PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The efficacy of Periacetabular osteotomy followed by progressive resistance training compared to progressive resistance training as non-surgical treatment in patients with Hip dysplasia (PreserveHip). A protocol for a randomised controlled trial.
AUTHORS	Reimer, Lisa Cecilie Urup; Jakobsen, Stig Storgaard; Mortensen, Louise; Dalgas, Ulrik; Jacobsen, Julie Sandell; Soballe, Kjeld; Bere, Tone; Madsen, Jan Erik; Nordsletten, Lars; Risberg, May Arna; Mechlenburg, Inger

VERSION 1 – REVIEW

REVIEWER	Yasuhiko Takegami Nagoya university graduate school of medicine
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	The author established the protocol to compare the short-term outcomes between the periacetabular osteotomy (PAO) and progressive resistance training (PRT). If PRT can be an alternative to PAO, it is one of the beneficial treatment options for DDH patients. This study design is sophisticated and robust. This research is very interesting in this field. However, several concerns remained in this manuscript. The reviewer's comments are as follows. 1) Page 3 The author wrote that the hip of DDH did not develop the osteoarthritis of the hip. The author quoted the result of Copenhagen City Heart Study (CCHS), which is a longitudinal population-based study. However, Morita et al. demonstrated that the probability of OA progression in the nonoperative hip was 13% in the contralateral hip of patients with DDH undergoing RAO, which is one of the acetabular osteotomies at 20 years postoperatively. (Ref 1) The subjects who attend in this research are those who are a candidate for osteotomy. Therefore, the patients' background is more similar to that of Morita et al. than that of patients who participated in CCHS. It suggested that it is possible that osteoarthritis of the hip may progress in this cohort. The author should change the description to show consideration on this point, and change the protocol to monitor the development of the OA at 5 or 10 years postoperatively. 2) Page 6 The author wrote "postoperative rehabilitation as usual" in this manuscript. If the usual care widely differed from PRT, it might affect the result. The author should mention the contents of usual care postoperatively in the method session.

	The reason why the postoperative rehabilitation period was also 4 months is unclear. The author should provide evidence for setting a rehabilitation period 4 months. 3)Page 12 In their pilot study (Ref 2), the authors screened 85 patients, they only included 17 patients (20%). The reason why the 68 patients (80%) did not participate in this pilot study was not described. The reviewer was worried that most of patients did not want to participate in this research. The author also mentioned the rate of adherence was 90.3% in the previous study. However, the training period was 8-weeks. In this manuscript, the authors planned 52-weeks training. It would lead to a decrease in adherence. Above these reasons, the reviewer is afraid that the authors are not able to get enough patients to complete the study. How will the author plan to recruit the patients? 4) Page 13 The author described that the change in the HAGOS pain subscale from baseline to 6 months after initial treatment was defined as a primary outcome. In table 3, the author planned the assessment at 4 months and 12 months after initial treatment. Please correct the sentence. There is no description of the statistical methods to compare between groups. Please describe the statistical methods. 5) Page 6 Ezoe et al. demonstrated that the strengths of flexion, extension, abduction, and adduction at 6 months were less than the preoperative level in acetabular osteotomy patients (Ref 3). In this protocol, the patient in the PAO group will receive the PRT training at 4 months after the operation. Thus, patients in the PAO group are likely to have muscle weakness at 4 months. The adherence to PRT and clinical outcomes in the PAO patients may be less than only the PRT group. This can be a bias that affects the outcome at 12 months postoperatively. 6) Page7 Fig 1 Among patients who have undergone PAO, there may be differences in clinical outcome between those who have achieved PRT and those who have failed. So that it was better to assess the results of the PAO group as subgroup analysis. 7)page8 Table3 The Exercise variable is overlapped; week 5-52, week 7-52. Please correct it. Reference 1. Morita D, Hasegawa Y, Seki T, et al. A Possible New Radiographic Predictor of Progression of Osteoarthritis in Developmental Dysplasia of the Hip. Clinical Orthopaedics and Related Research®. 2018;476(11):2157-2166. DOI:10.1097/CORR.0000000000000458. 2. Mortensen L, Schultz J, Elsner A, et al. Progressive resistance training in patients with hip dysplasia: A feasibility study. J Rehabil Med. 2018;50(8):751-758. DOI:10.2340/16501977-2371. 3. Ezoe M, Naito M, Asayama I. Muscle Strength Improves after Abductor-sparing Periacetabular Osteotomy. Clinical Orthopaedics and Related Research®. 2006;443(&NA;):161-168. DOI:10.1097/01.blo.0000196475.40151.8b.

VERSION 1 – AUTHOR RESPONSE

Authors' responses and changes

Responses to the Manuscript with the title: "The efficacy of Periacetabular osteotomy followed by progressive resistance training versus progressive resistance training as a non-surgical treatment in patients with Hip dysplasia (PreserveHip). A protocol for a randomised controlled trial."

At first, we would like to thank the reviewer for the valuable comments and suggestions for improving the manuscript. Below we present our response to these suggestions.

Comment to the Authors

The author established the protocol to compare the short-term outcomes between the periacetabular osteotomy (PAO) and progressive resistance training (PRT). If PRT can be an alternative to PAO, it is one of the beneficial treatment options for DDH patients. This study design is sophisticated and robust. This research is very interesting in this field. However, several concerns remained in this manuscript. The reviewer's comments are as follows.

Response: We thank the reviewer for the generally positive comments to our study protocol.

1) Page 3
The author wrote that the hip of DDH did not develop the osteoarthritis of the hip. The author quoted the result of Copenhagen City Heart Study (CCHS), which is a longitudinal population-based study. However, Morita et al. demonstrated that the probability of OA progression in the nonoperative hip was 13% in the contralateral hip of patients with DDH undergoing RAO, which is one of the acetabular osteotomies at 20 years postoperatively. (Ref 1) The subjects who attend in this research are those who are a candidate for osteotomy. Therefore, the patients' background is more similar to that of Morita et al. than that of patients who participated in CCHS. It suggested that it is possible that osteoarthritis of the hip may progress in this cohort. The author should change the description to show consideration on this point, and change the protocol to monitor the development of the OA at 5 or 10 years postoperatively.

Response: We thank the reviewer for this important remark, and have elaborated on the above mentioned issue and included the study by Morita et al. in the introduction. Regarding the monitoring of the development of OA at 5- and 10-years follow-up, we have included x-rays at 5- and 10-year follow-up.

Correction: "However, studies describing the natural history of hip dysplasia are lacking. The lack of knowledge is problematic since patients are offered a surgery with potential complications mainly based on pain indication without knowing if OA would progress. In a longitudinal trial, 136 controls were compared with 81 persons with mild or moderate radiological verified hip dysplasia (11). The participants were followed for a decade, but the results of the study did not document a tendency for radiological hip degeneration. In contrast, Morita et al. (12) found that the probability of OA progression was 13% in a cohort of 88 patients with hip dysplasia who had received a rotational acetabular osteotomy in the contralateral hip 20 years earlier."

2) Page 6
The author wrote "postoperative rehabilitation as usual" in this manuscript. If the usual care widely differed from PRT, it might affect the result. The author should mention the contents of usual care postoperatively in the method session. The reason why the postoperative rehabilitation period was also 4 months is unclear. The author should provide evidence for setting a rehabilitation period 4 months.

Response: Unfortunately, the content of "usual care" is not clearly defined as, since the rehabilitation focus is developed between the patients and the physiotherapist. In addition, it may differ between regions making it even more difficult to fully outline the content. Some physiotherapist might use pool training, some patients will receive group sessions whereas others will undertake individual sessions. Consequently, the usual care will differ substantially, but the main focus will always be on stability, strength and regaining a normal gait pattern. The study design should secure that patients from different regions is included, which should capture the differences and increase the ecological validity.

Correction: "Patients commence post-operative rehabilitation as usual until 4 months after the operation. Usual care means that the patients follow a rehabilitation program guided by a physiotherapist specialized in hip problems, with focus on stability and strength after the operation, as well as regain a normal gait pattern. The physiotherapist will adapt the post-operative rehabilitation to the patients need and thus usual care will differ between patients."

3) Page 12
In their pilot study (Ref 2), the authors screened 85 patients, they only included 17 patients (20%). The reason why the 68 patients (80%) did not participate in this pilot study was not described. The reviewer was worried that most of patients did not want to participate in this research. The author also mentioned the rate of adherence was 90.3% in the previous study. However, the training period was 8-weeks. In this manuscript, the authors planned 52-weeks training. It would lead to a decrease in adherence. Above these reasons, the reviewer is afraid that the authors are not able to get enough patients to complete the study. How will the author plan to recruit the patients?

Response: The reviewer raises a highly relevant point. The 68 decliners from the feasibility study were patients who did not want to participate or thought that the transportation time to training where too demanding, even though they lived less than 50 km away from the training site. In the RCT, the patients are offered a free membership to a local fitness center, based on this experience which means that they will be able to train close to their home after the first 4 months. The number of decliners was also a result of our workflow, since patients had already been assigned a date for the operation when they were asked to participate and thus may have felt less willing to participate in the progressive training program because they were already very focused on the PAO operation. In the present RCT, patients will be asked if they want to participate at their first meeting with the surgeon, which we believe will lower the number of decliners substantially. Regarding the longer training period, we believe that the free membership to a local fitness center will affect the the motivation to participate in the study and the adherence to the progressive resistance training positively.

4) Page 13
The author described that the change in the HAGOS pain subscale from baseline to 6 months after initial treatment was defined as a primary outcome. In table 3, the author planned the assessment at 4 months and 12 months after initial treatment. Please correct the sentence. There is no description of the statistical methods to compare between groups. Please describe the statistical methods.

Response: Thank you for pointing this out. We have corrected accordingly.

Correction: "The primary efficacy analysis will be assessment of the between-group difference in change in the HAGOS pain subscale from baseline to 12 months after initiating the treatment (primary end-point). The primary analysis will follow the intention-to-treat principle and a mixed effects model will be used."

5) Page 6
Ezoe et al. demonstrated that the strengths of flexion, extension, abduction, and adduction at 6 months were less than the preoperative level in acetabular osteotomy patients (Ref 3). In this protocol, the patient in the PAO group will receive the PRT training at 4 months after the operation. Thus, patients in the PAO group are likely to have muscle weakness at 4 months. The adherence to PRT and clinical outcomes in the PAO patients may be less than only the PRT group. This can be a bias that affects the outcome at 12 months postoperatively.

Response: The reason why the resistance training is starting after 4 months is that the usual care rehabilitation program that is offered post surgery at the two sites ends after 4 months. Moreover, the osteotomy in the index leg is considered to be stable after 4 months and the patients are therefore encouraged to start resistance training on their own at this time.

6) Page 7 Fig 1
Among patients who have undergone PAO, there may be differences in clinical outcome between those who have achieved PRT and those who have failed. So that it was better to assess the results of the PAO group as subgroup analysis.

Response: If, we understand the comment correctly, the reviewer is worried that some of the patients undergoing PAO will not be able to perform the resistance training, which of course will affect their result at the primary endpoint. We do believe that this will be the case for both groups of patients and due to the study design, the amount of non-compliant patients will be equal for the two groups. The primary analysis will be intention-to-treat where all patients who are randomized are included in the statistical analysis and analysed according to the group they were assigned to. We also plan to do an as-treated analysis as well as a per-protocol analysis based on the patients from both groups with good compliance (defined as participation in ≥70% of the training sessions).

7) Page 8 Table 3
The Exercise variable is overlapped; week 5-52, week 7-52. Please correct it.

Answer: Thank you, we have corrected this.

Correction: "Week 5-6 Week 7-52"

Reference

1. Morita D, Hasegawa Y, Seki T, et al. A Possible New Radiographic Predictor of Progression of Osteoarthritis in Developmental Dysplasia of the Hip. Clinical Orthopaedics and Related Research®. 2018;476(11):2157-2166. DOI:10.1097/CORR.0000000000000458.

2. Mortensen L, Schultz J, Elsner A, et al. Progressive resistance training in patients with hip dysplasia: A feasibility study. J Rehabil Med. 2018;50(8):751-758. DOI:10.2340/16501977- 2371.

3. Ezoe M, Naito M, Asayama I. Muscle Strength Improves after Abductor-sparing Periacetabular Osteotomy. Clinical Orthopaedics and Related Research®. 2006;443(&NA;):161-168. DOI:10.1097/01.blo.0000196475.40151.8b.

VERSION 2 – REVIEW

REVIEWER	Yasuhiko Takegami Nagoya University
REVIEW RETURNED	16-Nov-2019

GENERAL COMMENTS	The authors have properly revised their manuscript according to my comments.