Reviewer's report

Title: Effect of exercise training and dopamine agonists in patients with uremic Restless Legs Syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study

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Reviewer: Kirsten Johansen

Reviewer's report:

Giannaki and colleagues report on a randomized controlled trial of intradialytic exercise vs. ropinirole vs. placebo for six months among hemodialysis patients with restless legs syndrome. Although this is an interesting study, there are numerous issues that need to be addressed.

Major compulsory revisions:

First, although the stated aim of the study was to compare the effectiveness of exercise training and ropinirole (p. 5), the main emphasis of the results and discussion is on the results of the individual treatments. Paired t-tests and an emphasis on changes within each group is not the right approach. There is no need for a placebo control group if the primary analysis is not a comparison of the changes across groups.

Second, the introduction does not do a good job of establishing or stating clear hypotheses for this study. There seem to be a lot of outcomes that would be likely to be affected by exercise but are not clearly related to RLS. The emphasis on within-group changes mentioned above exacerbates this so that it’s not really clear whether this was meant to be a paper about the general effects of exercise rather than a real comparison of treatments for RLS. (Incidentally, I don’t find the cited atrophy among RLS patients to be a compelling argument that pharmacological treatment of RLS would be likely to address atrophy because it seems unlikely that RLS causes atrophy and far more likely that the association is confounded by low physical activity.) Even the 2:1:1 distribution of patients within groups is odd if the goal was to compare exercise to ropinirole.

Third, the lack of dose titration of ropinirole is an important limitation because this does not represent “real world” RLS treatment. Therefore, exercise is being compared to a treatment strategy that does not represent what is usually done clinically, and the results are likely biased in favor of exercise. Although there is some discussion of this, it is not explicitly stated that the ropinirole treatment was not standard practice and that bias in favor of exercise might have been introduced by this design choice.

An additional issue favoring exercise is the lack of blinding for the exercise intervention. Of course, this may be unavoidable, but it should be mentioned as a limitation and a possible source of bias towards exercise.
Minor essential revisions:

1. The results section of the abstract is rather short and has few numbers and no p-values to support the statement that exercise and ropinirole were effective. The conclusion of the abstract mentions results that are not reported in the abstract.

2. The methods section does not report the dates of recruitment and enrollment into the study.

3. Why were patients with abnormal CRP excluded? What level was used to define abnormal?

4. On page 8, it says that “muscle size and composition were assessed by analyzing images collected by a computerized tomography system”. Which muscles? Was the size of the whole muscle compared or was it broken into contractile and non-contractile parts? The results mention EMCL, but how this was measured is not in the methods. Also, the results include measure of subcutaneous adipose tissue, which is also not mentioned in the methods.

5. There is no such thing as a total SF-36 score. This instrument has been extensively used and validated but there is no precedent for the validity of combining the 8 scales into a total score (and no description of how the authors may have done this). Please stick to validated scales or composite scales (MCS, PCS) from the SF-36.

6. The description of sample size on page 10 is confusing. First, this doesn’t appear to be the right sample size calculation since the primary comparison should have been between the effects of exercise and ropinirole according to the stated aims, whereas this calculation seems to be for each treatment individually. One would need a much larger sample size to be able to detect smaller differences between exercise and ropinirole. Second, it is typical to power for a type II error of 10 or 20% rather than 5%, and it seems unlikely that this sample size would truly have 95% power to detect these effects even within groups.

7. On page 11, the text states that ropinirole and exercise were equally effective in reducing RLS symptoms and depression score, but highly significant p-values are cited. Please clarify this. Also, the top of page 12 again mentions IRLS score but has different p-values.

8. The reporting on QOL is problematic. First, as mentioned above, there is no total SF-36 score. Second, the within group differences are being reported and emphasized but the key finding is that neither exercise nor ropinirole improved “total SF-36 score” statistically significantly more than placebo did.

9. The results of the depression score in the placebo group are confusing. The authors report a significant increase in this group, and the table labels the follow-up value as significantly different from the baseline, but the 95% confidence interval for the change crosses zero, which would imply a lack of statistical significance. Please check these results and clarify.

10. On page 13, the authors state that total lean body mass was increased after exercise training but the p-value cited is 0.14. The other problem with these results is (again) the emphasis on within group differences rather than between
group comparisons. Actually, the magnitude of the mean increase in LBM is
greater in the ropinirole group, but the change from baseline in that group did not
reach statistical significance (possibly because of the smaller group size). It is
really not appropriate to conclude that exercise is having an effect and ropinirole
is not in the setting of a change in LBM that is not qualitatively or statistically
different.

11. The changes in the physical performance tests do not appear to be normally
distributed. They should probably be shown in Table 3 as median [IQR], and a
non-parametric statistical test would be in order.

12. On page 12 and Figure 2, the ratio of muscle percentage to EMCL
percentage is compared. There is no mention of this ratio in the methods, and it
is not clear what clinical significance it has. Why generate a figure to highlight a
result that is nonsignificant statistically and is also of unclear clinical significance?

13. The correlations presented are not compelling. They do not reflect
randomized results and were not stated as a priori hypothesis-driven
comparisons. How many different correlations were tested?

14. The discussion is too long.

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Needs some language corrections before being
published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.