PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Helmet noninvasive ventilation for COVID-19 patients "Helmet-COVID": study protocol for a multicenter randomized controlled trial
AUTHORS	Arabi, Yaseen; Tlayjeh, Haytham; Aldekhyl, Sara; Al-Dorzi, Hasan; Abdukahil, Sheryl Ann; Al Harbi, Mohammad Khulaif; Al Haji, Husain; Al Mutairi, Mohammed; Al Zumai, Omar; Al Qasim, Eman; Al Wehaibi, Wedyan; Al Qahtani, Saad; Al-Hameed, Fahad; Chalabi, Jamal; Alshahrani, Mohammed; Alharthy, Abdulrahman; Mady, Ahmed; Bin Eshaq, Abdulhadi; A. Al bshabshe, Ali; Al Aseri, Zohair; Al Duhailib, Zainab; Kharaba, Ayman; Alqahtani, Rakan; Al Ghamdi, Adnan; Altalag, Ali; Alghamdi, Khalid; Almaani, Mohammed; Algethamy, Haifa; Al Aqeily, Ahmad; Al Baseet, Faisal; Al Samannoudi, Hashem; Al Obaidi, Mohammed; Ismaiel, Yassin; Al-Fares, Abdulrahman A

VERSION 1 – REVIEW

REVIEWER	Alonso Mateos-Rodriguez Universidad Francisco de Vitoria
REVIEW RETURNED	02-May-2021

GENERAL COMMENTS	This is a port of call for a very interesting clinical trial on the use of NIMV in patients with COVID pneumonia. The use of this therapy, although initially contraindicated, has proven useful in many patients. This study aims to further clarify this terrain.

REVIEWER	Sandro Luigi Di Domenico ASST Grande Ospedale Metropolitano Niguarda, emergency medicne
REVIEW RETURNED	05-May-2021

GENERAL COMMENTS	Thank you for the opportunity of reviewing this study protocol. The study is well designed and it will address an important clinical question: whether there is a safe alternative to treat ARDS, avoiding the complication associated to mechanical ventilation. I have only few questions and minor suggestions that could improve the quality of the study. 1) My main concern is about the heterogeneity of the control group. There is no protocol to guide the use of NIV or HFNC. The outcome of control group could be influenced by different approaches for similar patients. Please address the issue. 2) The author stated that Helmet should be continuously applied for at least 48 hours (row 14). What does it mean? I can presume that after 48 hours helmet can be alternated to different oxygen supports for feeding or patient's comfort? Or do you mean that in case of intubation or intolerance in the first 48 hour, the patient will be considered as withdrawn? 3) PaO2/FiO2 less than 100 is a criterion for intubation. However the

	author includes patients with severe ARDS with paO2/FIO2 < 100 in subgroup analysis (row 48-53). It seems to me a contradiction. Could you please explain? 4) Row 36: the definition of suspected case of covid is not enough specific and it can be applied to almost every case of respiratory failure with no alternative diagnosis. Please amend.

REVIEWER	C. Rabec Centre Hospitalier Universitaire de Dijon
REVIEW RETURNED	20-May-2021

GENERAL COMMENTS	In this multicenter, randomized controlled trial the authors are expected to compare helmet noninvasive ventilation with "usual care" in 1:1 ratio. They search to include 320 patients. The primary outcome is 28-day mortality The manuscript is clear and well written. The English is correct. The subject is relevant and results could have a potential impact in clinical practice However a major issue needs to be raised The hypothesis the authors intend to test is if use of helmet interface is able to impact clinical outcomes in Covid 19 related ARDS (in this case the outcome chosen is 28-day mortality). But this reviewer thinks that there is a conceptual error in the study design: helmet is not a therapeutic modality, but a type of interface used to provide NIV. The authors propose to include patients with severe ARDS (Pa/FiO2 < 200). Compulsorily including in one arm patients on NIV ventilation but in a control group a mixed population of patients on standard oxygen, HFT or NIV by using nasal of facial mask (the decision of the type of treatment in the control arm let at the discretion of the treating team) could induce a major bias in the trial, as it is logically expected a better result in those severe patient by using NIV as compared to a mixed control group including may be a third or less of patients on NIV Then the comparator should not be "standard therapy" (that includes a pool of standard oxygen, HFT or NIV by using nasal or facial masks) but NIV itself by using others interfaces) Minor comments Page 8: “Due to this design, it has advantages over the nasal and oro-nasal interfaces…”. The inconvenients of this interface need also to be described (increase in dead space, claustrophobia, risk of aspiration if vomiting, etc) Page 14 “Assuming a mortality rate of 40% in patients with COVID-19 pneumonia and moderate to severe ARDS…” What does this rate come from? Why assume that for data of AHRF and ARDS while there are nowadays enough data reported from COVID 19-related ARDS to powering the study for those data and not for a global population of ARDS? Methods: Method used to generate the random allocation sequence is not well explicated. Please clarify that in the text

REVIEWER	Christopher Howard Baylor College of Medicine
REVIEW RETURNED	15-Jun-2021

GENERAL COMMENTS	1. goals are clear and described adequately 2. statistical methods will need to be reviewed once finalized 3. considering add PMID: 32844113 to list of references for helmet NIV and COVID, also all the studies from U of Chicago

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Alonso Mateos-Rodriguez, Universidad Francisco de Vitoria

Comments to the Author. This is a port of call for a very interesting clinical trial on the use of NIMV in patients with COVID pneumonia. The use of this therapy, although initially contraindicated, has proven useful in many patients. This study aims to further clarify this terrain.

Response: *Thank you very much for this comment.*

Reviewer 2: Dr. Sandro Luigi Di Domenico, ASST Grande Ospedale Metropolitano Niguarda

Comments to the Author. Thank you for the opportunity of reviewing this study protocol. The study is well designed and it will address an important clinical question: whether there is a safe alternative to treat ARDS, avoiding the complication associated to mechanical ventilation.

I have only few questions and minor suggestions that could improve the quality of the study.

Comment 1: My main concern is about the heterogeneity of the control group. There is no protocol to guide the use of NIV or HFNC. The outcome of control group could be influenced by different approaches for similar patients. Please address the issue.

Response: *Thank you for this comment. We added the following paragraph to the Discussion: "We planned our pragmatic trial to address whether using helmet NIV as the primary non-invasive respiratory support in patients with severe COVID-19, in addition to the commonly used high-flow nasal oxygen and mask NIV improves outcome. By nature of this question, there is heterogeneity of the control group; as patients in this group could receive standard oxygen, high-flow nasal oxygen or mask NIV at the decision of the treating team. This approach is supported by a recent network meta-analysis of randomized controlled trials that showed only a modest effect of high-flow nasal oxygen and mask NIV on mortality or intubation rate compared to standard oxygen, while patients treated with helmet NIV had more than 50% reduction in mortality and intubation rate compared to the other three modalities.1 In addition, this approach is likely to be more representative of usual practice in which patients may get oxygen therapy, high-flow nasal oxygen and NIV at different times during their acute illness. Given the fact that the use of helmet NIV has not been widespread across ICUs, we thought*

that the broader question addressed by our study might be more relevant to deciding whether to introduce this modality or not in a given ICU."

Comment 2: The author stated that Helmet should be continuously applied for at least 48 hours (row 14). What does it mean? I can presume that after 48 hours helmet can be alternated to different oxygen supports for feeding or patient's comfort? Or do you mean that in case of intubation or intolerance in the first 48 hour, the patient will be considered as withdrawn?

Response: *Thank you for this comment. We revised this sentence to the following: "Interruptions of helmet should be avoided or kept at minimum at least in the first 48 hours".*

Comment 3: PaO2/FiO2 less than 100 is a criterion for intubation. However the author includes patients with severe ARDS with paO2/FIO2 <100 in subgroup analysis (row 48-53). It seems to me a contradiction. Could you please explain?

Response: *Subgroup analysis is based on baseline value of PF ratio, ie before randomization. The decision to intubation is based values during the course of ICU. In addition, the decision to intubate is not based on PF ratio alone, but rather on the general response, and it left to the treating team.*

Comment 4: Row 36: the definition of suspected case of covid is not enough specific and it can be applied to almost every case of respiratory failure with no alternative diagnosis. Please amend.

Response: *Thank you for this comment. We have used the Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) 2020 Interim Case Definition, Approved April 5, 2020. https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/. We added this definition along with the website as a footnote to Table 1..*

Reviewer 3: Dr. C. Rabec, Alize Bourgogne

Comments to the Author. In this multicenter, randomized controlled trial the authors are expected to compare helmet noninvasive ventilation with "usual care" in 1:1 ratio. They search to include 320 patients. The primary outcome is 28-day mortality

The manuscript is clear and well written. The English is correct. The subject is relevant and results could have a potential impact in clinical practice

However a major issue needs to be raised

Comment: The hypothesis the authors intend to test is if use of helmet interface is able to impact clinical outcomes in Covid 19 related ARDS (in this case the outcome chosen is 28-day mortality).

But this reviewer thinks that there is a conceptual error in the study design: helmet is not a therapeutic modality, but a type of interface used to provide NIV.

Response: *Thank you for this important comment. A recent network metanalysis showed that the interface for NIV (helmet versus mask) affects mortality. We added the following sentence in the Discussion: "…This approach is supported by a recent network meta-analysis of randomized controlled trials that showed only a modest effect of high-flow nasal oxygen and mask NIV on mortality or intubation rate compared to standard oxygen, while patients treated with helmet NIV had more than 50% reduction in mortality and intubation rate compared to the other three modalities.1 In addition, this approach is likely to be more representative of usual practice in which patients may get oxygen therapy, high-flow nasal oxygen and NIV at different times during their acute illness. Given the fact that the use of helmet NIV has not been widespread across ICUs, we thought that the broader question addressed by our study might be more relevant to deciding whether to introduce this modality or not in a given ICU.".[1]"*

Comment: The authors propose to include patients with severe ARDS (Pa/FiO2 < 200). Compulsorily including in one arm patients on NIV ventilation but in a control group a mixed population of patients on standard oxygen, HFT or NIV by using nasal of facial mask (the decision of the type of treatment in the control arm let at the discretion of the treating team) could induce a major bias in the trial, as it is logically expected a better result in those severe patient by using NIV as compared to a mixed control group including may be a third or less of patients on NIV. Then the comparator should not be "standard therapy" (that includes a pool of standard oxygen, HFT or NIV by using nasal or facial masks) but NIV itself by using others interfaces)

Response: *Thank you for this comment. We have addressed this comment now in the Discussion as follows: "We planned our pragmatic trial to address whether using helmet NIV as the primary non-invasive respiratory support in patients with severe COVID-19, in addition to the commonly used high-flow nasal oxygen and mask NIV improves outcome. By nature of this question, there is heterogeneity of the control group; as patients in this group could receive standard oxygen, high-flow nasal oxygen or mask NIV at the decision of the treating team. This approach is supported by a recent network meta-analysis of randomized controlled trials that showed only a modest effect of high-flow nasal oxygen and mask NIV on mortality or intubation rate compared to standard oxygen, while patients treated with helmet NIV had more than 50% reduction in mortality and intubation rate compared to the other three modalities.1 In addition, this approach is likely to be more representative of usual practice*

in which patients may get oxygen therapy, high-flow nasal oxygen and NIV at different times during their acute illness. Given the fact that the use of helmet NIV has not been widespread across ICUs, we thought that the broader question addressed by our study might be more relevant to deciding whether to introduce this modality or not in a given ICU."

Minor comments

Page 8: "Due to this design, it has advantages over the nasal and oro-nasal interfaces…". The inconvenient of this interface need also to be described (increase in dead space, claustrophobia, risk of aspiration if vomiting, etc)

Response: *Thank you for this comment. We added "However, helmet interface may be associated with increase in dead space (if the settings are not used appropriately), claustrophobia, discomfort, and difficulty in access for suction and feeding."*

Comment: Page 14 "Assuming a mortality rate of 40% in patients with COVID-19 pneumonia and moderate to severe ARDS…" What does this rate come from? Why assume that for data of AHRF and ARDS while there are nowadays enough data reported from COVID 19-related ARDS to powering the study for those data and not for a global population of ARDS?

Response: *Thank you. We added the following: "A systematic review found an overall pooled mortality estimate among 10,815 ARDS cases in COVID-19 patients to be 39% (95% CI: 23–56%).*[2]*"*

Comment:

Methods: Method used to generate the random allocation sequence is not well explicated. Please clarify that in the text

Response: *Thank you for this comment. We have added in the methods section: This is an investigator-initiated, pragmatic parallel RCT that will compare helmet NIV with usual care to usual care alone in 1:1 ratio in patients with suspected or confirmed COVID-19 pneumonia and AHRF. Randomization is performed using a computer-generated randomization schedule using permuted blocks, of variable sizes (4 or 6) and is stratified by site.*

Reviewer 4: Dr. Christopher Howard, Baylor College of Medicine

Comments to the Author:

Comment: 1. goals are clear and described adequately]

Response: *Thank you very much for this comment.*

Comment 2: Statistical methods will need to be reviewed once finalized

Response: *Thank you. We have submitted the statistical analysis plan manuscript for publication.*

Comment 3: Considering add PMID: 32844113 to list of references for helmet NIV and COVID, also all the studies from U of Chicago

Response:

1. *Thank you. We added PMID: 32844113.*
2. *We added: "One study reported the cost-effectiveness of helmet NIV.[3]". The other studies from U Chicago are already cited.*

VERSION 2 – REVIEW

REVIEWER	Sandro Luigi Di Domenico ASST Grande Ospedale Metropolitano Niguarda, emergency
REVIEW RETURNED	08-Jul-2021

GENERAL COMMENTS	The protocol is clear and well designed and the Authors addressed all the requests of the reviewers.

REVIEWER	C. Rabec Centre Hospitalier Universitaire de Dijon
REVIEW RETURNED	21-Jul-2021

GENERAL COMMENTS	All the concerns underlined by this reviewer are answered by the authors

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Sandro Luigi Di Domenico, ASST Grande Ospedale Metropolitano Niguarda

Comments to the Author:

The protocol is clear and well designed and the Authors addressed all the requests of the reviewers.

Response: Thank you.

Reviewer: 3

Dr. C. Rabec, Alize Bourgogne

Comments to the Author:

All the concerns underlined by this reviewer are answered by the authors

Response: Thank you.