



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Orthopedics

**Manuscript NO:** 39142

**Title:** Vascular endothelial growth factor for the treatment of femoral head osteonecrosis:  
An experimental study in canines

**Reviewer’s code:** 00058340

**Reviewer’s country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-04-11

**Date reviewed:** 2018-04-20

**Review time:** 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The authors demonstrated in this study that local administration of Vascular Endothelial Growth Factor (VEGF) is effective treatment of femoral head osteonecrosis in a canine model. Comments 1) The study is reasonably performed, however it does not provide



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7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** bpgoffice@wjgnet.com  
**https://**www.wjgnet.com

in depth insight into the mechanism of VEGF action. Is it the therapeutic effect of VEGF due to stimulation of angiogenesis, stimulation of osteoblasts and/or activation of progenitor cells. Answer to these questions will definitely enhanced this manuscript. The authors have the histologic specimens, so they can use them to evaluate above factors. 2) Comparative boxplot of the TbTh values. Please explain what does it mean. 3) Tables 1 and 2 contain numbers e.g., 29,437 etc Do you mean 29.437 ??? 4) Histologic figures should be labelled with arrowhead, asterics and letters so the readers, who are not expert pathologists can fully understand them. 5) A diagram summarizing potential mechanisms of VEGF action on femoral head osteonecrosis healing would be very useful. 6) Manuscript requires linguistic improvements, e.g. "apart from" should be replaced with except "analogous differences" should be replaced with similar differences, "were sacrificed" should be replaced with were euthanized, etc, etc. 7) In the reference related to VEGF and angiogenesis the authors should cite paper of Napoleone Ferrara, who identified, sequenced and named VEGF 8) The authors may consider adding below reference Tannast M1,2, Wolfer N2, Ryan MK3, Nuss KM2, von Rechenberg B2, Steppacher SD1. The Vascular Supply of the Femoral Head in Sheep - Implications for the Ovine Femoroacetabular Impingement Model. J Orthop Res. 2018 Mar 25. doi: 10.1002/jor.23897 Xu T, et al Administration of erythropoietin prevents bone loss in osteonecrosis of the femoral head in mice. Mol Med Rep. 2017 Dec;16(6):8755-8762. doi: 10.3892/mmr.2017.7735. PMID: 29039481

## INITIAL REVIEW OF THE MANUSCRIPT

### *Google Search:*

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7901 Stoneridge Drive, Suite 501,  
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**Telephone:** +1-925-223-8242  
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[Y] No

***BPG Search:***

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[Y] No



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**Name of journal:** World Journal of Orthopedics

**Manuscript NO:** 39142

**Title:** Vascular endothelial growth factor for the treatment of femoral head osteonecrosis:  
An experimental study in canines

**Reviewer's code:** 00505434

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-04-21

**Date reviewed:** 2018-04-23

**Review time:** 2 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

**Abstract:** 1. Change "femoral head osteonecrosis" to "osteonecrosis of the femoral head (ONFH)". 2. Chang "FHON" to "ONFH" as indicated above 3. Clear state how many groups, and how many animals in each group in method section **Introduction:**



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Change the first sentence to "osteonecrosis (ON), also known as avascular necroiss (AVN)...". use ON to replace AVN throughout the entire manuscript since ARCO recommended to use the new term ON to replace the old term AVN. Materials and Methods 1. Briefly state the surgical techniques, including anesthesia, sterile techniques, and pain management after surgery, as well as weight bearing status. 2. Clearly state how the specimens were fixed? in what solutions? 3. How did the uncalcified specimens were sectioned? Discussion 1. Change "Avascular necrosis (AVN) of the FH" to "Osteonecrosis of the femoral head (ONFH)" 2. Again, eliminate the term "AVN" from the entire manuscript.

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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Orthopedics

**Manuscript NO:** 39142

**Title:** Vascular endothelial growth factor for the treatment of femoral head osteonecrosis:  
An experimental study in canines

**Reviewer’s code:** 02444711

**Reviewer’s country:** China

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-04-21

**Date reviewed:** 2018-04-24

**Review time:** 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

This study targets to investigate the treatment effect of VEGF on femoral head osteonecrosis (FHON) in canine model. I have the following concerns: 1. Abstract is not clear, esp. grouping. I cannot get the full picture of the study after reading it. 2.



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What is the hypothesis of this study? I cannot find the hypothesis in Introduction. 3.

The first sentence of Method states the ethical approval. Please provide the reference number, if available. 4. The animals were sacrificed at 12 weeks. Why choose this time point? Any literature support to select this time point? 5. I am a bit confused of the sample allocation. There were 6 groups with n=5 in each group. They were cut half, which one half underwent decalcification, while another half of two canines per group were subjected to undecalcification. Then how about the another half of the remaining 3 samples? Also, it specifies "the exception of the t-NS group, why? I am confused with these and please clarify. 6. I wonder for all the animals, any one of them showed bone collapse? 7. On page 11, last paragraph, it mentions "In the present study the influence of the VEGF on angiogenesis and osteogenesis ..." but this study did not examine anything about angiogenesis?! Please clarify. This is also related to the keyword selection of this study. 8. Discussion should have a part to discuss study limitations. 9. This study only demonstrated the general effect on bone without any in-depth mechanistic work done.

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