**Peer Review File**

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**Reviewer A**

This paper reports the results of a pilot study extracted Tanshinone compounds for treating superficial infantile hemangiomas (IH). I have a few observations, questions and suggestions for the authors which may improve this paper.

1. The conclusions about the safety and efficacy should be toned down. This is a small, pilot study. It is not "groundbreaking." It has not proved efficacy (without a control group) or safety (without rigorous assessment and collection of side effects/adverse events).
**Reply 1:** The reviewer has a very deep insight of this field and we are grateful for the suggestions. We have revised the conclusion paragraph and hope that it is now more proper.
**Changes in the text:** Please see page 8-9 of the revised manuscript, lines 270-276.

2. "Safety analysis primarily incorporated the incidence of systemic and local adverse events were recorded in the process of treatment by a researcher." This is vague and imprecise. It appears that safety was assessed only by parents reports, presumably based on questions asked at follow up assessments. Unless additional information can be provided, this is a major limitation.
**Reply 2:** We thank the reviewer for kindly pointing the limitations out. We have added a brief description on how the adverse events were observed by researchers. The researchers evaluated adverse events in every follow-up and also questionnaires were answered by parents of the participants together.
**Changes in the text**: Please see page 4-5 of the revised manuscript, lines 135-138.

3. For eligibility, "superficial" was not defined. This should be clearly stated that this was a subjective inclusion criterion. It should be emphasized in the discussion that included patients had superficial IH.
**Reply 3**: Thank you for the suggestion. We took the advice and emphasized the definition of "superficial IHs" in inclusion criterion. The confirmed diagnosis of superficial IHs in line with the International Society for the Study of Vascular Anomalies (ISSVA) classification and nomenclature criteria, identified by strawberry-like erythema on the skin surface with no apparent underlying cyanosis.
**Changes in the text**: Please see page 3-4 of the revised manuscript, lines 101-104.

4. Can the authors present data on the size of IH in the study? Were patients with large, superficial IH included?
**Reply 4**: Yes we did record the sizes of IHs. Most of them were relatively small and within the range of 3cm×3cm. There were no large superficial IHs included. Since the main indicator of response was the change in erythema of IHs, size records were not presented in the article.
Changes in the text: none.

5. I recommend including a brief description of how the ointment is made, or at least a reference to a paper describing it.

**Reply 5**: We thank the reviewer for pointing this out. The formula and detail of Tanshinone ointment was recorded on a scientific and technological report as an achievement of Shanghai Science and Technology Innovation Action Plan in 2018 supported by Shanghai Science and Technology Commission, China. (Project No.18401931800)

Changes in the text: none.

6. Applying a plastic wrap for 10 minutes would be very hard to do in infants, especially on places like the face and hands. This is hardly "convenient administration" as stated in the discussion. Do you have any data as to how many parents complied with this recommendation? Is it even necessary? I would think an ointment would stick to the skin well, without the need for a plastic wrap.

**Reply 6**: The reviewer's concern is absolutely right. In order to make sure the ointment staying on lesion, we suggested parents to apply ointment when infants are sleeping or resting, under the supervision of grown-ups. A plastic wrap was actually only an option (not a must-do) for those lesions on trunk of the body to avoid the ointment being removed accidentally by contacting or covering with clothes. We deleted the plastic wrap.

**Changes in the text**: Please see page 4 of the revised manuscript, lines 117-120.

7. "A total of 36 patients underwent the screening process; two patients did not meet the inclusion criteria, and five refused to participate in the study." This contradicts Figure 1, which says 5 patients "discontinued intervention" after enrollment. Please clarify.

**Reply 7**: Thank you for the suggestion. This has been clarified in the revised version of the manuscript. "five refused to participate in the study" should be "five participants failed to continue the intervention on the first follow-up of the study"

**Changes in the text**: Please see page 5 of the revised manuscript, lines 149-151.

8. Many of the reported (and cited) side effects of topical timolol, as well as the risk of systemic side effects, are hypothetical and overblown, in my opinion. Please reword/clarify. The authors state that this treatment may have "fewer side effects." Compared to what? The existing literature to date shows that topical timolol is safe and effective for small, superficial IH, and has virtually no side effects. It is hard to find a treatment with fewer side effects. And since there was no control or comparison group, the authors should reword this section of the discussion.

**Reply 8**: Yes, we fully agree with the reviewer that topical timolol is safe and effective for small, superficial IH and has rare side effects, mostly local skin changes. Our treatment was intended to compare to old conventional methods or systematic use of beta blockers, as an innovative option of topical therapy may have "fewer side effects". Our future working plan is to carry out a larger scale of multi-centered randomized controlled clinical trial and we'll probably choose topical timolol as double-blinded control group. Before that we deleted words such as "fewer side effects than others" to be more precise according to the reviewer's instruction.

**Changes in the text**: Please see page 6, 8-9 of the revised manuscript, lines 192-194, 270-276.

9. The section of the discussion titled "Comparison with similar studies" should be deleted or completely rewritten. It is confusing at best, and incorrect at worst.
**Reply 9**: We appreciate your suggestions regarding the section of the discussion. Based on your guidance, we've rewritten the section and hope that it is now more proper.
**Changes in the text**: Please see page 6 of the revised manuscript, lines 200-210.

10. "The treatment was more effective on lesions located on the palm and between the fingers, yet less effective on the face, forehead, and scalp, possibly due to the local retention of the drug." This should be in the results section (not in the discussion), and the data shown.
**Reply 10**: Thank reviewer for the suggestion. Only 2 cases located on the palm and between the fingers. The hypothesis was based on the subjective feelings of observers, which are not statistically significant, and will be further verified when the sample is expanded. We reworded the text.
**Changes in the text**: Please see page 7 of the revised manuscript, lines 216-219.

11. "Parents expressed high satisfaction with the treatment, particularly its long-term effects." This should be in the results section, and the data shown. Also, it does not appear that parents were asked about "long-term effects."
**Reply 11**: We thank the reviewer for pointing this out. In long-term follow-ups (9 months), the parents were given a simple questionnaire, as described in table3 (satisfaction of parents: total score of 5 represents very satisfied, 1 represents not satisfied at all) 23/29 parents scored 5/5 on the results, indicating that the therapy had met their expectations.
**Changes in the text**: Please see page 4 line 133-138 and page 16 table3 of the revised manuscript.

12. "such as anxiety and low self-esteem in parents..." This should be deleted or rewritten.
**Reply 12**: Thank reviewer for the advice. We rephrased the point and added a new reference. Peng W, Liu H, Chen J, et al. Development and validation of psychological status questionnaire for parents of infantile hemangiomas. Transl Pediatr. 2021;10(12):3261-3272. doi:10.21037/tp-21-554
**Changes in the text**: Please see page 7 of the revised manuscript, lines 221-224.

13. I suggest deleting pulse dye laser and surgery as treatments for IH. Thse have become obsolete and should rarely, if ever, be used.
**Reply 13**: We totally agree that pulse dye laser and surgery are conventional treatments for IHs. The reason why we keep them in article is that the readers of the work may include doctors of pediatric surgery, dermatology, plastic surgery, etc. In clinical situations, pulse dye laser and surgery are now mainly applied to those cases which didn't respond well to beta blockers either topical or systematic used. We reworded the text.
**Changes in the text**: Please see page 8 of the revised manuscript, lines 249-252.

14. The entire page starting with "In the early laboratory work with Tanshinone extracts" should

be deleted. Alternatively, those background results could be succinctly summarized in a few sentences.

**Reply 14**: Thanks a lot for the suggestion. Actually this part of research work was originally presented by our team and was rewarded with a Chinese national patent (ZL2017 1 0819070.3). At the same time, it serves as the theoretical basis and explanation of mechanism, which we hope would be helpful to readers in this field. We'd like to keep the information but we reduced the length of this part following the reviewer's advice.

**Changes in the text**: Please see page 7-8 of the revised manuscript, lines 228-246.

15. The "Highlight box" statements need to be rewritten.

**Reply 15**: We valued the reviewer's advice and amended the relevant part in "Highlight box".

**Changes in the text**: Please see page 9-10 of the revised manuscript, lines 295-312.

16. I find Figure 2 confusing. Can these data be presented in a different format? Or could additional explanation be provided?

**Reply 16**: Thank you for the suggestion. The legend of Figure 2 was rewritten to make it clearer.

**Changes in the text**: Please see page 12 of the revised manuscript, lines 398-402.

17. Please use "male" and "female" instead of "boy" and "girl."

**Reply 17**: Thanks a lot for the reviewer's suggestion. We've revised the text and Table-1 based on the reviewer's guidance, changing "boy" and "girl" to "male" and "female".

**Changes in the text**: Please see page 13-14 of the revised manuscript, text and Table-1.

18. Table 1: is the age the age at enrollment? Please clarify.

**Reply 18**: Yes. The age in manuscript means age(days) on enrollment, we clarified this in the text based on the reviewer's guidance.

**Changes in the text**: Please see page 5 of the revised manuscript, lines 153.

**Reviewer B**

The idea about using this safe and potentially effective topical agent for the treatment of superficial hemangiomas is well done and important to pursue. There are a few minor errors in your abbreviation of infantile hemengiomas IHs like lines 69, 180, and 186. Is there any way to combine the information in tables 1 and 2? If this is not possible, dont worry about it.

**Reply 1**: We sincerely thank the reviewer for thoroughly examining our manuscript and providing very helpful comments to guide our revision. We've checked every abbreviation of infantile hemangiomas as IHs and adjusted some information on tables.

**Changes in the text**: We've checked every abbreviation of infantile hemangiomas as IHs.

I agree that a randomized control trial would be the next step. Since the results were quick, you could probably do this for 6-8 weeks max.

**Reply 2**: We are grateful to the reviewer for your positive feedback. And as you mentioned, in our following working plan, a larger scale of multi-centered randomized controlled clinical trial will be carried out in the near future.

**Changes in the text**: Please see page 6 of the revised manuscript, lines 192-197.

**Reviewer C**

1) First, the title needs to indicate safety and the clinical research design of this study, i.e., a single-arm clinical trial.

**Reply 1**: We sincerely thank the reviewer for the kind suggestion. Yes, the pilot study was a single-arm clinical trial and we indicated that at the beginning of the abstract and research design as the reviewer suggested.

**Changes in the text**: Please see page 2, line 35 and page 3, line 90 of the revised manuscript.

2) Second, the abstract needs some revisions. The background needs to have more detailed comments on the limitations of available treatments for His. The methods need to describe the inclusion of subjects, duration of treatment, and measures of safety outcomes. The conclusion needs comments for the limitations of this study and the clinical implications of the findings.

**Reply 2**: We are grateful to the reviewer for thoroughly examining our manuscript and providing very helpful comments to guide our revision. We rewrote the abstract and hope that it is now more proper.

**Changes in the text**: Please see page 1-2 of the revised manuscript, lines 29-48.

3) Third, in the introduction of the main text, the authors analyzed the limitations of available treatments but they did not analyze why tanshinone compounds can address the limitations of available treatments. Please also explain the physiological mechanisms of tanshinone compounds and analyze why it is potentially effective and safe.

**Reply 3**: Thank you very much for the suggestion. We introduced and explained the possible physiological mechanisms of tanshinone compounds in discussion.

**Changes in the text**: Please see page 3 line 77-81, page 7-8 line 228-246 of the revised manuscript.

4) Fourth, in the methodology of the main text, please describe the assessment of baseline clinical factors and estimation procedures of the sample size of this study. In statistics, please ensure $P<0.05$ is two-sided.

**Reply 4**: Thank you for pointing out this deficiency. We added descriptions of the baseline clinical factors in methodology part. We failed to estimate the sample size in advance. Actually the 29 complete samples were all that we could collect during the past epidemic years as a pilot study. We guarantee that in our following working plan, sample size will be calculated before a possible large-scale randomized controlled clinical trial. Yes, the $P<0.05$ is two-sided and were added to the text.

**Changes in the text**: Please see page 5 of the revised manuscript, lines 140-146.

5) Finally, please consider to cite several related papers: 1. Zheng JW, Wang XK, Qin ZP, Fan XD, Li K, Yang YW, Huo R, Liu SH, Zhao JH, Wang XY, Zhou DK, Liu XJ. Chinese expert consensus on the use of oral propranolol for treatment of infantile hemangiomas (version 2022). Front Oral Maxillofac Med 2022;4:32. 2. Peng W, Liu H, Chen J, Zheng

Y, Xu X, Tang H, Liu Q. Development and validation of psychological status questionnaire for parents of infantile hemangiomas. Transl Pediatr 2021;10(12):3261-3272. doi: 10.21037/tp-21-554. 3. Wu ZB, Shi SL, Pan FJ, Li L, Chen HY. Propranolol inhibits infantile hemangioma by regulating the miR-424/vascular endothelial growth factor-A (VEGFA) axis. Transl Pediatr 2021;10(7):1867-1876. doi: 10.21037/tp-21-244.

**Reply 5**: Thank you very much for the encouraging and kind comments. We found the papers you recommended very helpful and used all 3 of them as attached references.

**Changes in the text**: Please see page 10 (References) of the revised manuscript, Reference (16), (18), (20).