucose in normal saline for 48 h at an infusion rate of 60 mL/h post-TACE (as shown in [Supplementary Figure 1](#)). If mild-to-moderate allergic symptoms developed (e.g., urticarial rash or bronchospasm), treatment was temporarily stopped for 1 h and intravenous antihistamine was immediately administered; treatment was resumed after the symptoms subsided. If severe allergic or anaphylactoid reaction occurred, treatment was permanently stopped, and the patient was treated according to standard protocol for severe allergic reaction. cTACE was performed by two interventional radiologists (Tanasoontrarat W and Claimon T) who were blinded to the randomization assignment. Pre-procedure single intravenous dose of ceftriaxone (1 g) or amoxicillin-clavulanic acid (1.2 g) along with single intravenous dose of ondansetron (8 mg) was administered to all patients. The femoral artery was catheterized under local anesthesia. A thorough angiographic examination was performed to locate all of the tumor-feeding arteries. An emulsion of lipiodol (2.5-15 mL) and chemotherapeutic agent (mitomycin, 5-20 mg) was infused into the feeders at an optimal dose determined by the interventional radiologist to be sufficient for tumor control. Thereafter, gelatin sponge particles were injected through the tumor-feeding branch. Selective cTACE was defined as occlusion of the segmental or subsegmental arterial feeder.

Post-procedural assessment

After completion of the procedure, all patients were admitted in the hospital for at least 72 h. During

hospitalization period, the following parameters were recorded: Symptoms (nausea, vomiting, fever, abdominal pain, and anorexia), vital signs, and other adverse events. Laboratory parameters, including liver function test, erythrocyte sedimentation rate, and C-reactive protein, were assessed at 24 and 48 h post-procedure. Hemoculture, urinalysis, complete blood count, and chest X-ray were performed if body temperature was $> 38^{\circ}\text{C}$.

Outcome measurement

The primary outcome was the development of PES after TACE within 48 h. In the present study, PES was identified using three different definitions: (1) SWOG toxicity coding score characterized by fever, nausea, vomiting, and/or abdominal pain within 48 h post-procedure, defined as calculated sum score more than two point (Supplementary Table 1)[7]; (2) Criteria defined by Ogasawara *et al*[11] in a randomized double-blind control study of DEXA, based on Common Terminology Criteria for Adverse Events (CTCAE) [version 5 (Supplementary Table 2) with symptoms other than those of grade I]; and (3) Criteria defined by Siramolpiwat *et al*[17] in a randomized controlled trial of single NAC dose (temperature $\geq 38.5^{\circ}\text{C}$ and 3-fold higher alanine transaminase level from baseline within 48 h post-procedure). The secondary outcome was the development of post-TACE liver decompensation, defined as an increase in Child-Pugh score of more than two points or newly developed decompensating events, such as ascites, hepatic encephalopathy, or serum total bilirubin $> 2\text{ mg/dL}$. Other cumulative adverse events (classified by CTCAE) and length of hospital stay were compared between the two groups. In patients with suspected infection or $> 38^{\circ}\text{C}$ body temperature, laboratory testing and septic work-up were performed; moreover, these patients were treated with empirical antibiotic therapy until fever subsided or hemoculture was negative. All patients were followed up after 7 d to evaluate other post-procedure events.

Statistical analysis

Continuous data are presented as mean with standard deviation (SD) or median with range. Student's *t* test or the Mann-Whitney *U* test was performed to compare between two groups. For categorical data, Chi-square test or Fisher's exact test was applied. Statistical significance was set at $P < 0.05$. For analysis of factors that impact PES development, a logistic regression analysis was performed. Data are reported as odds ratio (OR) with 95% confidence interval (CI). All serious adverse events were reported to the Institutional Review Board of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University.

RESULTS

Patient characteristics

A total of 124 patients with HCC were screened from November 2020 to January 2022. Eighteen patients who refused to participate in this study, four patients who progressed to Child-Pugh class C, and two patients with main portal vein thrombosis were excluded. The remaining 100 patients who underwent TACE randomly received NAC-DEXA ($n = 50$) or placebo ($n = 50$) treatment. Figure 1 illustrates a flow chart of patients enrolled in this study. The mean age of patients was 60.6 years, with a male predominance (89%). The prevalence of comorbid diabetes was not different between the NAC-DEXA and placebo groups (34% *vs* 32%, $P = 0.83$). All patients exhibited cirrhosis, the majority of which with an etiology of chronic hepatitis B and alcoholic cirrhosis, followed by chronic hepatitis C, and a minority showing non-alcoholic steatohepatitis etiology. Most patients (83%) were classified as Child-Pugh class A, with no difference in mean Child-Pugh scores between the two groups (5.5 ± 0.8 in NAC-DEXA *vs* 5.5 ± 0.9 in placebo). Almost all patients (91%) were in BCLC stage B. Nine patient in BCLC stage A were justified for TACE as it would serve as a bridging therapy before curative treatment. Nearly half of the patients exhibited alpha fetoprotein (AFP) level > 200 ; however, the distribution of AFP level was not statically significant in both groups. Per tumor characteristics, no difference in the median tumor diameter between the two groups (NAC-DEXA, 5.5 cm; range 1.4-19 cm *vs* placebo, 7.95 cm; range 1.4-17.2 cm; $P = 0.39$) was observed. More than 50% of patients in both groups had multiple nodules (Table 1). Approximately 34% of the patients underwent their first TACE session. The type of chemotherapy and the volume of lipiodol did not differ between the two groups. Level of embolization was selected based on tumor position. In the same TACE episode, more than one-third (36%) of patients in the NAC-DEXA group had embolization of more than two branches.

Primary outcome

According to the various pre-defined criteria mention above, PES was detected in 43% of the patients. Most patients with PES had fever (93.0%) and nausea (72.1%), while only five (11.6%) patients had abdominal pain. The occurrence of PES after TACE was significantly lower in the NAC-DEXA group than in the placebo group in all PES-defining criteria (SWOG score more than 2 point, 6% *vs* 80%; Siramolpiwat *et al*[17] criteria, 2% *vs* 54%; and Ogasawara *et al*[11] criteria, 10% *vs* 84%; all $P < 0.001$) as shown in Figure 2A. The NAC-DEXA group had a lower mean SWOG PES score than the placebo group

Table 1 Baseline characteristics of patients with intermediate-stage hepatocellular carcinoma

	N-acetylcysteine + dexamethasone	Placebo	P value
Sex			
Male	44 (88%)	45 (90%)	0.75
Age (mean ± SD)	60.8 ± 10.52	60.46 ± 11.27	0.88
Underlying disease			
Diabetic mellitus	17 (34%)	16 (32%)	0.83
Hypertension	22 (14%)	28 (56%)	0.23
Dyslipidemia	14 (28%)	18 (36%)	0.40
CKD	1 (2%)	2 (4%)	0.56
HIV	1 (2%)	1 (2%)	1.00
Tumor characteristic			
Size			
Median (range)	5.5 (1.4-19)	7.95 (1.4-17.2)	0.39
> 3 cm	40 (80%)	42 (84%)	0.65
Number			
Median (range)	2 (1-10)	2 (1-10)	0.21
1	23 (46%)	17 (34%)	0.56
≥ 2	27 (54%)	33(66%)	
Etiology			
Hepatitis B	23 (46%)	28 (56%)	0.31
Hepatitis C	15 (30%)	12 (24%)	0.50
Alcoholic	22 (44%)	20 (40%)	0.67
Non-alcoholic steatohepatitis	3 (6%)	4 (8%)	0.70
Staging			
BCLC-A	6 (12%)	3 (6%)	0.23
BCLC-B	44 (88%)	47 (94%)	
Child-Pugh Score			
A (5-6)	40 (80%)	43 (86%)	0.42
B (7-8)	10 (20%)	7 (14%)	
ALBI score (mean ± SD)	-2.61 ± 0.58	-2.54 ± 0.53	0.54
Alpha fetoprotein (ng/mL)			
< 20	18 (36%)	19 (38%)	0.50
20-200	14 (28%)	9 (18%)	
201-1000	10 (20%)	9 (18%)	
> 1000	8 (16%)	13 (26%)	
Episode of TACE			
1	16 (32%)	18 (36%)	0.67
2-5	34 (68%)	32 (64%)	
Embolization agents			
Mitomycin (mg)			
5-10	1 (2%)	3 (6%)	0.07
10.1-15	20 (40%)	10 (20%)	

15.1-20	29 (58%)	37 (74%)	
Lipiodol (mL)			
< 5	1 (2%)	1 (2%)	0.47
5-10	13 (26%)	8 (16%)	
> 10	36 (72%)	41 (82%)	
Level of embolization			
Left hepatic artery	17 (34%)	14 (28%)	0.51
Right hepatic artery	46 (92%)	44 (88%)	0.50
Middle hepatic artery	5 (10%)	3 (6%)	0.46
≥ 2 major branches	18 (36%)	8 (16%)	0.02

ALBI: Albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; SD: Standard deviation; TACE: Transarterial chemoembolization.

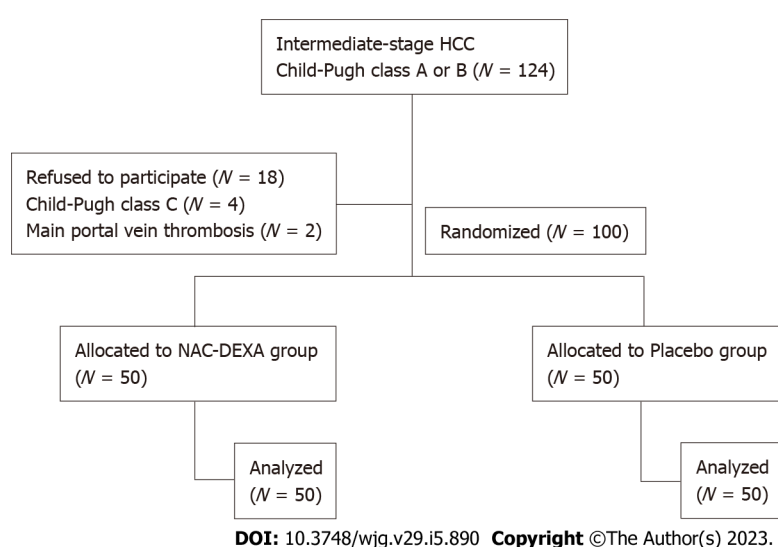


Figure 1 Flow chart of patient screened, recruited, and analyzed in the study (consort diagram). HCC: Hepatocellular carcinoma; NAC: N-acetylcysteine; DEXA: Dexamethasone.

(0.38 ± 1.1 vs 4.04 ± 2.2 ; $P < 0.001$). Baseline characteristic comparison of patients with or without PES after TACE is shown in Table 2. The PES group had a higher proportion of patients with large tumor size (> 5 cm) (67.4% vs 47.4%; $P = 0.045$) and massive tumor burden (up to 12 criteria; 48.8% vs 26.3%; $P = 0.02$). Neither volume of embolizing agents nor level of vessels embolization influenced PES occurrence. Nevertheless, most (86%) patients in the PES group underwent TACE with single vessel embolization technique.

Secondary outcomes

Interestingly, post-TACE liver decompensation occurred only in the placebo group (14% vs 0%; $P < 0.006$). All cases were accompanied by PES. A higher proportion of patients with baseline Child-Pugh class B was observed in the post-TACE liver decompensation group, but no statistical significance was found (28.6% vs 16.1%, $P = 0.39$). A higher proportion of patients with abnormal liver function test, except albumin levels, was observed in the liver decompensation group. Neither tumor burden nor number of cTACE episodes influenced the occurrence of post-TACE liver decompensation. Multiple vessel embolization was performed for more patients in the post-TACE liver decompensation group compared with the group without liver decompensation (57.1% vs 28%, $P = 0.02$). A shorter median duration of hospital stay was observed in the NAC-DEXA group (4 vs 6 d; $P < 0.001$) as seen in Figure 2B. Most patients with PES were febrile, requiring empirical antibiotics therapy that was provided until negative hemoculture was obtained; this was the main reason for increased duration of hospitalization. Acute kidney injury was observed in three patients with baseline chronic kidney disease. All of them showed improved creatinine level and glomerular infiltration rate and received standard intravenous fluids at a rate of 60 mL/h from 24 h pre-TACE till 48 h post-TACE.

Table 2 Comparison between patients based on the occurrence of post-embolization syndrome and liver decompensation after conventional transarterial chemoembolization

	PES after cTACE		<i>P</i> value	Liver decompensation after TACE		<i>P</i> value
	Yes (<i>n</i> = 43)	No (<i>n</i> = 57)		Yes (<i>n</i> = 7)	No (<i>n</i> = 93)	
Male	40 (93%)	49 (86%)	0.26	7 (100%)	82 (88.2%)	0.34
Age (mean ± SD)	60.72 ± 11.11	60.56 ± 10.74	0.26	63.57 ± 7.91	60.41 ± 11.04	0.35
Child-Pugh score	5.35 ± 0.69	5.61 ± 0.9	0.09	5.86 ± 0.9	5.47 ± 0.82	0.24
A (5-6)	40 (93%)	43 (75.4%)	0.02	5 (71.4%)	78 (83.9%)	0.4
B (7-8)	3 (7%)	14 (24.6%)	0.02	2 (28.6%)	15 (16.1%)	0.4
ALBI (median; IQR)	-2.72 (-3.05, -2.29)	-2.65 (-2.93, -2.2)	0.47	-1.95 (-2.74, -1.77)	-2.69 (-3.04, -2.29)	0.09
MELD (mean ± SD)	11.67 ± 3.54	12.05 ± 3.78	0.61	12.71 ± 3.86	11.83 ± 3.66	0.54
Staging						
BCLC-A	3 (7%)	6 (10.5%)	0.54	1 (14.3%)	8 (8.6%)	0.61
BCLC-B	40 (93%)	51 (89.5%)	0.54	6 (85.7%)	85 (91.4%)	0.61
Tumor characteristics						
AFP ≥ 200 ng/mL	17 (39.5%)	27 (47.4%)	0.44	3 (42.9%)	28 (30.1%)	0.48
Median (range)	9.6 (4.13,2)	5 (3.2,10)	0.05	5.7 (3.2,15)	7 (3.2,13)	0.8
Large tumor ≥ 5 cm	29 (67.4%)	27 (47.4%)	0.045	4 (57.1%)	52 (55.9%)	0.95
Number						
1	18 (41.9%)	22 (38.6%)	0.74	4 (57.1%)	36 (38.7%)	0.34
≥ 2	25 (58.1%)	35 (61.4%)		3 (42.9%)	57 (61.3%)	
Size plus number						
Up to 7	32 (74.4%)	37 (64.9%)	0.31	4 (57.1%)	65 (69.9%)	0.48
Up to 12	21 (48.8%)	15 (26.3%)	0.02	3 (42.9%)	33 (35.5%)	0.7
cTACE episode						
1	15 (34.9%)	19 (33.3%)	0.87	4 (57.1%)	30 (32.3%)	0.18
≥ 2 (2-5)	28 (65.1%)	38 (66.7%)		3 (42.9%)	63 (67.7%)	
Embolization agent						
Mitomycin (mg)						
< 10	2 (4.7%)	2 (3.5%)	0.44	0 (0%)	4 (4.3%)	0.51
10-15	10 (23.3%)	20 (35.1%)		1 (14.3%)	29 (31.2%)	
15.1-20	31 (72.1%)	35 (61.4%)		6 (85.7%)	60 (64.5%)	
Lipiodol (mL)						
< 5	1 (2.3%)	1 (1.8%)	0.32	0 (0%)	2 (2.2%)	0.82
5-10	6 (14%)	15 (26.3%)		1 (14.3%)	20 (21.5%)	
> 10	36 (83.7%)	41 (71.9%)		6 (85.7%)	71 (76.3%)	
Level of embolization						
Left hepatic artery	10 (23.3%)	18 (31.6%)	0.36	3 (42.9%)	28 (30.1%)	0.32
Right hepatic artery	38 (88.4%)	44 (77.2%)	0.15	7 (100%)	83 (89.2%)	0.37
Middle hepatic artery	1 (2.3%)	7 (12.3%)	0.07	0 (0%)	8 (8.6%)	0.43
1 vessel	37 (86%)	34 (59.6%)	0.004	3 (42.9%)	67 (72%)	0.25
≥ 2 vessels	6 (14%)	23 (40.4%)	0.007	4 (57.1%)	26(28%)	0.02
Baseline laboratory						

(median; IQR)						
Hct (%)	36.8 (32.3, 40.3)	35 (32.6, 38.9)	0.33	39.8 (36.6, 40.6)	35.2 (32.2, 39)	0.04
WBC ($\times 10^9/L$)	5.83 (4.50, 7.18)	5.48 (4.13, 6.97)	0.18	5.49 (4.14, 6.08)	5.58 (4.29, 7.07)	0.57
Platelet ($\times 10^9/L$)	186 (125, 241)	144 (103, 204)	0.09	105 (65, 226)	171 (117, 230)	0.39
PTT (s)	12.9 (12.3, 13.8)	13.5 (12.7, 14.7)	0.02	13 (12.1, 13.2)	13.1 (12.4, 14.2)	0.34
AST (U/L)	51 (35, 102)	47 (37, 79)	0.78	163 (102, 169)	49 (36, 77)	0.003
ALT (U/L)	35 (20, 80)	33 (21, 51)	0.29	106 (80, 139)	31 (20, 51)	< 0.001
ALP (U/L)	124 (104, 290)	120 (93, 153)	0.211	290 (121, 386)	120 (94, 169)	0.111
Albumin (g/dL)	4 (3.6, 4.2)	3.9 (3.5, 4.2)	0.569	3.7 (3.2, 4.1)	3.9 (3.6, 4.2)	0.360
Total bilirubin (mg/dL)	0.59 (0.39, 1)	0.69 (0.51, 1.3)	0.163	1.59 (0.82, 2.11)	0.59 (0.42, 1.01)	0.005
Direct bilirubin (mg/dL)	0.35 (0.24, 0.65)	0.39 (0.26, 0.78)	0.415	0.91 (0.49, 1.76)	0.35 (0.24, 0.65)	0.004
Presence of PES, <i>n</i> (%)	-	-	-	7 (100%)	36 (38.7%)	0.002
Fever	40 (93.0%)	5 (8.8%)	< 0.001	7 (100%)	38 (40.9%)	0.002
Vomit	25 (58.1%)	2 (3.5%)	< 0.001	3 (42.9%)	24 (25.8%)	0.327
Pain	5 (11.6%)	0 (0.0%)	0.008	0 (0.0%)	5 (5.37%)	0.529
Anorexia	21 (48.8%)	2 (3.5%)	< 0.001	4 (57.1%)	17 (18.3%)	0.015

AFP: Alpha fetoprotein; ALBI: Albumin-bilirubin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; cTACE: Conventional transarterial chemoembolization; Hct: Hematocrit; IQR: Interquartile range; MELD: Model of end-stage liver disease; PES: Post-embolization syndrome; PTT: Prothrombin time; SD: Standard deviation; WBC: White blood cell.

Predictors of PES

In univariate analysis of tumor volume, calculated increase in Albumin-Bilirubin (ALBI) score of more than 0.5 and a dynamic change in liver function (more than 20-fold and 1.5-fold increase from baseline in transaminase and bilirubin levels, respectively) within 48 h post-TACE were associated with the development of PES. Multivariate analysis showed that only intravenous NAC-DEXA pre-procedure could reduce the incidence of PES (OR = 0.04; 95%CI: 0.01-0.2; $P < 0.001$) (Table 3).

Predictors of liver decompensation

In univariate analysis, an occurrence of PES after TACE with an SWOG score > 4, more than 0.5 point increase in ALBI score, and a 1.5-fold increase from baseline in bilirubin level were associated with the development of liver decompensation (Table 3). In multivariate analysis, only a dynamic change in ALBI score > 0.5 point was considered an important risk for occurrence of liver decompensation with an OR of 42.77 (95%CI: 1.01-1810; $P = 0.049$).

Safety

Only two patients in the NAC-DEXA group developed a minor allergic skin reaction; in which, we disrupted treatment immediately. Six hours after drug discontinuation and administration of anti-allergic medication, the symptoms resolved. Subsequently, both patients completed the NAC-DEXA protocol with a lower infusion rate. No serious adverse event was reported in the NAC-DEXA group (Figure 2C). One patient in the placebo group died within 90 d post-procedure due to severe sepsis with liver decompensation. Although most patients were febrile post-TACE procedure, none contracted intrahospital secondary bacterial infection. The incidence of hyperglycemia did not differ between the NAC-DEXA and placebo groups (34% *vs* 32%, $P = 0.83$). Only three patients experienced grade 3 CTCAE hyperglycemia that was managed with antidiabetic therapy. According to changes in the liver function test at 48 h post-TACE, the 3-fold increase in total bilirubin level from baseline, but not transaminase, was more pronounced in the placebo group compared with that in the NAC-DEXA group (58% *vs* 18%, $P = 0.006$; Supplementary Table 3).

DISCUSSION

Pathogenesis of PES is conceivably related to multiple factors, such as direct toxic effects of chemotherapeutic agents and release of inflammatory cytokines related to tumor cell necrosis or ischemic hypoxic injury of normal hepatocytes[13,17,20]. The incidence of PES after TACE, per previous reports, ranges

Table 3 Univariate and multivariate analyses of patients with post-embolization syndrome and liver decompensation after conventional transarterial chemoembolization

Parameter	PES after cTACE						Liver decompensation after cTACE					
	Crude OR	95%CI	P value	aOR	95%CI	P value	Crude OR	95%CI	P value	aOR	95%CI	P value
NAC + DEXA	0.02	0-0.06	< 0.01	0.04	0.01-0.2	< 0.01	0	0-1	1.00	0	0-1	1.00
Size + number up to 12	1.09	1-1.19	0.04	1.08	0.92-1.27	0.33	0.99	0.84-1.16	0.88	-	-	-
AST rise > 20 folds in 48 h	1.51	1.09-2.09	0.01	1.35	0.72-2.52	0.35	1.7	0.95-3.03	0.07	1.3	0.56-3.02	0.54
ALBI change > 0.5	7.58	1.96-29.36	0.003	3.03	0.39-23.67	0.29	122.52	5.6-2681	0.002	42.77	1.01-1810	0.049
Total bilirubin rising > 1.5 folds	3.83	1.8-8.14	< 0.01	1.43	0.42-4.87	0.57	2.79	1.23-6.31	0.01	1.46	0.52-4.1	0.48
South west oncology grading > 4	1	0-1	0.99	-	-	-	1.43	1.04-1.96	0.03	0.94	0.51-1.76	0.86

ALBI: Albumin-bilirubin; aOR: Adjusted odds ratio; AST: Aspartate aminotransferase; CI: Confidence interval; DEXA: Dexamethasone; NAC: N-acetylcysteine; OR: Odds ratio; PES: Post-embolization syndrome; TACE: Transarterial chemoembolization.

widely (45%-83%). Studies that did not provide a strategic prophylaxis for PES reported an incidence of up to 80%. The incidence of PES in the present study was 43%. PES was verified by the occurrence of symptoms such as fever, nausea, vomiting, and abdominal pain, using SWOG toxicity code score of more than two point[7]. Fever is the most common symptom exhibiting a heterogeneity of prevalence (11.6%-74%), followed by nausea (11.6%-80.6%) and vomiting (16.2%-58.9%)[6,9,12,13,21]; in this study, the reported prevalence is 90%, 66%, and 54% for fever, nausea, and vomiting, respectively. Amelioration of nausea and vomiting by ondansetron premedication (8 mg) and selection of the less adverse chemotherapeutic events-causing agent, mitomycin C, may explain the lower incidence of nausea/vomiting in the present study than that in previous studies. Despite the application of super-selective single vessel embolization technique by radio-intervention at our center, a large tumor burden and a trend of higher mitomycin dose (> 10 mg) was observed and may have affected both tumor and normal liver cell necrosis, resulting in a higher PES occurrence.

NAC not only lowers free-radical levels, attributed to its antioxidant properties, but also acts as an indirect antioxidant by increasing the glutathione level and anti-inflammatory effect[22]. Therefore, many gastrointestinal guidelines recommend NAC for the treatment of alcoholic hepatitis[23], acetaminophen overdose[24], and non-acetaminophen acute liver failure[25]. Other favorable effects could be linked to its hepatoprotective activity. Interestingly, Siramolpiwat *et al*[17] demonstrated this protective effect; intravenous NAC minimized PES compared with the placebo group even though criteria for PES diagnosis was defined as only occurrence of fever and elevated serum alanine transaminase, without reference to clinical symptoms.

The beneficial effects of DEXA were presumably attributed to its antiemetic and inflammation dampening properties. Kogut *et al*[26] demonstrated that patients receiving prophylactic DEXA tended to require lower doses of antiemetic agents than those who do not. Ogasawara *et al*[11] reported that intravenous administration of a combination of DEXA and antiemetics (total 36 mg) for 3 d ameliorated PES by 52.5%. Recently, a randomized controlled trial by Sainamthip *et al*[12] demonstrated that a single

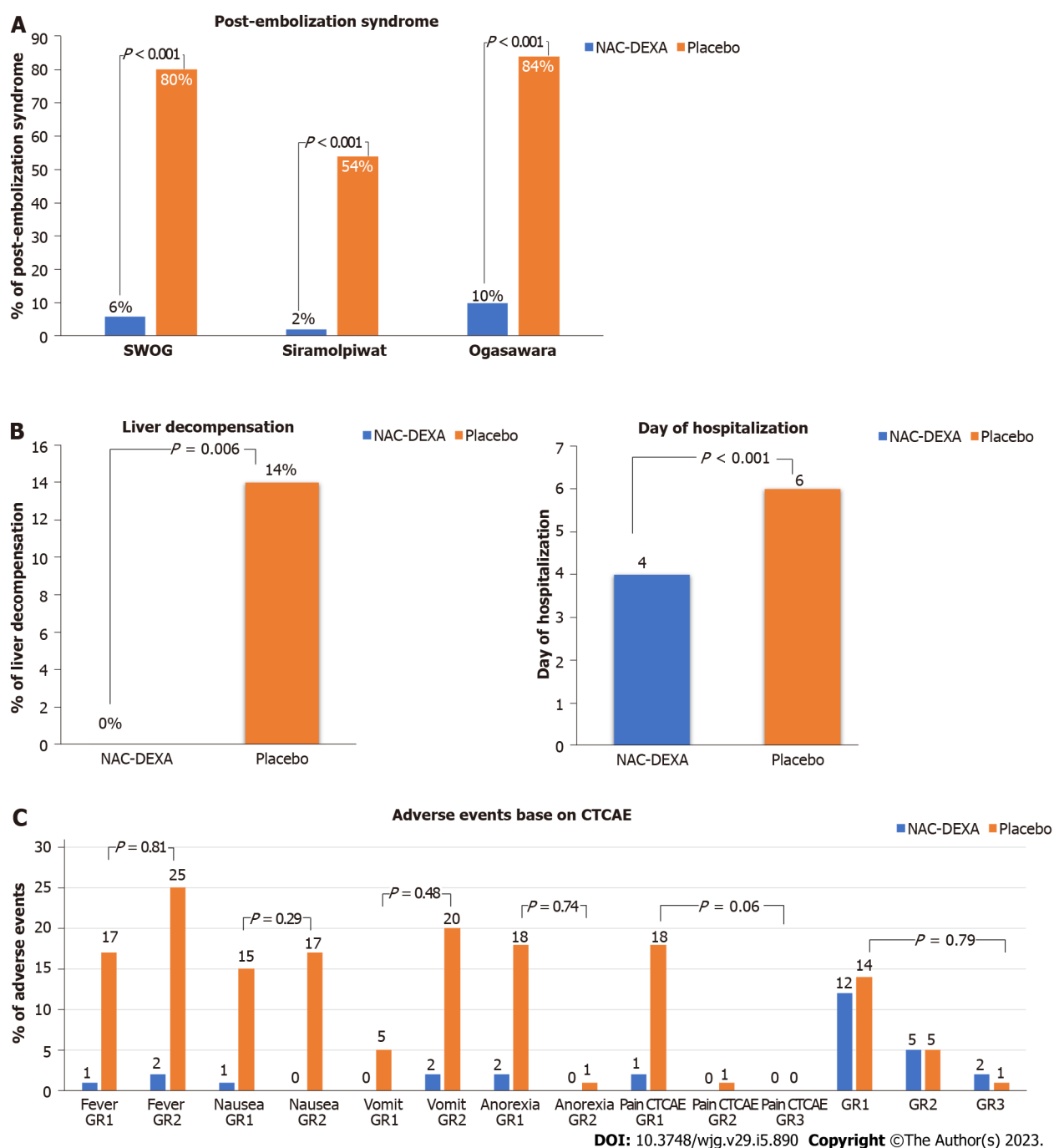


Figure 2 Post-embolization syndrome, liver decompensation and length of hospital stay and adverse events after conventional transarterial chemoembolization. A: Post-embolization syndrome after conventional transarterial chemoembolization; B: Post-conventional transarterial chemoembolization liver decompensation and length of hospital stay; C: Post-conventional transarterial chemoembolization adverse events. NAC: N-acetylcysteine; DEXA: Dexamethasone.

dose of intravenous DEXA (8 mg) can prevent PES, achieving a negative PES rate of 63.3%.

We decided to maximize the protective effect of DEXA and NAC in prevention of PES by combining the two, with intravenous administration of DEXA (cumulative dose of 36 mg) and NAC 24 h before and continuous infusion until 48 h after cTACE. Interestingly, our study found that pre-TACE therapy with NAC-DEXA regimen led to a lower PES occurrence of less than 10%, which is the lowest incidence compared with those reported in previous publications (24.6% in a NAC study[17] and 37%-47% in DEXA studies[11,12]. The synergistic effect of NAC and DEXA can diminish systemic inflammatory response and ischemic hepatitis[27-29]. Hence, this study emphasizes the advantage of NAC-DEXA combination due to its synergistic PES-reducing effect.

Post-TACE liver decompensation is one of the most important complications and is associated with significant morbidity and mortality[21,30]. It is characterized by an increase in Child-Pugh score of more than 2 points, ≥ 2 mg/dL rise in serum total bilirubin level, newly developed ascites, or hepatic encephalopathy within two weeks post-procedure. In the present study, seven patients developed post-TACE

liver decompensation. Previous studies reported that portal vein thrombosis, poor baseline liver status, high serum AFP, and PES were associated with this complication[17,27,28]. Correspondingly, all patients with liver decompensation in our study had concurrent PES. In patients who underwent post-TACE without any prophylaxis treatment, we observed a lower incidence (14%) of liver decompensation compared with those in previous reports (13.4%-17.3%)[28,29]; the lower incidence in our study is attributed to the fact that a majority of patients had good liver reserve with Child-Pugh class A. Because all eligible cTACE patients in the present study fulfilled BCLC staging criteria, neither Child-Pugh nor Model for End-Stage Liver Disease score influenced the outcome. Further, more than half of our decompensated patients received cTACE intervention with multiple vessel embolization technique, which may have compromised the vessels; however, owing to the small sample size in this group, further studies are warranted.

ALBI score is the only objective parameter to stratify patients into different grades and is used to predict the prognosis of all HCC stages. This new model outperforms the Child-Pugh score for evaluation of liver function reserve. In a previous study, evaluation of baseline ALBI score in HCC patients who underwent cTACE not only predicted survival but also estimated liver decompensation and liver failure[31]. In our study, the mean pre-treatment ALBI score was not significantly different between the NAC-DEXA and placebo groups. Our findings indicate that the proportion of preserved liver, defined by ALBI grade 1, was comparable between the two groups. Moreover, all patients who developed post-TACE liver decompensation had a baseline ALBI grade 1 or 2 with a mean pre-treatment ALBI score of -2.57. The increase in ALBI score was hypothesized to be a novel non-invasive tool for earlier prediction of post-TACE liver decompensation than Child-Pugh score. Our study demonstrated that a dynamic increase in ALBI score of more than 0.5 point had a marked impact on liver decompensation. Thus, the application of dynamic increase in ALBI score, but not albumin level, for a prediction of early post-TACE liver decompensation requires further research.

Limitation

Our study had some limitations. First, we did not perform dose optimization for DEXA and NAC in order to minimize PES. Second, this dual treatment was not compared with single DEXA. The dynamic changes in cytokine levels due to this dual treatment is an interesting topic for further study.

CONCLUSION

A combination of DEXA and NAC can not only maximize the reduction in PES incidence but also shorten hospitalization period in HCC patients undergoing cTACE procedure. Dynamic alterations in ALBI score, but not CPS, may predict liver decompensation.

ARTICLE HIGHLIGHTS

Research background

Transarterial chemoembolization (TACE) is the current standard treatment for intermediate-stage hepatocellular carcinoma (HCC). Post-embolization syndrome (PES) is a complex clinical syndrome which may occur after conventional TACE (cTACE). Either N-acetylcysteine (NAC) or dexamethasone (DEXA) is used to prevent PES.

Research motivation

The synergistic effect of the combined therapy for preventing PES and liver decompensation has not been determined.

Research objectives

The aim of this study was to evaluate the efficacy of NAC and DEXA combination in preventing PES and liver decompensation after cTACE.

Research methods

A single-center randomized controlled clinical trial.

Research results

Our study provides clinical evidence that intravenous NAC plus DEXA administration ameliorates the occurrence of post-TACE PES in patients with intermediate-stage HCC. Interestingly, we found that a dynamic change in Albumin-Bilirubin (ALBI) score was a risk factor for post-TACE liver decompensation.

Research conclusions

A combination of NAC and DEXA ameliorated the occurrence of PES after cTACE in patients with intermediate-stage HCC.

Research perspectives

The application of dynamic increase in ALBI score for a prediction of early post-TACE liver decompensation requires further research.

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FOOTNOTES

Author contributions: Simasingha N and Sethasine S contributed to the conception and design of the study, data collection, and statistical analysis, and data interpretation; Tanasoontrarat W and Claimon T conducted TACE; Sethasine S contributed to drafting of the article and critical revision of the manuscript; and all authors read and approved the final manuscript.

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