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Efficacy of *Andrographis Paniculata* for Alleviating Postembolization Syndrome after TACE

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ABSTRACT

Background: Postembolization syndrome (PES) is a common sequelae after transcatheter arterial chemoembolization (TACE). Currently, most therapies of postembolization syndrome following TACE are aimed at a single symptom, thus leading to limitations. *Andrographis paniculata* (*A. paniculata*) has been used as a traditional medicine in India, China, Thailand, and Scandinavia. There have been several clinical reports on the use of *A. paniculata* for antipyretic, analgesic, anti-inflammatory and hepatoprotective effects.

Objective: The aim of this study was to evaluate the efficacy of *A. paniculata* for the treatment of postembolization syndrome following TACE procedure.

Methods: This study was a randomized, double-blinded and controlled trial. Forty-eight patients with primary liver cancer were randomized into 2 groups of 24 to receive either oral *A. paniculata* or placebo for 3 days following TACE. Clinical symptoms and related laboratory tests before TACE, 24 hours, 72 hours and 7 days after TACE were monitored.

Results: Of the 48 patients, 43 (89.6%) were male. The overall mean age was 62.41 ± 10.25 years. Most patients had cirrhosis CTP A (87.5%). The etiologies of cirrhosis were chronic hepatitis B (43.8%), chronic hepatitis C (33.3%), alcoholic liver disease (12.5%) and NASH (22.9%). The incidence of fever was 50.0% (12/24) in the *A. paniculata* group and 66.7% (16/24) in the placebo group ($p = 0.242$). The incidence of pain was 41.7% (10/24) in the *A. paniculata* group and 50.0% (12/24) in the placebo group ($p = 0.562$). The changes of TB, AST, ALT and ALP at 24 hours, 72 hours and at 7 days after TACE were not significantly different between two groups.

Conclusion: There were no significant difference in fever, hepatalgia and changing of the TB, AST, ALT, ALP after TACE between the *A. paniculata* and the placebo group.

Keywords: *Andrographis paniculata*, Postembolization syndrome, TACE

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Introduction

Hepatocellular carcinoma (HCC) is a common cancer and a major disease burden worldwide, especially so in South-East Asia and Africa[1]. In Thailand, the prevalences of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) infections in Thailand are also considerable[2,3]. Hepatocellular carcinoma is often asymptomatic and the disease is often advanced at the time of diagnosis, making curative treatment feasible in only about 20% of patients[26,27]. The prognosis for HCC is poor because curative resection or liver transplantation is applicable to only a small proportion of patients[4]. Transcatheter arterial chemoembolization (TACE) has been approved as a palliative treatment modality in several standard guidelines, such as the "Barcelona clinic liver cancer staging classification and treatment"[5]. A common adverse event of TACE is the so-called post-TACE syndrome (PTS), characterised by fever, abdominal pain, nausea, vomiting, leukocytosis and elevated liver enzymes lasting for a few hours to a few days[6].

Andrographis paniculata (Burm.f.) Nees (Acanthaceae) has been used as a traditional medicine in India, China, Thailand, and Scandinavia[7]. Extracts of the plant have been reported to exhibit a wide range of biological activities of therapeutic importance, including antibacterial, antiviral, anti-inflammatory, antipyretic, analgesic, antimalarial, immunosti- mulant, hepatoprotective, antithrombotic, antivenomous, antitumorous, hypoglycemic and hypotensive properties[10]. The active constituents of *A. paniculata* are diterpene lactones, including andrographolide, dehydroandrographolide and neoandrographolide. Among these compounds, andrographolide is considered the most active and most important, exerting analgesic and antiinflammatory effects in vitro[8,9].

There have been several clinical reports on the antipyretic, analgesic, anti-inflammatory and hepatoprotective properties of *A. paniculata*. The first report was a multi-center study conducted in Thailand by Thamlikitkul et al., which showed that *A. paniculata* at the dose of 6 g per day in 4 divided doses was effective for the relief of fever and pharyngotonsillitis[11]. In another prospective, randomized, double blind, and placebo-controlled study in patients with rheumatoid arthritis, an extract of *A. paniculata* (30% total andrographolides) was given to 60 patients with active rheumatoid arthritis three times a day for 14 weeks, after a 2 week washout period[12]. WHO Several drugs have been reported as hepatoprotective, including *Silybum marianum*, *Andrographis paniculata*, *Swertia chirata, Cichorium intybus, Boerhavia diffusa* and *Picrorhija kurroa*[13-15]. Andrographolide, the major antihepatotoxic component of the plant, exerted a pronounced protective effect in rats against hepatotoxicity induced by CCl_4, D-galactosamine, paracetamol and ethanol[16].

Although antipyretic, analgesics and cytoprotective agents may relieve symptoms of PES, the combination of several drugs could exacerbate the metabolic load of the liver. In addition, these drugs are aimed directly at a single post-surgical symptom and are single-targeted and not effective in preventing and treating PES. The aim of this study was to evaluate the efficacy of *Andrographis paniculata* for alleviating postembolization syndrome (PES) after TACE procedure.

Material and Methods

Enrollment criteria

Between March 2015 and December 2015, 48 consecutive patients with inoperable HCC who underwent TACE at the Department of Medicine, Bhumibol Adulyadej Hospital, were recruited for study. The inclusion criteria were (1) aged over 18 and (2) HCC previously treated with TACE. The exclusion criteria were (1) fever over 38.0˚C within two weeks before TACE and (2) history of allergy to Andrographis paniculata or other herbs. Forty-eight patients who fulfilled the criteria were enrolled and completed the study. An ethic was approval by the Ethics Committee of Bhumibol Adulyadej Hospital. A trial enrollment, informed consent was obtained from all patients prior to study entry.

Randomization

Randomization was prepared using a computer-generated 4-block randomized double blind format. Details of the assignment and administration were blinded to any of the investigators and the coordinator. All study personnel and participants were also blinded to treatment assignment for the duration of the study.

Interventions

TACE was performed under standard aseptic technique. After super selection of the tumor feeding ar-

Table 1. Patient characteristics.

Variables	*Andrographis paniculata* (n=24)	Placebo (n=24)	*p*-value
Age	61.08 ± 9.53	63.75 ± 10.97	0.373
BW (kg)	68.79 ± 13.17	63.54 ± 10.5	0.134
Ht (cm)	166.08 ± 6.3	166.08 ± 6.06	1.000
BMI (kg/m^2)	24.94 ± 4.74	23.11 ± 4.16	0.160
CHB	11 (45.8%)	10 (41.7%)	0.771
CHC	7 (29.2%)	9 (37.5%)	0.540
Alcohol	5 (20.8%)	1 (4.2%)	0.188
NASH	7 (29.2%)	4 (16.7%)	0.303
Sex			
Female	2 (8.3%)	3 (12.5%)	0.637
Male	22 (91.7%)	21 (87.5%)	0.637
Cirrhosis	24 (100%)	24 (100%)	NA
CTP			
A	21 (87.5%)	21 (87.5%)	1.000
B	3 (12.5%)	3 (12.5%)	
MELD	9.38 ± 1.89	10.09 ± 2.45	0.268
No PVT	24 (100%)	24 (100%)	NA
Underlying	11 (45.8%)	14 (58.3%)	0.386
DM	6 (25%)	5 (20.8%)	0.731
HT	7 (29.2%)	10 (41.7%)	0.547
DLP	5 (20.8%)	6 (25%)	0.731
Size	5.21 ± 3.09	5.07 ± 3.67	0.889
< 5 cm	13 (54.2%)	16 (66.7%)	0.376
≤ 5 cm	11 (45.8%)	8 (33.3%)	
No. of HCC			
1	13 (54.2%)	18 (75%)	0.223
2	6 (25%)	1 (4.2%)	
3	3 (12.5%)	3 (12.5%)	
4	2 (8.3%)	2 (8.3%)	
Mitomycin (mg)	10 ± 3	12 ± 4	0.126
Lipiodal (mL)	10 ± 2	10 ± 1	0.866
No. of TACE			
1	12 (50%)	9 (37.5%)	0.601
2	8 (33.3%)	10 (41.7%)	
3	2 (8.3%)	2 (8.3%)	
4	1 (4.2%)	1 (4.2%)	
5	0 (0%)	2 (8.3%)	
7	1 (4.2%)	0 (0%)	
Hb	12.7 ± 1.9	12.1 ± 2.5	0.399
Hct	38 ± 5	36 ± 7	0.438
WBC	5588 ± 1968	5083 ± 1408	0.313
Plt	123417 ± 56126	127625 ± 65034	0.811
PT	13.7 ± 0.9	13.7 ± 1.1	1.000
PTT	26.2 ± 2.6	26.5 ± 2.9	0.748
INR	1.19 ± 0.06	1.19 ± 0.09	0.971
AFP	638.84 ± 1239.98	561.41 ± 1375.19	0.839
BUN	13 ± 5	13 ± 8	0.674
Cr	0.9 ± 0.3	1.1 ± 0.5	0.247
TP	7.4 ± 0.7	7.4 ± 0.6	1.000
Alb	3.5 ± 0.6	3.5 ± 0.5	0.574
TB	0.97 ± 0.6	1.03 ± 0.63	0.756
AST	56 ± 25	65 ± 45	0.380
ALT	42 ± 24	51 ± 41	0.369
ALP	136 ± 60	132 ± 69	0.840

Values presented as mean±SD and n (%). *P*-value corresponds to Independent *t*-test and Chi-square test.

tery, mitomycin mixed with lipiodol was infused, the dosage based on tumor size and vascularity assessment. This was followed with a permanent occluding agent such as gelfoam (gelatin sponge). Data was collected on the cumulative dosage of each chemo-agents and the usage of gelfoam embolization. The total dosage delivered (TDD) was calculated from the dosage of mitomycin (mg) and the dosage of lipiodol (mL).

Data collection

Data collection was made on the day of admission, including age, gender, underlying disease, etiology of HCC (Hepatitis B, C, alcohol , NASH, and other), tumor size and number, Child Turcotte Pugh score (CTP), portal vein involvement, complete blood count (CBC) , prothrombin time (PT), partial thromboplastin time (PTT) , international normalized ratio (INR) , liver function test (LFT) , blood urea nitrogen (BUN) , creatinine (Cr) , alfa-fetoprotein (AFP), model for end stage liver disease (MELD), dosage of mitomycin and dosage of lipiodol.

Medications

Drugs were initially administered to both groups on 3 consecutive days following TACE. Group A; patients were treated with oral *A. paniculata* capsule (1.5 g/capsule) 4 times after meal. Group B; patients were treated with oral placebo capsule 4 times after meal.

Clinical assessment

Clinical symptoms such as fever, and abdominal pain were monitored after TACE up to the day discharge from hospital. Liver function tests were performed at 24 hours, 72 hours and 7 days after TACE. The efficacy was assessed according to the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials of the USA Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research September 2007.

Statistical analysis

Data were analyzed by *t*-test and Chi-square test or Fisher's exact test. The *p*-value of < 0.05 was considered to be statistically significant.

RESULTS

All participants completed the trial. The effective size was 24 per group. Baseline demographic and clinical characteristics are listed in Table 1. There were no significant differences ($p > 0.05$) in the baseline characteristics.

Degrees of adverse effects after TACE in each group

Different degrees of fever and abdominal pain occurred in the 2 groups. The results of group comparison were as follows.

Fever: The incidence of fever was 50.0% (12/24) in the *A. paniculata* group and 66.7% (16/24) in the placebo group. No significant differences were seen between the two groups ($p = 0.242$), (Table 2 and Figure 1, 2).

Pain: The incidence of pain was 41.7% (10/24) in the *A. paniculata* group and 50.0% (12/24) in the placebo group. No significant differences were seen between the two groups (p=0.562), (Table 2 and Figure 3, 4).

Table 2. Incidence of fever and abdominal pain.

Grade	Fever		*p*-value	Abdominal pain		*p*-value
	Andrographis paniculata	Placebo (n=24)		*Andrographis paniculata*	Placebo	
None	12 (50%)	8 (33.3%)	0.513	14 (58.3%)	12 (50%)	0.641
grade 1	1 (4.2%)	3 (12.5%)		2 (8.3%)	2 (8.3%)	
grade 2	4 (16.7%)	6 (25%)		7 (29.2%)	10 (41.7%)	
grade 3	7 (29.2%)	6 (25%)		1 (4.2%)	0 (0%)	
grade 4	0 (0%)	1 (4.2%)		0 (0%)	0 (0%)	
No symptom	12 (50%)	8 (33.3%)	0.242	14 (58.3%)	12 (50%)	0.562
symptom	12 (50%)	16 (66.7%)		10 (41.7%)	12 (50%)	

Values presented as n (%). *P*-value corresponds to Chi-square test

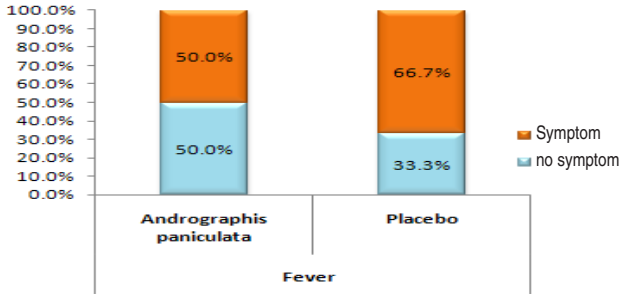

Figure 1. Comparison between fever and non-fever (%).

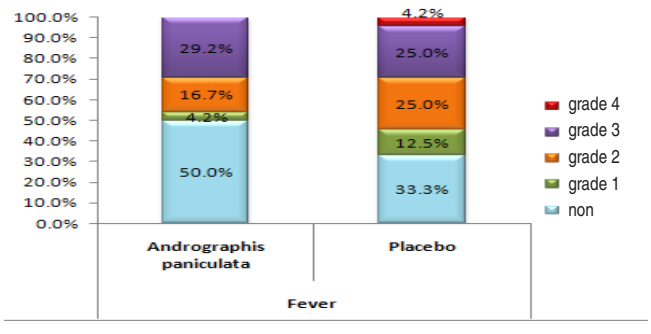

Figure 2. Comparison grading of fever between the two groups. The efficacy in the *A. paniculata* group was not significantly different from the placebo group. Grade 1=mean body temperature 38.0 - 38.4 ˚C, Grade 2=mean body temperature 38.5 - 38.9 ˚C, Grade 3=mean body temperature 39.0 - 40 ˚C, Grade 4=mean body temperature > 40 ˚C.

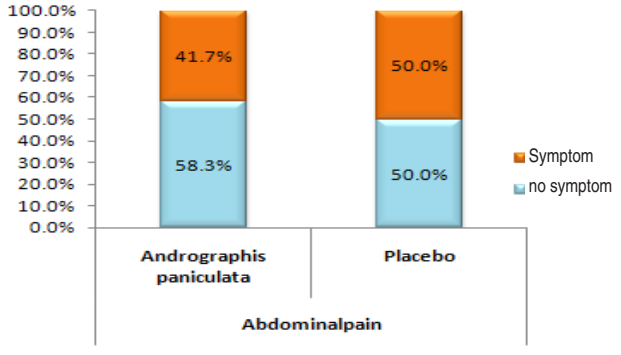

Figure 3. Comparison between pain and non-pain (%).

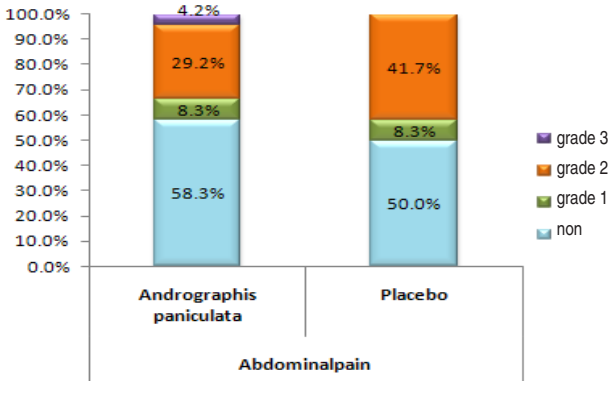

Figure 4. Comparison of grading of pain between the two groups. The efficacy in the *A. paniculata* group was not significantly different from the placebo group. Grade 1=no interference with activity, Grade 2=repeated use of non-narcotic pain reliever > 24 hrs. or interference with activity, Grade 3= any use of narcotic pain reliever or preventing daily activity, Grade 4=emergency room visit or hospitalization.

Liver function tests after TACE

Total bilirubin (TB): At 24 hours, 72 hours and 7 days after TACE, the TB level rising were noted in 66.7% (16/24) , 91.7% (22/24) , 54.2% (13/24) in the *A. paniculata* group, and 70.8% (17/24), 91.7% (22/24), 50.0% (12/24) in the placebo group, respectively. No significant differences were seen between the two groups. (Table 3, Figure 5, 6).

Aspartase aminotransferase (AST): At 24 hours, 72 hours and 7 days after TACE, the AST level rising were noted in 91.7% (22/24), 79.2% (19/24), 37.5% (9/24) in the *A. paniculata* group, and 79.2% (9/24), 87.5% (21/24), 50.0% (12/24) in the placebo group, respectively. No significant differences were seen between the two groups. (Table 3, Figure 7, 8).

Alanine aminotransferase (ALT): At 24 hours, 72 hours and 7 days after TACE, the ALT level rising were noted 91.7% (22/24), 91.7% (22/24), 37.5% (9/24) in the *A. paniculata* group, and 79.2% (19/24), 91.7% (22/24), 54.2% (13/24) in the placebo group, respectively. No significant differences were seen between the two groups. (Table 3, Figure 9, 10).

Alkaline phosphatase (ALKP): At 24 hours, 72 hours and 7 days after TACE, the ALK level rising were noted in 29.2% (7/24), 12.5% (3/24), 25.0% (6/24) in the *A. paniculata* group, and 25.0% (6/24), 25.0% (6/24), 33.3% (8/24) in the placebo group, respectively. No significant differences were seen between the two groups. (Table 3, Figure 11, 12).

Prescribed paracetamol and/or tramaldol after TACE

Paracetamol was prescribed after TACE in 45.8% (11/24) in the *A. paniculata* group and in 62.5% (15/24) in the placebo group, respectively. No significant differences were seen between the two groups (*p*

Table 3. LFT after TACE.

		24 hrs		72 hrs		7 days	
	Variables /grade	***Andrographis paniculata***	**Placebo (n=24)**	***Andrographis paniculata***	**Placebo**	***Andrographis paniculata***	**Placebo**
TB	None	8 (33.3%)	7 (29.2%)	2 (8.3%)	2 (8.3%)	11 (45.8%)	12 (50%)
	grade 1	5 (20.8%)	11 (45.8%)	4 (16.7%)	4 (16.7%)	4 (16.7%)	5 (20.8%)
	grade 2	5 (20.8%)	2 (8.3%)	6 (25%)	4 (16.7%)	6 (25%)	4 (16.7%)
	grade 3	5 (20.8%)	3 (12.5%)	7 (29.2%)	10 (41.7%)	2 (8.3%)	3 (12.5%)
	grade 4	1 (4.2%)	1 (4.2%)	5 (20.8%)	4 (16.7%)	1 (4.2%)	0 (0%)
	***p*-value**		**0.392**		**0.904**		**0.781**
	No symptom	8 (33.3%)	7 (29.2%)	2 (8.3%)	2 (8.3%)	11 (45.8%)	12 (50%)
	symptom	16 (66.7%)	17 (70.8%)	22 (91.7%)	22 (91.7%)	13 (54.2%)	12 (50%)
	***p*-value**		**0.755**		**1.000**		**0.773**
AST	None	2 (8.3%)	5 (20.8%)	5 (20.8%)	3 (12.5%)	15 (62.5%)	12 (50%)
	grade 1	8 (33.3%)	8 (33.3%)	10 (41.7%)	12 (50%)	7 (29.2%)	12 (50%)
	grade 2	5 (20.8%)	3 (12.5%)	4 (16.7%)	7 (29.2%)	2 (8.3%)	0 (0%)
	grade 3	5 (20.8%)	5 (20.8%)	4 (16.7%)	2 (8.3%)	0 (0%)	0 (0%)
	grade 4	4 (16.7%)	3 (12.5%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)
	***p*-value**		**0.749**		**0.530**		**0.161**
	No symptom	2 (8.3%)	5 (20.8%)	5 (20.8%)	3 (12.5%)	15 (62.5%)	12 (50%)
	symptom	22 (91.7%)	19 (79.2%)	19 (79.2%)	21 (87.5%)	9 (37.5%)	12 (50%)
	***p*-value**		**0.416**		**0.701**		0.383
ALT	None	2 (8.3%)	5 (20.8%)	2 (8.3%)	2 (8.3%)	15 (62.5%)	11 (45.8%)
	grade 1	10 (41.7%)	10 (41.7%)	8 (33.3%)	13 (54.2%)	4 (16.7%)	12 (50%)
	grade 2	4 (16.7%)	3 (12.5%)	7 (29.2%)	2 (8.3%)	3 (12.5%)	1 (4.2%)
	grade 3	5 (20.8%)	4 (16.7%)	4 (16.7%)	4 (16.7%)	2 (8.3%)	0 (0%)
	grade 4	3 (12.5%)	2 (8.3%)	3 (12.5%)	3 (12.5%)	0 (0%)	0 (0%)
	***p*-value**		**0.783**		**0.410**		**0.055**
	No symptom	2 (8.3%)	5 (20.8%)	2 (8.3%)	2 (8.3%)	15 (62.5%)	11 (45.8%)
	symptom	22 (91.7%)	19 (79.2%)	22 (91.7%)	22 (91.7%)	9 (37.5%)	13 (54.2%)
	***p*-value**		**0.416**		**1.000**		**0.247**
ALP	None	17 (70.8%)	18 (75%)	21 (87.5%)	18 (75%)	18 (75%)	16 (66.7%)
	grade 1	6 (25%)	5 (20.8%)	3 (12.5%)	6 (25%)	5 (20.8%)	7 (29.2%)
	grade 2	1 (4.2%)	1 (4.2%)	0 (0%)	0 (0%)	1 (4.2%)	1 (4.2%)
	***p*-value**		0.942		0.267		0.798
	No symptom	17 (70.8%)	18 (75%)	21 (87.5%)	18 (75%)	18 (75%)	16 (66.7%)
	symptom	7 (29.2%)	6 (25%)	3 (12.5%)	6 (25%)	6 (25%)	8 (33.3%)
	***p*-value**		**0.745**		**0.461**		**0.525**

Values presented as n (%). *P*-value corresponds to Chi-square test.

=0.247) (Table 4, Figure 13).

Tramadol was prescribed after TACE in 41.5% (10/24) in the *A. paniculata* group and in 50.0% (12/24) in the placebo group, respectively. No significant differences were seen between the two groups (p = 0.247) (Table 4 , Figure 13).

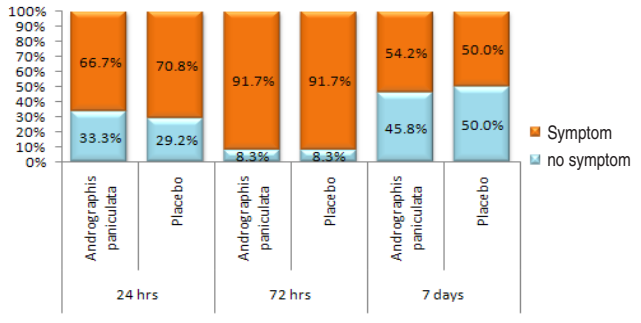

Figure 5. Total bilirubin (TB) after TACE.

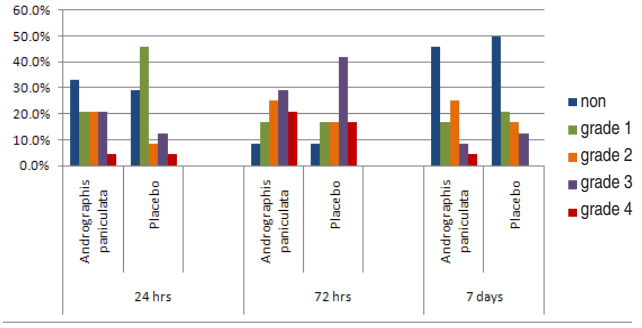

Figure 6. Comparison grading of total bilirubin between the two groups. The efficacy in the *A. paniculata* group was not significantly different from the placebo group. Bilirubin - when accompanied by any increase in LFT increase by factor (Grade 1- 1.1 - 1.25 × ULN, Grade 2- 1.26 - 1.5 × ULN, Grade 3- 1.51 - 1.75 × ULN, Grade 4- > 1.75 × ULN). Bilirubin - when LFT is normal; increase by factor (grade 1- 1.1 - 1.5 × ULN, grade2- 1.6 - 2.0 × ULN, grade 3- 2.0 - 3.0 × ULN, grade 4- > 3.0 × ULN).

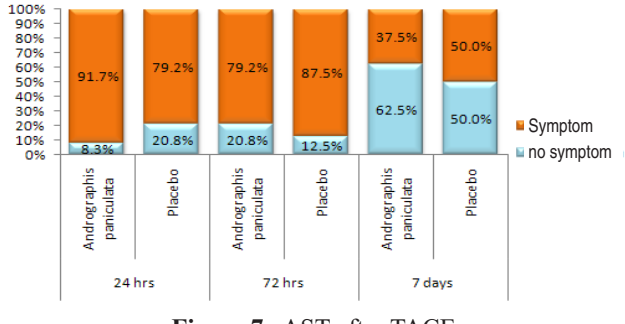

Figure 7. AST after TACE.

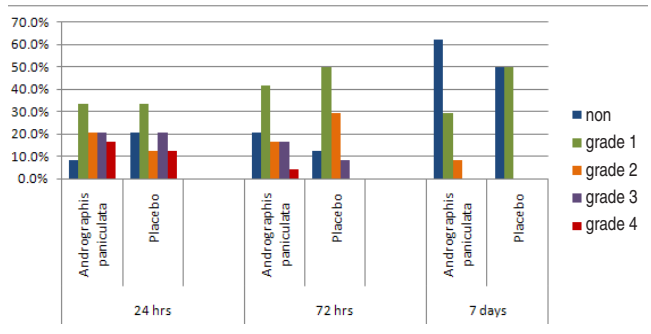

Figure 8. Comparison grading of AST between the two groups. The efficacy in the A. paniculata group was not significantly different from the placebo group. Liver Function Tests - AST (Grade 1- 1.1 - 2.5 x ULN, Grade 2- 2.6 - 5.0 x ULN, Grade 3- 5.1 - 10 x ULN, Grade 4- > 10 x ULN).

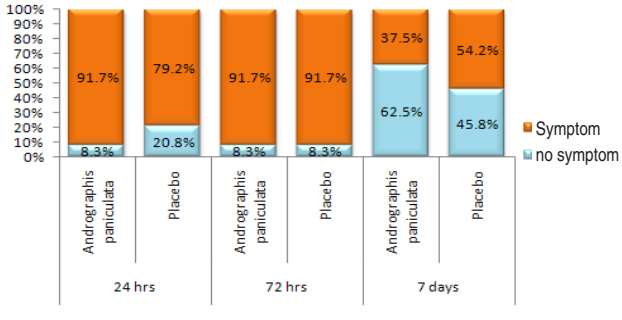

Figure 9. ALT after TACE.

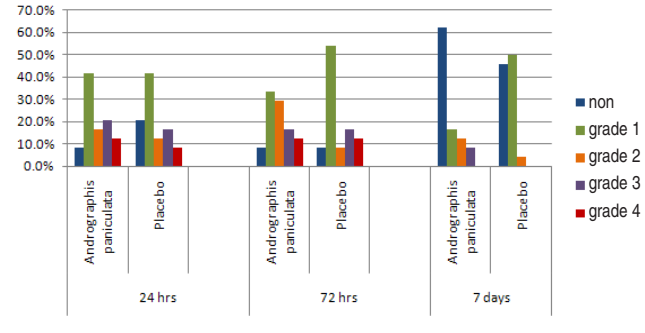

Figure 10. Comparison grading of ALT between the two groups.The efficacy in the *A. paniculata* group was not significantly different from the placebo group. Liver Function Tests - ALT (grade 1- 1.1 - 2.5 × ULN, grade 2- 2.6 - 5.0 × ULN, rade 3- 5.1 - 10 × ULN, grade 4- > 10 × ULN).

Table 4. Prescribed analgesics after TACE.

	A. paniculata	Placebo	*p*-value
Paracetamol	11 (45.8%)	15 (62.5%)	0.247
Tramadol	10 (41.7%)	12 (50.0%)	0.562

Values presented as mean ± SD. and n (%). *P*-value corresponds to Independent *t*-test and Chi-square test.

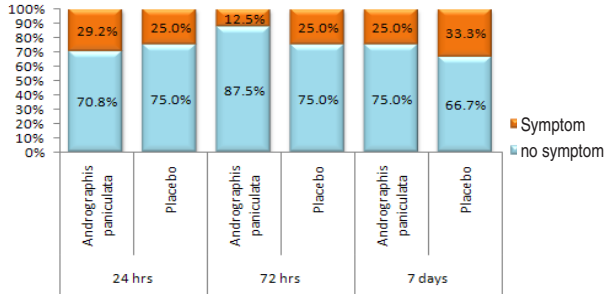

Figure 11. ALP after TACE.

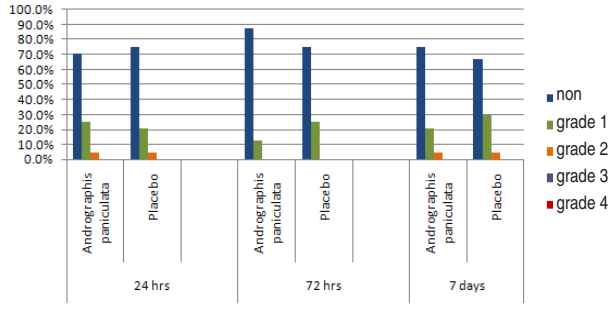

Figure 12. Comparison grading of ALP between the two groups. The efficacy in the A. paniculata group was not significantly different from the placebo group. Alkaline phosphatase - increase by factor (Grade 1- 1.1 - 2.0 x ULN, Grade 2- 2.1 - 3.0 x ULN, Grade 3- 3.1 - 10 x ULN, Grade 4- > 10 x ULN).

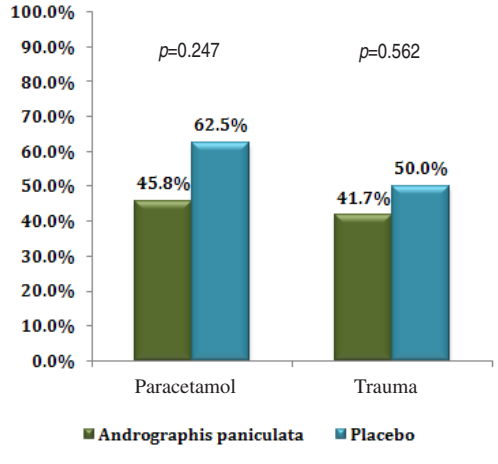

Figure 13. Prescribed paracetamol and tramadol after TACE.

Discussion

TACE is often chosen as the initial non-operative ablative treatment for HCC. TACE has also been used for preventing recurrence of liver cancer after surgery[17,18]. The procedure is performed by selectively blocking the hepatic artery that supplies blood for the tumor and infusing chemotherapeutics to achieve the goal of tumor necrosis and shrinkage. In clinical practice, postembolization syndrome is a common condition after TACE. The pathogenesis of the syndrome is complicated. The main aspects are as follows: (1) lipiodol-induced embolism may result in ischemia, hypoxia, and necrosis in some normal hepatic cells; (2) the chemotherapeutic drugs themselves generate toxicities[19]; (3) the procedure can lead to considerable release of inflammatory factors[20]; (4) procedural injury and drugs can contribute to stress responses in the human body. Up to now, there has not been a single drug that can improve the postembolization syndrome effectively.

There are several clinical reports on the antipyretic, analgesic, anti-inflammatory and hepatoprotective efficacies of *A. paniculata* in human. The active constituents of *A. paniculata* are diterpene lactones, including andrographolide, dehydroandro-grapholide and neoandrographolide. Among these compounds, andrographolide is considered to be the most active and the most important constituent of this plant, exerting the analgesic and anti-inflammatory effects *in vitro*[8,9]. Although the exact mechanisms of andrographolide and its derivatives in regulating analgesic, antipyretic and anti-inflammatory effects remain unknown, it has recently been reported that andrographolide can inhibit NF-κB binding to DNA, thus reducing the expression of proinflammatory proteins such as cyclooxygenase-2 (COX-2)[21]. COX-2 is an inducible enzyme and plays an important role in any pathological processes such as inflammation.

Prostaglandins are also involved in the pathogenesis of fever, pain and inflammation, prostaglandin E_2 (PGE_2) being the most important. PGE_2 is the ultimate mediator of the fever response, and the set point temperature of the body will remain elevated until PGE_2 is no longer present. In regard to pain, PGE_2 induces hyperalgesia because it makes the skin hypersensitive to pain stimuli. In the case of inflammation, PGE_2 causes vasodilation and increases the permeability of post capillary veins, thus potentiating edema formation[22]. Liver damage is associated with cellular necrosis, increases in tissue lipid peroxidation and depletion of reducing glutathione levels[23]. An antioxidant property (reducing lipid peroxidation and maintaining high level glutathione[24] of Andrographolide is claimed to be one of the mechanisms of hepatoprotective effect[25]. These pharmacologic actions are in accordance with the pathogenesis of postembolization syndrome mainly

following TACE. Therefore, we hypothesized that the *A. paniculata* would prevent and treat postembolization syndrome more effectively.

In this study, the efficacy of AP for alleviating fever and hepatalgia was not statistically significantly difference between the AP and the placebo groups (p = 0.242 and p = 0.562 respectively), although reduction of fever and hepatalgia seemed better in the AP group (66.7% vs. 50.0% and 50.0% vs. 41.7% respectively). For abnormal LFT (TB, AST, ALT, ALP), there was essentially no significant differences between the AP and the placebo group at 24 hours, 72 hours and 7 days. For the medications to relieve fever (paracetamol) and abdominal pain (tramadol), the differences between AP and placebo were not statistically different (p = 0.247), (p = 0.562).

However, when comparing the percentage of AP and placebo, the investigations all show that AP could be reduced the use of paracetamol and tramadol significantly (45.8% vs. 62.5%), (41.7% vs. 50.0%).

The present study has some limitations which have to be pointed out. First, there were a small numbers of patients because there was less time to enrolled patients for study. Second, the previous study showed that AP affected platelet aggregation[28, 29], which unable prescribed AP before TACE. Thus, obtaining AP after TACE may not help prevent PES due to the liver injured before receiving AP.

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