PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of mesenchymal stem cells for the treatment of patients infected with 2019 novel coronavirus (COVID-19): a systematic review and meta-analysis protocol
AUTHORS	Chen, Yunhui; Zhang, Qing; Peng, Wei; Liu, Dan; You, Yanyan; Liu, Xinglong; Tang, Songqi; Zhang, Tiane

VERSION 1 – REVIEW

REVIEWER	Cynthia So-Osman Sanquin Blood Supply Foundation, Amsterdam, the Netherlands Erasmus Medical Center, Rotterdam, The Netherlands
REVIEW RETURNED	13-Aug-2020

GENERAL COMMENTS	This study protocol describes a meta-analysis of RCTs, CCTs, case control studies and case series on the efficacy and safety of mesenchymal stem cells for COVID-19 patients. The authors will search 10 databases and have no language restrictions which is very good. They also will use sound methodology to gather and interpret the extracted data. Some issues need to be described in more detail, however, such as study outcomes as clinical recovery rate (what is meant by that: respiratory improvement /days from ventilator, etcetera?), improvement of symptoms (please define this). Minor comments: p.3 Suggest to include the word “mesenchymal” stem cells in the title p.4 abstract: it is not known if stem cell therapy is one of the most promising therapeutic approaches, so this needs to be adapted: for example into: “stem cell therapy may be a promising therapeutic approach…” Could the authors explain what is meant by doses of hormonotherapy, do they refer to dexamethasone doses? Please be more specific. p.5 I think the authors meant to report quantitative data, if this is correct, please correct this. Please define the grey literature used. p.6 please delete COVID-2019 and replace by COVID-19 p.7 Methods : it should be clear that NO case reports are reported, but case series are. Also mention, that snowballed papers from references will be included. Include the word “mesenchymal” when using stem cells, when appropriate “western conventional medicine” can be replaced by “standard care” p.8 primary outcome: needs to be specified, see the general comments above. Why is safety (incidence and severity of adverse events) not regarded as primary outcome, since it is important and placed in the

	title of the protocol? p.9 typo: “odd ration” should be odds ratio p.10 add “disease” to “severity of included patients” to make "disease severity" for better clarity. "Types of stem cells", do the authors mean origin of the stem cells? May be corrected as such. p.11 I wonder how the authors will deal with ongoing incoming literature. Will the meta-analysis be regularly updated with new incoming data from randomized studies? This should be reported in the protocol. p.11 Discussion: I suggest to rephrase the first sentence, for example into: “This meta-analysis will analyse the efficacy and safety of MSC therapy for treatment of COVID-19 patients, using a structured and valid methodology”. It is not known if the result of this meta-analysis will end up with a convincing conclusion. p.14 Fig 1 flow chart: include grey lit/snowballed literature numbers. Please define as such.

REVIEWER	Bruce A Bunnell University of North Texas Health Science Center, Fort Worth, TX, USA
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	The manuscript by Chen et. al. entitled "Efficacy and safety of stem cells for the treatment of patients infected with 2019 novel coronavirus (COVID-19): a systematic review and meta-analysis protocol" describes the methodology, protocols, and data analysis associated with an analysis of mesenchymal stem cell-based interventions for COVID-19 infected patients enrolled into approved clinical trials. The performance of such an analysis is timely and should be informative to the scientific community. One potential limitation is whether a sufficient number of trials have been started/completed such that patient data is widely available to make interpretations or draw conclusions. If the analysis will be done over time, then data from more and more trials will come available. As for collection and analysis, the authors appear to have everything in place. As the authors will be searching databases and retrieving de-identified information there are no ethical concerns that I am aware of.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Cynthia So-Osman

Institution and Country

Sanquin Blood Supply Foundation, Amsterdam, the Netherlands

Erasmus Medical Center, Rotterdam, The Netherlands

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
This study protocol describes a meta-analysis of RCTs, CCTs, case control studies and case series on the efficacy and safety of mesenchymal stem cells for COVID-19 patients.
The authors will search 10 databases and have no language restrictions which is very good. They also will use sound methodology to gather and interpret the extracted data.

1) Some issues need to be described in more detail, however, such as study outcomes as clinical recovery rate (what is meant by that: respiratory improvement /days from ventilator, etcetera?), improvement of symptoms (please define this).
Response: Thank you for your valuable comments. The respiratory improvement/days from ventilator are more specific, and we have made the corresponding revision to the manuscript. The improvement of symptoms has been defined as the improvement of serious symptoms including difficult breathing or shortness of breath, chest pain or pressure, and loss of speech or movement. Corresponding revisions have been made on the manuscript in the Abstract section and Method section.
Before revision: The primary outcomes include mortality, clinical recovery rate, duration of fever, progression rate from mild or moderate to severe, improvement of symptoms, biomarkers of laboratory examination, and changes in computed tomography. The secondary outcomes include the dosage of hormonotherapy, incidence and severity of adverse events, and quality of life.
After revision: The primary outcomes include mortality, incidence and severity of adverse events, respiratory improvement, days from ventilator, duration of fever, progression rate from mild or moderate to severe, improvement of such serious symptoms as difficult breathing or shortness of breath, chest pain or pressure, and loss of speech or movement, biomarkers of laboratory examination, and changes in computed tomography.

Minor comments:
2) p.3
Suggest to include the word “mesenchymal” stem cells in the title
Response: Thank you for your valuable suggestions. we have included the word “mesenchymal” in the title.
Before revision: Efficacy and safety of stem cells for the treatment of patients infected with 2019 novel coronavirus (COVID-19): a systematic review and meta-analysis protocol
After revision: Efficacy and safety of mesenchymal stem cells for the treatment of patients infected with 2019 novel coronavirus (COVID-19): a systematic review and meta-analysis protocol

3)p.4 abstract: it is not known if stem cell therapy is one of the most promising therapeutic approaches, so this needs to be adapted: for example into: “stem cell therapy may be a promising therapeutic approach…”
Response: Thank you for your valuable comments, and revision has been made accordingly.
Before revision: Stem cell therapy has been considered as one of the most promising therapeutic approaches that may reduce the high mortality in critical cases.
After revision: Stem cell therapy may be a promising therapeutic approach that reduces the high mortality in critical cases.

4) Could the authors explain what is meant by doses of hormonotherapy, do they refer to dexamethasone doses? Please be more specific.
Response: thank you for your valuable comments. The doses of hormonotherapy refer to the dexamethasone doses, and corresponding revision has been made on the manuscript.
Before revision: The secondary outcomes include the dosage of hormonotherapy, incidence and severity of adverse events, and quality of life.
After revision: The secondary outcomes include dexamethasone doses incidence and severity of

adverse events (has been included into the primary outcomes upon your valuable comments, thank you very much) and quality of life.

5) p.5 I think the authors meant to report quantitative data, if this is correct, please correct this.
Response: sorry and thank you for your valuable correction. We have made corresponding correction to the manuscript.
Before revision: The study will systematically review qualitative data from various medical databases for an in-depth interpretation of the efficacy and safety of stem cell therapy on patients with COVID-19.
After revision: The study will systematically review quantitative data from various medical databases for an in-depth interpretation of the efficacy and safety of stem cell therapy on patients with COVID-19.

6) Please define the grey literature used.
Response: Thank you for your valuable comments. We have defined the grey literature used in the section of Search methods for identification of studies-Searching other resources.
Before revision: Not provided.
After revision: Grey literature such as guidelines, research and committee reports, government reports, and conference papers will be obtained from WHO, U.S National Library of Medicine, China Centre for Disease Control and Prevention, and online official news websites.

6) p.6 please delete COVID-2019 and replace by COVID-19
Response: Sorry and thank you for your valuable correction.
Before revision: Hence, MSCs therapy may improve the outcome of COVID-2019 patients through immunomodulation, regulating the inflammatory response, and promoting tissue repair.
After revision: Hence, MSCs therapy may improve the outcome of COVID-19 patients through immunomodulation, regulating the inflammatory response, and promoting tissue repair.

7) p.7 Methods: it should be clear that NO case reports are reported, but case series are. Also mention, that snowballed papers from references will be included. Include the word “mesenchymal” when using stem cells, when appropriate
Response: Thank you for your valuable comments, and we have made corresponding revisions.

Before revision: Randomized controlled trials (RCTs), clinical controlled trials (CCTs), case-control, and case series of stem cells treatment for COVID-19 will be included. Animal-based research and literature review will be excluded.
After revision: Randomized controlled trials (RCTs), clinical controlled trials (CCTs), and case series of MSCs treatment for COVID-19 will be included. Snowballed papers from references will be included. Animal-based research and literature review will be excluded.

8) “western conventional medicine” can be replaced by “standard care”
Response: Thank you for your valuable comments, and corresponding revision has been made.
Before revision: The intervention group will be treated by stem cells and western conventional medicine. There will be no restriction regarding western conventional medical regimen (such as supportive treatment, IFN-α, lopinavir, or ritonavir).
The control group will be treated with the same conventional western medical regimen as the intervention group in the same original study. No restrictions are imposed regarding conventional western medicine treatment regimen.

After revision: The intervention group will be treated by MSCs and standard care. There will be no restriction regarding standard care regimen (such as supportive treatment, IFN-α, lopinavir, or

ritonavir).
The control group will be treated with the same standard care regimen as the intervention group in the same original study. No restrictions are imposed regarding standard care regimen.

9) p.8 primary outcome: needs to be specified, see the general comments above.
Response: Thank you for your valuable comments, and corresponding revision has been made.
Before revision: Primary outcome measures include the mortality, clinical recovery rate, duration of fever, progression rate from mild or moderate to severe, improvement of symptoms, biomarkers of laboratory examination, and changes in computed tomography.
After revision: The primary outcomes include mortality, incidence and severity of adverse events, respiratory improvement, days from ventilator, duration of fever, progression rate from mild or moderate to severe, improvement of such serious symptoms as difficult breathing or shortness of breath, chest pain or pressure, and loss of speech or movement, biomarkers of laboratory examination, and changes in computed tomography.

10) Why is safety (incidence and severity of adverse events) not regarded as primary outcome, since it is important and placed in the title of the protocol?
Response: Thank you for your valuable comments, and corresponding revision has been made.
Before revision: Secondary outcomes include dosage of hormonotherapy, incidence and severity of adverse events, and quality of life.

After revision: Primary outcome measures include the mortality, incidence and severity of adverse events, duration of fever, progression rate from mild or moderate to severe, improvement of symptoms, biomarkers of laboratory examination, and changes in computed tomography.
The primary outcomes include mortality, incidence and severity of adverse events, respiratory improvement, days from ventilator, duration of fever, progression rate from mild or moderate to severe, improvement of such serious symptoms as difficult breathing or shortness of breath, chest pain or pressure, and loss of speech or movement, biomarkers of laboratory examination, and changes in computed tomography. Secondary outcomes include dexamethasone doses and quality of life.

11) p.9 typo: “odd ration” should be odds ratio
Response: sorry and thank you for your valuable correction, and we have made corresponding revision.
Before revision: A risk ratio or odd ration with 95% CIs will be adopted for dichotomous data
After revision: A risk ratio or odds ratio with 95% CIs will be adopted for dichotomous data.

12) p.10 add “disease” to “severity of included patients” to make "disease severity" for better clarity. "Types of stem cells", do the authors mean origin of the stem cells? May be corrected as such.
Response: thank you for your valuable corrections, and corresponding revisions have been made.
Before revision: If feasible, subgroup analyses will be performed in terms of the severity of included patients, duration of disease, routes of administration, dosage, and types of stem cells.
After revision: If feasible, subgroup analyses will be performed in terms of the disease severity of included patients, duration of disease, routes of administration, dosage, and origin of MSCs.

13) p.11 I wonder how the authors will deal with ongoing incoming literature. Will the meta-analysis be regularly updated with new incoming data from randomized studies? This should be reported in the protocol.
Response: thank you for your valuable comments. In the “discussion section” of the protocol, we have made corresponding revisions. Thank you.
Before revision: not reported

After revision: This meta-analysis will analyse the efficacy and safety of MSCs therapy for treatment of COVID-19 patients, using a structured and valid methodology. Conclusions drawn from this review may benefit patients, clinicians, investigators, and policymakers. The process of conducting this review will be divided into identification, study inclusion, data extraction, and data synthesis. If amendments to this protocol are necessary, the date of each amendment with a statement of the changes and the corresponding reasons will be provided. For the ongoing incoming literature, this meta-analysis will be regularly updated with new incoming data from randomized studies.

14) p.11 Discussion: I suggest to rephrase the first sentence, for example into: “This meta-analysis will analyse the efficacy and safety of MSC therapy for treatment of COVID-19 patients, using a structured and valid methodology”.
It is not known if the result of this meta-analysis will end up with a convincing conclusion.
Response: thank you very much for your suggestion.
Response: thank you very much for your valuable suggestion. Corresponding revisions have been made.
Before revision: This meta-analysis will provide a relatively convincing conclusion of whether MSCs therapy is effective and safe for treating patients with COVID-19.
After revision: This meta-analysis will analyse the efficacy and safety of MSCs therapy for treatment of COVID-19 patients, using a structured and valid methodology.

15) p.14 Fig 1 flow chart: include grey lit/snowballed literature numbers. Please define as such.
Response: thank you for your valuable comments, and the grey lit/snowballed literature numbers have been included in the flow chart.
Before revision:
After revision:

Reviewer: 2

Reviewer Name

Bruce A Bunnell

Institution and Country

University of North Texas Health Science Center, Fort Worth, TX, USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
The manuscript by Chen et. al. entitled "Efficacy and safety of stem cells for the treatment of patients infected with 2019 novel coronavirus (COVID-19): a systematic review and meta-analysis protocol" describes the methodology, protocols, and data analysis associated with an analysis of mesenchymal stem cell-based interventions for COVID-19 infected patients enrolled into approved clinical trials. The performance of such an analysis is timely and should be informative to the scientific community.

One potential limitation is whether a sufficient number of trials have been started/completed such that patient data is widely available to make interpretations or draw conclusions. If the analysis will be done over time, then data from more and more trials will come available. As for collection and analysis, the authors appear to have everything in place. As the authors will be searching databases and retrieving de-identified information there are no ethical concerns that I am aware of.

Response: thank you very much for your valuable comments, and we have made corresponding revisions in the section of “Strength and limitations”.

Before revision: The potential for low and inconsistent quality in the reporting of process evaluations, the publication bias, and the methodological quality of the grey literature found may be the limitations of the study.
After revision: The potential for low and inconsistent quality in the reporting of process evaluations, the publication bias, and the methodological quality of the grey literature found may be the limitations of the study. Other potential limitation might be whether a sufficient number of trials would be completed such that patient data is widely available to make interpretations or draw conclusions. And if that is the case, if the meta-analysis is not feasible, a narrative description of the results will be provided as described in the section of “Data synthesis”.