August 25, 2021

Dr. Lian-Sheng Ma

Editor in Chief, Baishideng Publishing Group Inc

Manuscript NO: 69365 Title: Single dose dexamethasone prophylaxis of postembolisation syndrome after transcatheter arterial chemoembolisation: a randomised, double-blind, placebo-controlled study

Dear Dr. Lian-Sheng Ma

Thank you for the opportunity to reconsider our manuscript for publication. We would like to provide a point-by-point response to the referee comments and two copies of the revised manuscript, one with changes underlined and one without changes underlined for you.

Once again, thank you for consideration of our work

Sincerely,

Dr. Sakkarin Chirapongsathorn

Associate Professor
Phramongkutklao College of Medicine
Division of Gastroenterology and Hepatology
315 Rajvithee st. Ratchathewi District
Bangkok
10400
Thailand

Response to Reviewer #1:

We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Our response follows (the reviewer's comments are in ***italics***).

Major points:

1) The below limitation should be added into Discussion; After observation period, 48 hours, adverse events were not evaluated in both groups.

Reply:

We appreciate the feedback from the reviewer. We add the limitation into the discussion section as you suggested as shown here; Also, our study did not record the quality of life of any patients and after 48 hours of the procedure, collection of adverse events from patients who admitted due to the post embolization syndrome were not perform. However, our composite SWOG score may represent the symptoms of all patients.

Response to Reviewer #2:

We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Our response follows (the reviewer's comments are in ***italics***).

Major points:

1) I understood the patients' care during TACE. The conventional on demand therapy was useful for patients after TACE. Was it necessary to use steroids for prevention of PES?

Reply:

We thank the reviewer for this suggestion. The conventional on demand therapy was useful when the patients had postembolisation syndrome after TACE. However, patients who had postembolisation syndrome could have decline in quality of life during the treatment and may eventually demand to stop the further intervention. So, it would be better to prevent the syndrome before it would occur. With our data there were minimal adverse events occurred using steroid to prevent this syndrome.

Major points:

2) The present study allowed the administration of antipyretic or anti-emetic drug to patients in both groups. Such drugs could modify the SWOG score. This was a critical problem in the present study. The evaluation point was not clear; for 48 hours or after seven days? I wondered that single dose dexamethasone delayed the occurrence of PES. How about it?

Reply:

We appreciate the feedback from the reviewer. Our method use only incidence occur within 48 hours after chemoembolization and the SWOG score was evaluated before patients received any rescue therapy such as antipyretic or anti-emetic drug. We decide to state this issue in manuscript as the reviewer suggestion in method section on page 10 of this manuscript.

We decide to revise sentence to

"Primary outcome was a negative result of post-embolisation syndrome (PES), which was defined as score <2 of SWOG toxicity coding using fever, nausea, vomiting and pain to calculate within 48 hours after the procedure." and

"Patients were evaluated for the presence of fever, anorexia, and nausea/vomiting for 48 hours to measure the primary outcome and were followed up after seven days to evaluate the adverse event after the procedure. Laboratory tests including hematologic parameters, blood chemistry and hemoculture were conducted at baseline and day 2. Rescue therapy such as antipyretic or anti-emetic therapies were allowed to patients developing fever, anorexia, or nausea/vomiting in consultation with the treating physician. The SWOG score was evaluated before patients received any rescue therapy."

for better understanding and as reviewer's suggestion.

3) Table 2 showed that tumor size > 3cm was independent risk for development of PES syndrome. How about number of patients with tumor size > 3cm in dexamethasone and placebo groups? Table 1 showed that median tumor size was greater in placebo group than those in dexamethasone group. Authors should add the additional data in Table.

Reply:

We thank the reviewer for this suggestion. We decide to add the number of patients in with tumor size > 3cm in dexamethasone and placebo groups in manuscript in table 1 on page 25 of this manuscript as the reviewer suggestion.

As shown here

Table 1 Baseline characteristics

	Dexamethasone (n =49)		**Placebo** (n =51)		**p-value**
	n	%	n	%	
Sex					0.721
Male	40	81.6%	43	84.3%	
Female	9	18.4%	8	15.7%	
Age (year)					0.679
Mean±SD.	61.18	±11.13	61.82	±10.68	
Size (cm)					0.154
Median (min–max)	3.90	(0.40-18.30)	5.40	(0.80-18.00)	0.061
>3 cm	30	61.2%	40	78.4%	
Etiology					0.209
Hepatitis B	22	44.9%	22	43.1%	
Hepatitis C	17	34.7%	14	27.5%	
Cryptogenic	3	6.1%	11	21.6%	
Alcoholic cirrhosis	5	10.2%	3	5.9%	
NASH	1	2.0%	0	0%	
BCLC staging,					0.154
A	11	22.4%	7	13.7%	
B	36	73.5%	44	86.3%	
ECOG performance status					0.845
0	7	14.3%	10	19.6%	
1	39	79.6%	39	76.5%	
Child-Pugh class					0.511
A	41	83.7%	45	88.2%	
B	8	16.3%	6	11.8%	
AFP level					0.72
None	46	93.9%	50	98.0%	
> 400 ng/ml	10	20.4%	9	17.6%	
No of TACE					0.744
1	29	59.2%	31	60.8%	
2	9	18.4%	9	17.6%	
Embolization agent					0.619
Lipiodol plus doxorubicin	15	30.6%	18	35.3%	
Lipiodol plus mitomycin-C	34	69.4%	33	64.7%	
Lipiodol dose					0.483
Mean±SD.	10.67	±3.01	10.14	±1.60	

	Dexamethasone (n =49)		Placebo (n =51)		p-value
	n	%	n	%	
Level of embolisation					0.612
Right branch	30	61.2%	36	70.6%	
Left branch	11	22.4%	8	15.7%	
Main trunk	7	14.3%	7	13.7%	
Diabetes Mellitus					0.806
none	30	61.2%	30	58.8%	
Diabetes Mellitus	19	38.8%	21	41.2%	

*NASH, non-alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation

And there were no significant different between two group and we added this in the manuscript section on page 14 of this manuscript as shown here

Predictors of PES

From univariate analysis, tumour diameter more than 3 cm of the HCC mass and receiving intravenous dexamethasone were associated with developing PES after TACE (Table 2). Receiving dexamethasone was a protective factor against PES with an OR of 0.24 (0.10 to 0.55, P = 0.001) from binary logistic regression. Also, using multivariate analysis, both factors were independently associated with developing PES (Table 2). Patients with HCC diameter more than 3 cm were associated with developing postembolization syndrome after TACE with an OR of 3.66 (1.39 to 9.6, P= 0.008) and receiving dexamethasone was a protective factor against PES with an OR of 0.27 (0.11 to 0.64, P = 0.003). However, patients with tumor > 3cm in dexamethasone and placebo groups were similar as shown in table 1. All other factors were compare using univariate analysis showed in supplementary table S3, S4.

4) *In the refereed paper 12, patients with DM were excluded from the study. On the hand, patients with DM were enrolled into the present study. How about serum glucose level in dexamethasone group?*

Reply:

We thank the reviewer for this suggestion. We decide to declare the result of serum glucose level in this table for the reviewer. In the manuscript we had concluded the adverse event of patients who had more than grade 3 hyperglycemia in dexamethasone group was not statistical significance different compare to the placebo group (22.4 vs. 15.7%; P =0.743). And we add some detail in the Safety section on page 14 of this manuscript as shown here "No serious adverse events were associated with dexamethasone and the TACE procedure did not differ. Regarding other specific adverse events that seemed to be associated with dexamethasone, patients had more than grade 3 hyperglycemia, higher than that of the placebo group, but without statistical significance (22.4 vs. 15.7%; P =0.743). Even though we included all patients with or without diabetes the mean serum glucose measure in the fasting state in the morning after the procedure were not significant different between dexamethasone and placebo group 151.12 mg/dL vs 140.57 mg/dL respectively; P= 0.643."

Table 1 serum glucose level

	Dexamethasone						Placebo						**p-value**
	N	Mean	SD.	Median	Min	Max	N	Mean	SD.	Median	Min	Max	
Serum glucose (mg/dL)	49	151.12	70.42	122.00	98	373	51	140.57	60.99	123.00	82	386	0.643