July 6, 2015

Re: **ESPS Manuscript NO:** 19256

Dear Editor:

We have revised our manuscript "Development of Biodegradable Radiopaque Microsphere for Arterial Embolization – a Pig Study" according to the reviewers' comment and the editor's request. The changes are highlighted in the revised manuscript and are listed as follows. Thanks for your review and comments to our manuscript.

(For note, pages and lines listed below are corresponding to the change-highlighted copy of the manuscript.)

Response to Reviewers:

Reviewer 19256

Q1. The main purpose of this article is to make biodegradable microsphere for chemoembolization. But, the microsphere does not contain chemotherapeutic drug. The experiment is designed for bland embolization.

Response:

Thanks for reviewer's suggestion. Creating Drug eluting microsphere is our ultimate goal, however, adding chemotoxic agent to microsphere at current experiment may complicate the evaluation of adverse effect of our microsphere if its safety has not been proved in advance (Page 14, the 2nd paragraph, line 6-9). We will add chemotoxic drugs in the future study after the approval of our calibrated, biodegradable microsphere.

Q2. Blood test was obtained at 1 day and 25 days. I think that blood test should be done at 1 day, 3 days, 7 days, 2 weeks, and 28 days.

Response:

We agree that the above mentioned check points will be better for blood tests. However, pig is unlike rabbit, it requires anesthesia for drawing blood. To avoid the potential interference of anesthesia on pigs (Page 7, line 8-9), we limited the blood sampling time at 1 day before and after TAE and 25 days after TAE to determine the immediate and mid-term embolization effects.

Q3. The method of manufacturing of microsphere is ambiguous and very roughly described.

Response:

We reported our novelties of manufacturing microsphere instead of detail method since we suspect that reporting the novelties may be more interesting to the WJR readers who mostly have medical background. As indicated in the last paragraph of page 7 and the first paragraph of page 8, our novelties include the atomization technique and use of excipient to construct our microsphere.

Q4. What is end point of embolization of hepatic artery and splenic artery?
Response:
As we mentioned in the last 3 lines of the 2nd paragraph of page 8, the end point of the procedure was to obtain blood flow stasis of the selected hepatic and splenic arteries.

Q5. I think that pathologic evaluation of vasculitis caused by microsphere should be done by elastic staining or etc.
Response:
We thank for the reviewer's suggestion. Although the ingredients we used for our microsphere were all pharmaceutical excipient, the possible liver toxicity caused by such mixture is still a concern until it can be proved otherwise (Page 11, the 4th paragraph, line 1-3). The pathology pictures we shown in Figure 6a-c were therefore to prove that the liver lobules adjacent to the embolized arterioles were not affected by our microsphere as those seen with embosphere and gelfoam. To indicate this point, we add ***black arrows*** *in the revised figures 6a-c. Vasculitis after embolization can be an advantage as it causes more severe obliteration of artery and subsequent ischemia but can also be a disadvantage as it may prohibit repetitive TAE. To focus on proving our new microsphere as a useful embolization material, we pointed out the reaction of vessels (Figures 6a-c,* ***arrows****) but did not emphasize this debating issue in our paper.*

Q6. In M&M, CT scan was obtained at 1 day and 25 days after embolization, but figure 5 showed CT scan obtained 4, 12, 25 days after embolization.
Response:
We are sorry to make such a mistake in the statement of methodology, it should be 4, 12, and 25 days after embolization and we have corrected it in the revised methodology (page 7, Line 11).

Q7. Authors described that gradual fade out was noted, but I cannot see this fade out.
Response:

To clarify such evolution change, we have added white arrows in Figure 5 to indicate the fade out of lipiodol contained microsphere.

Q8. *A*uthors' microsphere showed severe atrophy of spleen, but gelfoam and embosphere did not cause atrophy.

Response:

Because complete embolization of spleen can cause a significant morbidity and mortality, we therefore, embolized only a branch of splenic artery (page 8, the 2nd paragraph, the last 3rd to 5th line). As seen in the figures 8a-c, on microscopy examination, all three embolization materials were shown to successfully obliterate the selected artery. The different severity of splenic infarction among gelfoam, embosphere, and our microsphere as shown in the figure 7a-c may be caused by the selection of arterial branch on TAE rather than the character of embolization materials per se (page 11, the last 5 lines and page 12, the 1st 3 lines).

Reviewer 0009760

Novel, useful, promising work on different embolic particles

Response:

We thanks for reviewer's support of our work.

Reviewer 0092680

I have no comment.

Response:

We thanks for reviewer's support of our work.

Changes according to the Editor's request:

1. *The manuscript has been formatted according to the guideline for revision.*
2. *We have added the animal care and use statement in the methods of our manuscript.*
3. *The PubMed citation number of references has been added.*
4. *Besides, we change the references 1 and 2 with the most update report as reference 1.*