RESPONSE TO EDITOR

Dear mr Yan,

Thank you for your time to edit our manuscript. We have adjusted our manuscript to meet all of your recommendations. We hope you agree with the changes we made.

On the pages below, you can find a point-by-point answer to the questions and recommendations by the reviewers. We have tried to answer all questions extensively, and we have made some changes to the manuscript when needed. For clarity purposes, our answers are listed in green. We hope you agree with our reaction to the reviewers' suggestions.

If there are any further changes required, please let me know and I can adjust the manuscript further.

Thank you in advance for your efforts while judging and editing our manuscript,

Sincerely,

On behalf of Dirk Jan Moojen, Marc van Ogtrop and Rudolf Poolman,

Ewout Veltman

RESPONSE TO PEER-REVIEW REPORT #1

Name of journal: World Journal of Orthopedics

Manuscript NO: 49236

Title: Two-Stage Revision Arthroplasty for Coagulase-Negative Staphylococcal Periprosthetic Joint Infection of the Hip and Knee

Reviewer's code: 02694731

Reviewer's country: Switzerland

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-23 10:14

Reviewer performed review: 2019-05-23 13:09

Review time: 2 Hours

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[ ] Grade E: Do not publish	[ ] Grade D: Rejection	[ ] Major revision	[Y] Advanced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

SPECIFIC COMMENTS TO AUTHORS

+ thank you for the effort of thoroughly judging our manuscript.

This study addresses a difficult diagnosis in total joint arthroplasty (TJA), not only infection per se being a major complication in TJA but in particular considering a difficult to treat germ such as Coagulase-Negative Staphylococci. Your treatment regime corresponds to the generally accepted procedure and your results in treating CoNS corresponds to what can be expected realistically. You also reported complications that occur during the course of time during the treatment of these patients that are not directly related to infection but can be part of the treatment. The incidence of these

complication is also within the expected range. The specific trade mark of your study is that ii focuses on CoNS. So, it is a good report providing realistic expectations when treating such patients.

+ Thank you for your kind comments.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[   ] The same title

[   ] Duplicate publication

[   ] Plagiarism

[   ] No

BPG Search:

[   ] The same title

[   ] Duplicate publication

[   ] Plagiarism

[   ] No

RESPONSE TO PEER-REVIEW REPORT #2

Name of journal: World Journal of Orthopedics

Manuscript NO: 49236

Title: Two-Stage Revision Arthroplasty for Coagulase-Negative Staphylococcal Periprosthetic Joint Infection of the Hip and Knee

Reviewer's code: 02488945

Reviewer's country: India

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-06-11 16:43

Reviewer performed review: 2019-06-13 12:07

Review time: 1 Day and 19 Hours

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

SPECIFIC COMMENTS TO AUTHORS

+ thank you for the effort of thoroughly judging our manuscript.

This retrospective study though well written does not deliver any new message. Also, the following points can be considered:

(1) Why P. acne organism cases were not included. While some patients with multiple

organism infection have been included the why not include "Low Virulence organisms" as a group?

+ Thank you for your suggestion. In this study, our aim was to report on the results of treatment of CoNS infections specifically. That is why we have also included the polymicrobial cases of which one was CoNS.

The P. acnes isolates we find are often easy to treat infections, while the CoNS infections are more frequently difficult to treat, therefore in our clinic the two organisms are not comparable.

(2) Very small number of cases. Backward sample size calculation can be done, presuming 100% eradication of PJI to determine whether sample size is adequate.

+ Thank you for your comment, we agree the number of patients is limited. This is caused by the scarcity of prosthetic joint infections in our clinic, as mentioned in the fifth paragraph of the discussion (limitations section).

We have performed the sample size calculation which you advised, using 100% infection eradication, power of 80% and alpha of 0.05. This results in a required sample size of 15.

However as we are not comparing treatment protocols and an infection eradication rate of 100% is purely theoretical, we do not believe reporting such a sample size calculation adds value to the study. If the editor disagrees, we would be willing to add it to the methods section.

(3) Why the difference between THR and TKA outcome?....a recent published data shows the results which are opposite. [Alvand A, Grammatopoulous G, de Vos F, et al, Clinical Outcome of Massive periprosthetic Joint infections of Hip and Knee. J Arthroplasty, 2018 Mar: 33 (3): 829-8344]

+ Thank you for the comment. Alvand and colleagues report a cohort of patients treated with revision to a megaprosthesis in either a one-stage (30%) or a two-stage setting (70%), after failure of previous revision or after periprosthetic fracture. Only 65% of patients

were treated because of an infection. Only 28% of these patients had a CoNS infection, while 36% had a polymicrobial infection. The patient characteristics of Alvand's population and our study are not comparable.

The conclusions of Alvand and colleagues are ambivalent. The authors of this study report no difference in survivorship of the hip and knee at follow-up, while at the same time they report infection recurrence in 17% of hips and 41% of knees.

The study by Alvand and colleagues is interesting as it describes treatment outcome in the very worst category of patients (those with failed prior revisions and persisting infection or non-union of periprosthetic fractures), but it is not comparable to the study we currently present to you.

We believe your example justifies analyzing the results for hips and knees separately and comparing the results. Also, by analyzing the results for hips and knees separately, our study could be included in meta-analyses or reviews performed in the future, especially if they specifically target only one of the joints.

(4)   Were all patients in THA group had primary arthroplasty due to Femoral fracture? If not then how many?

+ thank you for your question. As mentioned in the discussion, 10 out of 29 hip patients had primary arthroplasty due to a femoral fracture. In the other 19 cases primary arthroplasty was performed due to osteoarthritis. We have tried to clarify this further in the manuscript, discussion paragraph 4.

(5) What was the percentage of total THA and TKA performed between 2003 and 2016 that got infected? And what percentage of those were coagulase negative staphylococcal infection?

+ The infection percentage in our hospital is about 0,5-1%. However we are a referral center for joint infections, so many patients that we treat for infection were primarily treated elsewhere. The percentage of CoNS infections on the total of treated infections is

about 25%, however due to the referrals that does not necessarily reflect the infections of patient primarily treated in our hospital. Therefore we have not mentioned these percentages in this manuscript.

If the editor feels mentioning these numbers would improve the manuscript, we would be willing to add these.

(6) Only one factor is considered for failure for eradication..(Obesity)..Were other factors like diabetes, age, immunocompromised patients, time interval between the first and second stage arthroplasty, static or dynamic spacer, revision of spacer placement and smoking were related to the failure to eradicate the infection.

+ Thank you for the question. We have emphasized obesity, as it is known to increase the risk of (persistent) infection. For smoking, age and time interval this hasn't been proven that thoroughly yet.

However, we have found that obesity, gender, age, smoking status, timing to reimplantation and ASA-classification were not related to risk of infection recurrence or persistence. This is described in the third paragraph of the discussion.

Functional hip spacers and dynamic knee spacers seem to lead to lower risk of failure. We have amphasized this in the discussion, paragraph 3. Even though this study does not have enough power to conclude whether the spacer type (more or less dynamic) influences outcome, that is a very interesting topic for further studies.

(7) Were all surgeries performed by the author themselves or is it a mixed data as the manuscript describes as "we performed".. if not then it should be changed to "was performed.."

+ Thank for your comment. Surgeries were performed by several revision specialists, not only the authors of the study. We have adjusted the manuscript according to your suggestion (see track changes in the results section).

In some cases we have remained with "we treated" to achieve active voice instead of

passive voice.

(8) The title of the article implies that two stage arthroplasty is the answer to coagulase negative PJI. So the title should be changed.

+ Thank you for your comment, unluckily we are not sure how to interpret it. We do believe that two-stage revision is the correct treatment to handle coagulase-negative staphylococcal PJI, which is in concordance with the title. If you would have a suggestion for a more comprehensive title, of course we would consider changing it.

INITIAL REVIEW OF THE MANUSCRIPT

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[   ] No

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[   ] Plagiarism

[   ] No