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Risk of post-intubation cardiac arrest with the use of high dose rocuronium in COVID-19 patients with acute respiratory distress syndrome: A retrospective cohort study

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15-Sep-2021

Ref.: Ms. No. JCTRes-D-21-00143
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Dear Dr. Acharya,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Oct 15, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

EDITOR:
As you see reviewers 1 and 4 are very critical of your work and have recommended a reject and reject & resubmit verdict. In light of the favorable reviews from the other 4 reviewers the editorial board is willing to extend the opportunity to CONSIDERABLY improve the manuscript. This will require the inclusion of more cases to corroborate the current results. The editorial board has sided with reviewer 1 regarding the precarious nature of the conclusions, which are based solely 6 cases. We at all times want to prevent publishing conclusions that may have been formulated on the basis of incidental findings. Please make an effort to enable the drawing of more robust conclusions.

Moreover, the writing is a mess and reflects very poorly on the study. Please comply with our author guidelines and make the text compliant with academic level English. Eliminate all grammar/spelling/syntax errors in the revision.

Finally, please understand that the editorial board may ultimately reject the paper if the authors cannot meet the most crucial points of commentary with respect to substance.

Reviewer #1: The authors have provided a nice work presenting their experixnce with post-intubation cardiac arrest in Covid-19 ARDS patients using two rocuronium dosage regimes, one high and alower one.
My major concern is that the censored cases are rather few (only six), so that sufficient conclusions can not be drawn with the reported values. Definately a larger number of cases would give more sound information. Maybe the authors should try to increase their cohort or maybe include another center to increase validity. The information presented is interesting but the small censored cases precludes the significance of the results
In the regression analysis how can APACHE IV be a significant result when the CI is 0.97-1.09 and why isn't the pre-intubation PaO2/FiO2 not statistically significant as the CI is 1.00-1.01?
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Reviewer #2: I would like to congratulate the authors for this well-thought-out retrospective

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I recommend the article appropriate for a publication with minor reviews.

The following observations add value to the study.

Review Points

-The data is collected over an approximate 1-year duration, with an adequately powered sample size.
-Patients with ARDS were identified using a uniformly adjudicated chart review process.
-Statistical methods of univariate and multivariate logistic regression analysis are appropriately used.
-Is it possible to divide the cohort per -Berling definition into (mild, moderate, and severe ARDS). It would be interesting to see if clinical outcomes were different according to the severity of ARDS.
-Also, seeing the between-group differences in the PICA rate among mild-moderate and severe ARDS cohorts in low and high-dose groups can add value. However given the sample size and event rate, there may be challenges from a statistical standpoint.
-Studies [1, 2] suggest that only a small subset of patients with non-COVID ARDS die of insupportable oxygenation. A majority of them die from sepsis [2]. This study suggests the potential impact of acute hemodynamic instability from autonomic imbalance triggered by the procedures and medications administered during the procedure in critical care settings. I believe adding this point to the discussion would add value.
-Additionally, it is advised to brush up the write up and language so as to make it better to the audience.
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Reviewer #3: The authors defined the study as retrospective and observational. The ethical consideration, inclusion and exclusion criteria, statistical analysis, bias, strength and weakness of the study are clearly mentioned in the study. The inclusion criteria and the aim of the study was very specific so the sample size was small even for a year period, which is acceptable. The topic is novel and the study has merit for publication and the efforts of the authors is appreciable. Having said that I have few questions and suggestions:
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0.39 - 8.90, P= 0.430). I think the authors wanted to mention that high dose of rocuronium was not associated with higher mortality. The authors might have tried to make it sound reasonable with low mortality as there were less mortality in high rocuronium group. But I believe that in MV analysis the comparison was death vs (when compared to) survived patients (as survived as reference). It should be either removed from the abstract or corrected to higher mortality.
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Prolonged neuromuscular blockade may be associated with post-intubation complications, but the dose of locronim does not appear to affect prognosis.

Reviewer #5: This is a lesser explored area in the field of critical care. The study has declared all the necessary
components such as necessity for the study, patient selection, exclusion, data collection methods, IRB
approval, statistical analysis, results and conclusion. The statistical analysis is rigorously done and the
conclusion is nicely delivered.
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Lines 274-276: Consider this being a double negative sentence.

Line 343: to avoid or minimize laryngospasm?

Overall comment: While this is a small and simple study, it's results are relevant to current issues of the pandemic and showed no harm in the current standard of practice. Unfortunately, the sample size it small but otherwise well written and publishable with the small corrections listed.

Authors' response

EDITOR:
As you see reviewers 1 and 4 are very critical of your work and have recommended a reject and reject & resubmit verdict. In light of the favorable reviews from the other 4 reviewers the editorial board is willing to extend the opportunity to CONSIDERABLY improve the manuscript. This will require the inclusion of more cases to corroborate the current results. The editorial board has sided with reviewer 1 regarding the precarious nature of the conclusions, which are based solely 6 cases. We at all times want to prevent publishing conclusions that may have been formulated on the basis of incidental findings. Please make an effort to enable the drawing of more robust conclusions. Moreover, the writing is a mess and reflects very poorly on the study. Please comply

with our author guidelines and make the text compliant with academic level English. Eliminate all grammar/spelling/syntax errors in the revision.
Finally, please understand that the editorial board may ultimately reject the paper if the authors cannot meet the most crucial points of commentary with respect to substance.

Response: Thank you so much for the review.

--Increasing the 'cohort' will be very difficult, as it will have to go through the IRB and take a considerable amount of time. It included all patients within a year when the COVID-19 related hospitalization was at its peak. I do not think adding the patients for a few extra months will increase this number considerably, especially since the COVID-19 admission had decreased after the availability of vaccines. Adding another center is a lengthy process as the IRB from our health network has to collaborate with another health network. This involves legal and administration and many documentations. At this point, I do not see it as feasible. We believe this study is unique as we studied a phenomenon acknowledged by intensivists, but no study has been done so far. So this will serve as a reference for similar future studies.

--I agree that deriving a 'conclusion' based on 6 PICA events is probably not justifiable. We, therefore, removed the Logistic Regression analysis and revised the manuscript per suggestion. The conclusion is also changed in the revised manuscript. We removed Table 3 and the related text in the body. The total sample is 93 with N= 40 & 43 in the respective groups, so we believe this cohort is large enough to perform comparative statistical analysis between the groups. Hence we kept Tables 1 and 2 and related text.

--Grammar, spelling, and syntax errors are rigorously edited. The revised manuscript is now per the guidelines of JCTRes.

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Response: Thank you so much for the review.

--We realized that six PICA events are not a sufficient number to reach a conclusion. We are unable to include patients from different centers due to various reasons, which we explained earlier. But we removed the regression analysis entirely and edited the text in the manuscript per suggestion.
--We changed the material in supplementary data.

--We have 2 Tables to elaborate the findings.

--Visual abstracts now do not have regression analysis, but we added new findings.

Reviewer #2: I would like to congratulate the authors for this well-thought-out retrospective study on Post Intubation Cardiac Arrest (PICA) in patients with COVID-19 ARDS. High-dose rocuronium has been widely used during the pandemic and evidence is merely limited to expert opinion. This study definitely adds evidence and fills the existing knowledge gap.

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Response: Thank you so much for the review.

-- We could not divide patients into mild, moderate, and severe ARDS and analyze the association on PICA outcome due to only six PICA events. We recognized this as a limitation of the study and added this to limitations.

--We appreciate the suggestion for non-COVID ARDS mortality. We added article 2 in the discussion part of the manuscript.

Reviewer #3: The authors defined the study as retrospective and observational. The ethical consideration, inclusion and exclusion criteria, statistical analysis, bias, strength and weakness of the study are clearly mentioned in the study. The inclusion criteria and the aim of the study was very specific so the sample size was small even for a year period, which is acceptable. The topic is novel and the study has merit for publication and the efforts of the authors is appreciable. Having said that I have few questions and suggestions:
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Response: Thank you so much for the review.

--Per suggestions of the Academic Editor and Reviewer#1, all related logistic regression analysis has been removed.

--We changed the 268-271 as: "The reasoning behind the recommendation to use higher dose of rocuronium was because of dose-dependent onset of effect of rocuronium during RSI. The standard dose of rocuronium (0.9-1.2 mg/kg) was recommended for optimal intubation

conditions within 60 seconds of neuromuscular blocking agent administration."

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Prolonged neuromuscular blockade may be associated with post-intubation complications, but the dose of locronim does not appear to affect prognosis.

Response: Thank you so much for the review.

--References 1 and 2 were during the early pandemic days. The references were used to build the background of the study. Thank you so much for highlighting the fact.

--We removed the logistic regression analysis per the suggestion of the Academic Editor. Due to that reason, we cannot consider hypoxia and hypotension for logistic regression analysis.

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rephrased, especially, the standard dose of rocuronium was 0.9-1.2 mg/kg was recommended part.
Conclusion: Line 342: To maintain uniformity change rapid sequence intubation methods to technique.

Response: Thank you so much for the review.

--In the abstract, P-value is changed to 0.009

--The inclusion and exclusion criteria are now rephrased in bullet form.

--Logistic regression analysis and related texts were removed per the Academic Editor suggestion.

--The HDR and LDR full forms are mentioned in the 'study design and population' section as : Patients were divided into high-dose rocuronium (HDR) group defined as 1.5 mg/kg and above, and low-dose rocuronium (LDR) group defined as doses below 1.5 mg/kg.

--The sentence is changed as: "The reasoning behind the recommendation to use higher dose of rocuronium was because of dose-dependent onset of effect of rocuronium during RSI. The standard dose of rocuronium (0.9-1.2 mg/kg) was recommended for optimal intubation conditions within 60 seconds of neuromuscular blocking agent administration."

--We changed the conclusion after removing the logistic regression analysis data and related text as: "In comparison to pre COVID-19 era, the incidence of post-intubation cardiac arrest had increased among COVID-19 patients with ARDS who were intubated with high dose rocuronium using rapid sequence intubation technique."

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Overall comment: While this is a small and simple study, it's results are relevant to current issues of the pandemic and showed no harm in the current standard of practice. Unfortunately, the sample size it small but otherwise well written and publishable with the small corrections listed.

Response: Thank you so much for the review.

--Thank you, the error has been corrected.

--Our knowledge for treating COVID-19 as we progress through pandemic evolves, recommendations continue to evolve as well. At the time we did our study, doses of

rocuronium over 1.2 mg/kg were considered high. That is because the recommended standard dose of rocuronium for RSI was 0.6-1.2 mg/kg per manufacturer label (as approved by FDA). The standard high range of rocuronium was 1.2 mg/kg. The paper by Cook et al. recommended 1.5 mg/kg dosing, which is higher than the usual, and that's what we opted to use for our study. 2.0 mg/kg dosing referred to by the reviewer was most likely the RSI dosing for IV succinylcholine. We added this in the study as: "The recommended standard dose of rocuronium for RSI was 0.6-1.2 mg/kg per manufacturer label (as approved by FDA). The standard high range of rocuronium was 1.2 mg/kg. The pragmatic recommendations were to use 1.5mg/kg of rocuronium or 2 mg/kg of succinylcholine (4), which we opted for the study."

--Thank you, APACHE IV hyphens removed.

--Noted, thank you. The error is removed.

--Noted, thank you. The error is removed.

--The conclusion is rephrased.

2nd Editorial decision
30-Sep-2021

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: