

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of pulmonary rehabilitation in lung transplant candidates: A systematic review.
AUTHORS	Hoffman, Mariana; Chaves, Gabriela; Ribeiro-Samora, Giane; Britto, Raquel; PARREIRA, VERONICA

VERSION 1 - REVIEW

REVIEWER	Dr Felix S F Ram College of Health Massey University New Zealand
REVIEW RETURNED	24-Jul-2016

GENERAL COMMENTS	<p>This is a well conducted review of the literature following the usual Cochrane methodology. Unfortunately, as there weren't sufficient included studies a meta-analysis was not possible and only single study results are discussed. This makes this manuscript more of a review rather than a systematic review with meta-analysis. Unfortunately there is not statistical data to review and although the remainder to the methodology appears adequate this manuscript adds little to know is already known about the benefits afforded by PR post lung transplant.</p>
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REVIEWER	Dr. Dmitry Rozenberg Clinical Associate, Division of Respiriology/Lung Transplantation University Health Network, Toronto Canada
REVIEW RETURNED	05-Aug-2016

GENERAL COMMENTS	<p>In this systematic review, Hoffman M et al. examined the impact of pulmonary rehabilitation in lung transplant candidates on health-related quality of life and exercise capacity. Secondary outcomes planned included post-transplant survival, peripheral and respiratory muscle strength, and adverse effects. The authors identified 4 studies utilizing the PRISMA guidelines for reporting systematic reviews and the protocol for the review was identified in a priori.</p> <p>This is an important area of research that has not been previously investigated systematically. There are several major limitations that need to be addressed as outlined below.</p> <p>MAJOR: Abstract: 1) Objectives: With a cross-sectional study design, how can the effects of pulmonary rehabilitation be investigated?</p>
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	<p>2) Authors outline the secondary outcomes that were studied in the abstract such as post-transplant outcomes (survival, lung function, psychological aspects, etc), but no mention is made in the abstract or in the results section of the paper. This is important for a balanced synopsis.</p> <p>3) Conclusion: I'm not sure that Randomized Control trials are necessarily needed to answer some of these questions. Furthermore, pulmonary rehabilitation is standard of care at some lung transplant centers thus withholding pulmonary rehabilitation in a RCT might not be ethical. Perhaps, the conclusion should elaborate more on quality of life and exercise capacity observed in the 4 studies.</p> <p>Introduction:</p> <p>4) Reference 9 is a retrospective analysis; however, justification needs to be provided as to why retrospective studies were not included in the present systematic review if they addressed the primary outcome.</p> <p>5) I think the introduction can be strengthened by mentioning some of the previously published review articles on the topic of pulmonary rehabilitation even though some of them were post-transplant. (Langer et al. 2015, Wickerson L 2010).</p> <p>METHODS:</p> <p>6) The fourth study included (Wickerson et al - Ref 18) was a cross-sectional study looking at physical activity levels. How can the effects of pulmonary rehabilitation be assessed in this study design? In this study, the effects of pulmonary rehabilitation were not assessed directly on the outcomes, as pulmonary rehabilitation was standard of care at this center. This review should be limited to Randomized Control Trials and Cohort Studies, possibly retrospective as well. Was there a reason that retrospective studies were excluded from this systematic review?</p> <p>7) Figure 1, Study Flow Diagram - can you please specify the reasons for the 7 studies excluded.</p> <p>8) How come the study by Jastrzebski D Adv Exp Med Biol 2013. "Pulmonary rehabilitation in patients referred for lung transplantation" was not included? Was this study identified with the search?</p> <p>9) In the search strategy, there is no mention of "cohort" or observational studies and I worry with this search a few observational studies might have been missed. Please clarify.</p> <p>10) Methods (pages 5-6); the outcome measures are numbered. I'm wondering if it might be easier for the reader if this was written in paragraph format. Also, can you please elaborate on what is meant by "overall muscle strength".</p> <p>RESULTS:</p> <p>11) Page 13 (line 18, line 39); as per comment above, I don't think the study by Wickerson et al should be included in this review as it was cross-sectional and didn't assess the impact of pulmonary rehabilitation on these outcomes.</p> <p>DISCUSSION:</p> <p>12) Page 15 (line 11-14); this is potentially speculative with respect to increased physical activity levels could be achieved if pulmonary rehabilitation is offered.</p> <p>13) Page 15 (line 18-19), need reference for 6MWT and continuous variable. I think it's important to emphasize that dichotomous cut-offs</p>
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	<p>are not ideal to use for prognostication based on the most recent study in lung transplant candidates by Castelberry AW (2015).</p> <p>14) Page 15 (line 26-35); I think a greater discussion on the potential benefits of pulmonary rehabilitation with respect to quality of life domains is needed. Consider referencing literature from advanced lung disease (non-transplant populations) to strengthen discussion.</p> <p>15) Page 17 (Author's conclusions - paragraph 2); as mentioned above, I'm not sure there is strong justification for recommending RCTs at the present time. Could some of the secondary questions (post-transplant survival, association with lung function, muscle strength) be potentially determined through an observational study design?</p> <p>16) Also, discussion is lacking on the importance of secondary outcomes chosen (respiratory muscle strength, peripheral muscle strength, etc.). Consider discussion of some literature from other surgical populations (i.e. cardiac surgery for instance) where respiratory muscle strength has been associated with decreased pulmonary complications in the post-operative period.</p> <p>17) Consideration for further editing of Sentence structure should be given for the Introduction and Discussion sections specifically. I think this would improve the flow of the manuscript.</p> <p>MINOR:</p> <ul style="list-style-type: none"> - Abstract: Participants section: Might need to add "etc" at the end of the sentence as it seems limited to COPD and ILD only. Introduction: <ul style="list-style-type: none"> - Line 25-26 (page 3) of Introduction; consider rewording "prediction" of long term outcomes. - Line 28 - not clear what is meant by "facilitated". - Page 3 - Line (32-34): Reference required for the statement "Cardiovascular risk factors, muscular and nutritional conditions can influence prognosis" - Page 3, Line 35-36 - not clear, please consider rewording " Hence pulmonary rehabilitation (PR) is an important process focusing also in avoidance of comorbidities and complications" - Introduction, Page 4 (line 32-34) - requires reference. " It has been proven that exercise capacity (six minutes walking distance) and resting carbon dioxide in the arterial blood value are directly related to rate of success in lung transplantation." - Line 35 (introduction, page 4) - would avoid using the term "proved" --- unable to demonstrate causality but association should be described. <p>Methods:</p> <ul style="list-style-type: none"> - Page 6, Search Strategy (please specify the last date of the search in the article). - Page 9, Instead of trials, the term "studies should be used" as not all these studies had a control group and some were observational. This should be corrected in the abstract and introduction (page 9) on line 21, 23, 26, and 42. Also, throughout the article accordingly. - Results (page 10, line 30) - please reword " advised" as not clear. - References (#2 and 4) chosen are outdated and the following statements have been updated (should be substituted with the latest statements).
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VERSION 1 – AUTHOR RESPONSE

Answers to Reviewer #1

This is a well conducted review of the literature following the usual Cochrane methodology. Unfortunately, as there weren't sufficient included studies a meta-analysis was not possible and only single study results are discussed. This makes this manuscript more of a review rather than a systematic review with meta-analysis. Unfortunately there is not statistical data to review and although the remainder to the methodology appears adequate this manuscript adds little to know is already known about the benefits afforded by PR post lung transplant.

Answer: We appreciate your comments and review and we agree that there weren't sufficient studies included to perform a meta-analysis. However this study uncover a gap in the literature regarding the effects of pulmonary rehabilitation in candidates for lung transplantation. Studies included showed the results of Pulmonary Rehabilitation performed for patients in waiting list for lung transplantation and how this program can affect their exercise capacity and quality of life as a primary outcomes. A few studies could be founded which expose the necessity of more studies considering this topic.

Answer to Reviewer #2

In this systematic review, Hoffman M et al. examined the impact of pulmonary rehabilitation in lung transplant candidates on health-related quality of life and exercise capacity. Secondary outcomes planned included post-transplant survival, peripheral and respiratory muscle strength, and adverse effects. The authors identified 4 studies utilizing the PRISMA guidelines for reporting systematic reviews and the protocol for the review was identified in a priori.

This is an important area of research that has not been previously investigated systematically. There are several major limitations that need to be addressed as outlined below.

MAJOR LIMITATIONS:

Abstract:

1) Objectives: With a cross-sectional study design, how can the effects of pulmonary rehabilitation be investigated?

Answer: The cross-sectional study was excluded.

2) Authors outline the secondary outcomes that were studied in the abstract such as post-transplant outcomes (survival, lung function, psychological aspects, etc), but no mention is made in the abstract or in the results section of the paper. This is important for a balanced synopsis.

Answer: Secondary outcomes were included in the abstract.

3) Conclusion: I'm not sure that Randomized Control trials are necessarily needed to answer some of these questions. Furthermore, pulmonary rehabilitation is standard of care at some lung transplant centers thus withholding pulmonary rehabilitation in a RCT might not be ethical. Perhaps, the conclusion should elaborate more on quality of life and exercise capacity observed in the 4 studies.

Answer: The suggestion was incorporated on the abstract conclusion.

INTRODUCTION:

4) Reference 9 is a retrospective analysis; however, justification needs to be provided as to why retrospective studies were not included in the present systematic review if they addressed the primary outcome.

Answer: Retrospective studies were included in the study after reviewing the search – references 15 and 19 of the revised version.

5) I think the introduction can be strengthened by mentioning some of the previously published review articles on the topic of pulmonary rehabilitation even though some of them were post-transplant. (Langer et al. 2015, Wickerson L 2010).

Answer: The suggested articles were included to strength the introduction.

Page 5, last paragraph- reference 11 and page 6, 1st paragraph.

METHODS

6) The fourth study included (Wickerson et al - Ref 18) was a cross-sectional study looking at physical activity levels. How can the effects of pulmonary rehabilitation be assessed in this study design? In this study, the effects of pulmonary rehabilitation were not assessed directly on the outcomes, as pulmonary rehabilitation was standard of care at this center. This review should be limited to Randomized Control Trials and Cohort Studies, possibly retrospective as well. Was there a reason that retrospective studies were excluded from this systematic review?

Answer: We accepted the suggestion. The study of Wickerson et al. - reference 18 of the first version - was excluded from the review and retrospective studies were included.

7) Figure 1, Study Flow Diagram - can you please specify the reasons for the 7 studies excluded.

Answer: Reasons for excluded studies were specified at Figure 1 of the revised version.

8) How come the study by Jastrzebski D Adv Exp Med Biol 2013. "Pulmonary rehabilitation in patients referred for lung transplantation" was not included? Was this study identified with the search?

Answer: The study of Jastrzebski et al. was included in the revised version – reference 17.

9) In the search strategy, there is no mention of "cohort" or observational studies and I worry with this search a few observational studies might have been missed. Please clarify.

Answer: Cohort studies and observational studies were not included in the search strategies since the objective of this literature review was to evaluate effects of an intervention. Thus it was assumed that in observational or cohort studies results of an intervention could not be found.

10) Methods (pages 5-6); the outcome measures are numbered. I'm wondering if it might be easier for the reader if this was written in paragraph format. Also, can you please elaborate on what is meant by "overall muscle strength".

Answer: The outcome measures were written in paragraph format, on page 7.

"Overall muscle strength" was modified to upper and lower extremity muscle strength.

RESULTS

11) Page 13 (line 18, line 39); as per comment above, I don't think the study by Wickerson et al should be included in this review as it was cross-sectional and didn't assess the impact of pulmonary rehabilitation on these outcomes.

Answer: The study of Wickerson et al. – reference 18 of the first version was excluded from the revised version.

DISCUSSION

12) Page 15 (line 11-14); this is potentially speculative with respect to increased physical activity levels could be achieved if pulmonary rehabilitation is offered.

Answer: The phrase was rewrite in order to clarify the affirmation mentioned.

13) Page 15 (line 18-19), need reference for 6MWT and continuous variable. I think it's important to emphasize that dichotomous cut-offs are not ideal to use for prognostication based on the most recent study in lung transplant candidates by Castelberry AW (2015).

Answer: A reference was included – reference 26 - and additional information as well.

14) Page 15 (line 26-35); I think a greater discussion on the potential benefits of pulmonary rehabilitation with respect to quality of life domains is needed. Consider referencing literature from advanced lung disease (non-transplant populations) to strengthen discussion.

Answer: Additional references were included in order to explore more about quality of life.

15) Page 17 (Author's conclusions - paragraph 2); as mentioned above, I'm not sure there is strong justification for recommending RCTs at the present time. Could some of the secondary questions (post-transplant survival, association with lung function, muscle strength) be potentially determined through an observational study design?

Answer: The information was rewrite.

16) Also, discussion is lacking on the importance of secondary outcomes chosen (respiratory muscle strength, peripheral muscle strength, etc.). Consider discussion of some literature from other surgical populations (i.e. cardiac surgery for instance) where respiratory muscle strength has been associated with decreased pulmonary complications in the post-operative period.

Answer: Informational about muscle strength was included in order to discuss more this subject, on page 18 of the revised version.

17) Consideration for further editing of Sentence structure should be given for the Introduction and Discussion sections specifically. I think this would improve the flow of the manuscript.

Answer: The manuscript was written following the Cochrane model of literature review according to the Cochrane Handbook for Systematic Reviews of Interventions. So, we'd like to maintain the present structure.

MINOR:

Abstract: Participants section: Might need to add "etc" at the end of the sentence as it seems limited to COPD and ILD only.

Answer: The abstract was modified to incorporate suggestions.

Introduction:

Line 25-26 (page 3) of Introduction; consider rewording "prediction" of long term outcomes.

Answer: The text was reworded.

Line 28 - not clear what is meant by "facilitated".

Answer: The word was changed to simplified, on page 4, 2nd paragraph.

Page 3 - Line (32-34): Reference required for the statement "Cardiovascular risk factors, muscular and nutritional conditions can influence prognosis"

Answer: The reference was added, on page 4, 2nd paragraph.

Page 3, Line 35-36 - not clear, please consider rewording " Hence pulmonary rehabilitation (PR) is an important process focusing also in avoidance of comorbidities and complications"

Answer: The text was modified, on page 4, 2nd paragraph.

Introduction, Page 4 (line 32-34) - requires reference. " It has been proven that exercise capacity (six

minutes walking distance) and resting carbon dioxide in the arterial blood value are directly related to rate of success in lung transplantation."

Answer: The reference was added, on page 5, 2nd paragraph.

Line 35 (introduction, page 4) - would avoid using the term "proved" --- unable to demonstrate causality but association should be described.

Answer: The text was modified, on page 5, 2nd paragraph.

Methods:

Page 6, Search Strategy (please specify the last date of the search in the article).

Answer: The date of the search was revised.

Page 9, Instead of trials, the term "studies should be used" as not all these studies had a control group and some were observational. This should be corrected in the abstract and introduction (page 9) on line 21, 23, 26, and 42. Also, throughout the article accordingly.

Answer: The term trials was changed to studies throughout the revised version of the manuscript.

Results

Results (page 10, line 30) - please reword " advised" as not clear.

Answer: The word was changed to recommended, on page 12, 1st paragraph.

References (#2 and 4) chosen are outdated and the following statements have been updated (should be substituted with the latest statements.

Answer: The statements were updated - references 2 and 4 - of the revised version.

VERSION 2 – REVIEW

REVIEWER	Dr. Dmitry Rozenberg University Health Network, Toronto
REVIEW RETURNED	05-Oct-2016

GENERAL COMMENTS	<p>Thank you for addressing the comments. A few other comments:</p> <ol style="list-style-type: none">1) Introduction (page 35): Line 28-32; Need some clarification on the sentence transplantation "been simplified". This is an over-simplification of the transplant process which is complex.2) Introduction (pages 36/37): Both paragraphs added describing the systematic reviews pertaining to post-transplant outcomes. I would try to condense into one paragraph as it detracts from the introduction and rationale of the systematic review in my opinion.3) Discussion: Page 48; Line 12-16; Need further clarification on what is meant by "unpowered result".4) Important (MAJOR): Please clarify that the search performed had captured cohort studies, as per comment #9 response these studies were originally excluded from the search by the authors. I would like to be confident in a systematic review studies were not missed.**5) I feel that this manuscript could still benefit from grammatical corrections, especially in the introduction and Discussion sections. This would help the reader significantly as the content of the manuscript appears to be appropriate.
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VERSION 2 – AUTHOR RESPONSE

Answer to Reviewer: 2

1) Introduction (page 35): Line 28-32; Need some clarification on the sentence transplantation "been simplified". This is an over-simplification of the transplant process which is complex.

Answer: The phrase was rewritten in order to clarify the affirmation mentioned as follow: "The access to lung transplantation, a complex procedure, is becoming a more reasonable option for patients with advanced lung disease especially to chronic respiratory failure patients. 2nd paragraph of introduction.

2) Introduction (pages 36/37): Both paragraphs added describing the systematic reviews pertaining to post-transplant outcomes. I would try to condense into one paragraph as it detracts from the introduction and rationale of the systematic review in my opinion.

Answer: The suggestion was accepted and paragraphs were condensed.

3) Discussion: Page 48; Line 12-16; Need further clarification on what is meant by "unpowered result".

Answer: The sentence was modified in order to clarify the idea. 2nd paragraph of "Overall completeness and applicability of the evidence".

4) Important (MAJOR): Please clarify that the search performed had captured cohort studies, as per comment #9 response these studies were originally excluded from the search by the authors. I would like to be confident in a systematic review studies were not missed.

Answer: The initial objective of this systematic review was to include only Randomized Controlled Trials regarding the effects of Pulmonary Rehabilitation in Lung Transplant Candidates, thus this type of study was included in the search strategy. However, after the first evaluation of the reviewers it was suggested to include also retrospective and cohort studies on the results. The suggestion was accepted and those types of studies were included, based on the initial search. Moreover, a new search was conducted, based on the initial search strategy, removing only the terms related to the 'type of study' (following same search strategy) and the same number of studies was found. Thus, we might ensure that studies were not missed.

Search strategy is presented below:

1. Lung Transplantation/

2. (Lung\$ adj2 transplant\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3. 1 or 2

4. Exercise Therapy/

5. Exercise/

6. Physical Fitness/

7. Rehabilitation/

8. Physical Therapy Modalities/

9. Physical Exertion/

10. (rehabilitat\$ or fitness or exercis\$ or train\$ or Physiotherap\$ or physical therap\$ or respiratory therap\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11. 4 or 5 or 6 or 7 or 8 or 9 or 10

12. 3 and 11

**5) I feel that this manuscript could still benefit from grammatical corrections, especially in the introduction and Discussion sections. This would help the reader significantly as the content of the manuscript appears to be appropriate.

Answer: The manuscript was now revised by Elsevier Language Editing Services. Corrections are highlighted in green.

VERSION 3 - REVIEW

REVIEWER	Dr. Dmitry Rozenberg University Health Network, Toronto, Canada
REVIEW RETURNED	26-Nov-2016

GENERAL COMMENTS	<p>Thank you for making the required revisions (specifically language edits and updating the search strategy).</p> <p>A few MINOR edits:</p> <p>1) Throughout the manuscript the term "programme" is used. Shouldn't the program spelling be "program" or pleural "program(s)".</p> <p>2) Page 20 - Line 28 (Reference 1) - this is a review article and not original study. Thus, this needs to be clearly outlined.</p> <p>3) Page 18 - Line 41 - Reference 32 - this reference doesn't support the fact that ILD patients have lower quadriceps strength compared to COPD patients. This study only included ILD patients. Please correct accordingly.</p> <p>4) Style of Manuscript: I appreciate the amount of work that has gone into the revisions, but the article seems slightly lengthy (>5000 words). I leave this to the Editorial team to decide if some content needs to be included in a supplement.</p>
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VERSION 3 – AUTHOR RESPONSE

Thank you for your e-mail and suggestions.

1) Throughout the manuscript the term "programme" is used. Shouldn't the program spelling be "program" or pleural "program(s)".

Answer: The term was modified throughout the manuscript.

2) Page 20 - Line 28 (Reference 1) - this is a review article and not original study. Thus, this needs to be clearly outlined.

Answer: The sentence was modified as follows: "... Rochester et al. present in a review study the function of PR in the care of these patients. This review supports that although..."

3) Page 18 - Line 41 - Reference 32 - this reference doesn't support the fact that ILD patients have lower quadriceps strength compared to COPD patients. This study only included ILD patients. Please correct accordingly.

Answer: The sentence was modified as follows: "... Moreover, a relationship between quadriceps muscle function and exercise capacity has been found not only in patients with COPD but also in patients with interstitial lung disease (ILD) that presented weakness in the knee extensors..."