

November 26, 2018

Bao-gan Peng, MD, PhD
Editor-in-Chief
World Journal of Orthopedics
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Re: Revision and Resubmission of Manuscript ID 42879, "Investigational Growth Factors Utilized in Animal Models of Spinal Fusion: Systematic Review"

Dear Dr. Bao-gan Peng,

Thank you for the opportunity to revise and resubmit our manuscript (ID 42879) for consideration of publication in *World Journal of Orthopedics*. We similarly thank the reviewers for taking the time to review and provide feedback on our manuscript.

Please see on the following pages the compiled comments from all three reviewers, as well as our responses and indicated changes to the revised manuscript following each comment. In the revised manuscript (submitted separately), all changes are highlighted in yellow.

We believe that we have significantly improved our manuscript through the indicated revisions. We now submit our revised manuscript for your reconsideration of publication in *World Journal of Orthopedics*.

Thank you for taking the time to reconsider our manuscript. We look forward to hearing from you soon.

Yours sincerely,

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Reviewer 1

Reviewer comments: “The authors present a systematic review on the factors used in animal models of spinal arthrodesis. The study is well designed but obviates studying the BMP-7 (OP-1). The BMP-7 has been much used in animals as well as in humans, and although it is currently temporarily suspended its commercialization, its inclusion in a paper on animal experimentation is necessary. The clinical use of other proteins such as BMP-2 has also been subjected to other clinical problems.”

Authors’ response: We thank the reviewer for providing this feedback, which has generated thoughtful discussion amongst the co-authors. We agree that we present a systematic review on investigational growth factors utilized in animal models of spinal fusion. The reviewer recommends including BMP-7 (also called OP-1) in our systematic review. Respectfully, we disagree with this recommendation, for the following primary reason: as the reviewer indicates, BMP-7 has already seen clinical translation; that is, it is not a “preclinical, investigational growth factor,” which is an important distinction of our inclusion criteria. For example, there are multiple clinical trials reporting on the use of BMP-7 in spinal fusion^[1-3], including a recent meta-analysis of the randomized controlled clinical trials of BMP-7 in spinal fusion^[4]. This meta-analysis concluded that the use of BMP-7 “appeared to yield lower fusion rates [in instrumented posterolateral fusion patients]” compared to iliac crest bone graft, which may help to explain its suspension from current commercialization, as the reviewer rightfully noted.

Changes to the revised manuscript: In the revised Introduction section (2nd paragraph), we have (1) indicated that BMP-7 (along with BMP-2 and PTH) has been studied clinically in spinal fusion and (2) inserted a reference to the recent meta-analysis of the randomized controlled clinical trials of BMP-7 in spinal fusion. This acknowledges the historical importance of BMP-7 in this area. We again thank the reviewer for this helpful feedback and believe that we have strengthened our study by making these changes in the revised manuscript.

1 Delawi D, Dhert WJ, Rillardon L, Gay E, Prestamburgo D, Garcia-Fernandez C, Guerado E, Specchia N, Van Susante JL, Verschuur N, van Ufford HM, Oner FC. A prospective, randomized, controlled, multicenter study of osteogenic protein-1 in instrumented posterolateral fusions: report on safety and feasibility. *Spine*. 2010; 1185 [PMID: 20445470 10.1097/BRS.0b013e3181d3cf28: 10.1097/BRS.0b013e3181d3cf28]

2 Delawi D, Jacobs W, van Susante JL, Rillardon L, Prestamburgo D, Specchia N, Gay E, Verschuur N, Garcia-Fernandez C, Guerado E, Quarles van Ufford H, Kruijst MC, Dhert WJ, Oner FC. OP-1 Compared with Iliac Crest Autograft in Instrumented Posterolateral Fusion: A Randomized, Multicenter Non-Inferiority Trial. *The Journal of bone and joint surgery American volume*. 2016; 441 [PMID: 26984911 10.2106/JBJS.O.00209: 10.2106/JBJS.O.00209]

3 Guerado E, Cervan AM, Bertrand ML, Benitez-Parejo N. Allograft plus OP-1 enhances ossification in posterolateral lumbar fusion: A seven year follow-up. *Injury*. 2016; S78 [PMID: 27692113 10.1016/S0020-1383(16)30611-8: 10.1016/S0020-1383(16)30611-8]

4 Ye F, Zeng Z, Wang J, Liu H, Wang H, Zheng Z. Comparison of the use of rhBMP-7 versus iliac crest autograft in single-level lumbar fusion: a meta-analysis of randomized controlled trials. *J Bone Miner Metab*. 2018; 119 [PMID: 28342094 10.1007/s00774-017-0821-z: 10.1007/s00774-017-0821-z]

Reviewer 2

Reviewer comments: "The manuscript is an interesting systematic review of the all non-human, preclinical animal models of spinal fusion reported in the literature and the growth factors role growth factors in spinal fusion. After a 4806 articles research on the four principles science databases (PubMed, Embase, Cochrane Library, and Web of Science), only 26 articles were considerate eligible by the authors. Main growth factors investigated were: AB204; angiopoietin; calcitonin; erythropoietin; basic fibroblast growth factor; growth differentiation factor, combined insulinlike growth factor 1 + transforming growth factor beta; insulin; NELL-1; noggin; P-15; peptide B2A; and secreted phosphoprotein 24. The authors concluded that many of the investigated growth factors could inform the development of efficacious, clinically translatable materials for spinal fusion. Comment 1: The authors should implement the discussion, add their opinion on the future prospective of the main growth factors, which of the should be further investigated and their possible clinical use."

Authors' Response: We thank the reviewer for providing this feedback. We agree that we present an interesting systematic review of all the published investigational growth factors utilized in preclinical animal models of spinal fusion. The reviewer's recommendation for improvement – i.e., to include in the Discussion section our outlook regarding growth factors in this area – is well-received.

Changes to the revised manuscript: In the revised manuscript, we include in the Discussion section our viewpoint on the most promising investigational growth factors for clinical translation in spinal fusion. In addition, we recommend the investigation of additional growth factors, informed from other areas of bone tissue engineering, for preclinical investigation in spinal fusion. We believe that these additions to the Discussion section enhance the quality of our systematic review, and we again thank the reviewer for recommending these changes.

Reviewer 3

Reviewer comments: “Abstract In the results, preferably include a range in fusion rates
Introduction Please do not use trademarks in the introduction, use the name of the factor itself.
Methods Well described Results Be consistent in reporting data. For example, state % of fusion
rate for calcitonin. Also for BFGF report specific values. Similarly for IGF/TGFb Were there any
complications reported in these animal studies? Discussion Well presented. As described, the
applicability of these factors to clinical practice is not only related to translation of the findings
to humans, but also potential complications.”

Authors’ Response: We thank the reviewer kindly for providing this feedback. We agree that the successful clinical translation of the identified growth factors for spinal fusion will depend not only on their capacity to promote spinal fusion in humans, but also on their safety profiles (i.e., associated complications). We have addressed each comment as well as we can in the revised manuscript (below), which we believe has significantly improved the quality of our manuscript.

Changes to the revised manuscript:

- In the Results subsection of the Abstract, the ranges of the fusion rates for iliac crest bone graft and BMP-2 (the standards against which comparisons were made) are now provided. This now provides reference ranges for the other fusion rates reported in the Results subsection of the Abstract.
- In the Introduction, the pertinent sentence has been reworded; the trademark symbol has been removed.
- In the Results section, we confirm that we have included the fusion rates (%) for all studies specifying these values.
- None of the studies included in our review indicated complications directly related to the growth factors. Perioperative deaths, all caused by the surgical procedure and unrelated to the growth factors, are tabulated for each study in the “Excluded/perioperative death” column of the Supplemental Table. We especially appreciate this comment, nonetheless, as associated complications are obviously an extremely important factor regarding clinical translation. The Discussion section of the revised manuscript now notes this important consideration.