PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol
AUTHORS	Jaber, S.; MOLINARI, Nicolas; DE JONG, Audrey

VERSION 1 - REVIEW

REVIEWER	THILLE CHU DE POITIERS FRANCE
REVIEW RETURNED	15-Feb-2016

GENERAL COMMENTS	I read with interest the study planned by Jaber et al. The protocol is clear and well written However, I have 2 potential concerns: First, if the authors consider NIV as the reference treatment, the SHAM group is not exactly the standard. Indeed, the nasal cannula linked to the circuit is located under the NIV mask and may therefore generate leaks during NIV and decrease its efficacy. However, the 2 groups are treated similarly and the assessment will be preoxygenation with or without apnoeic oxygenation. Second, the number of patients needed to include is based to detect a 5% difference in the lowest SpO2. However, the same authors have defined in their previous studies that a profound desaturation occurred when SpO2 dropped below 80%. We can imagine reaching the 5% difference expected with a SpO2 markedly above 80%. For example, the authors may detect a difference from 95% to 90% and it is not sure that such difference has a real clinical impact.

REVIEWER	Daniel Talmor Harvard Medical School Boston USA
REVIEW RETURNED	18-Feb-2016

GENERAL COMMENTS	Jaber and colleagues present the protocol for a prospective randomized controlled trial of the benefit of adding high flow nasal cannula and apneic oxygenation to non- invasive ventilation in patients requiring intubation for hypoxic respiratory failure. The study is well thought out with a plausible hypothesis. Adequate explanation of the rationale, methods and analysis plan for the study is presented. I look forward to seeing the results of the study.

REVIEWER	Jean-Pierre FRAT Réanimation Médicale CHU Poitiers France Fisher-Paykel SOS oxygene LFB
REVIEW RETURNED	18-Feb-2016

GENERAL COMMENTS	The topic explored by this study is original and there are only publications in the area of ICU. The authors have experience in this topic with well known publications. The authors want to to assess in this new study high flow oxygen therapy, which use is growing in ICU. No study compared so far NIV to the association of NIV with high flow during preoxygenation. The rationale is strong to allow such a comparison. I have only minor comments or concerns about this study protocol: - primary outcome: it should be more interesting, in clinical point of view, to compare severe desaturation between groups (defined by a SPO2 drop under 80%) than the lowest SPO2; however as this variable is included in the secondary outcomes, this information will be assessed. - as concerned the strategy with the association of NIV with high flow: its application should cautious as many leaks may happen and challenge the potential beneficial effect of NIV; however as this device will be applyed in the control group (but not operating) results will be interpretable.

REVIEWER	Jean-Damien Ricard Paris Diderot University, Paris, France Fisher&Paykel have covered travel expenses for my participation to several scientific meetings and/or congresses
REVIEW RETURNED	29-Mar-2016

GENERAL COMMENTS	Authors must be commended for planning this interesting and well designed study. Nonetheless, I have a concern regarding the sample size calculation. Authors state they plan to detect a 5% difference in SpO2 with a SD of 6%. In the only study in the literature on the subject (performed by the authors), the lowest saturation in the NIV group was 93% with a SD of 8%. I'm concerned that the SD they chose may be too small. In addition, given the error of measure associated with SpO2 monitors (usually around 2%) and the error associated with the oxygen blender (again, around 2%) one could argue that in fact, difference in SpO2 could be solely due to devices' imprecision. This could be added in the limitation. Finally, authors should also acknowledge that their study does not answer the question of the best mode of preoxygenation in critically ill patients, i.e., use of high flow or of NIV. Their study will only answer the question of adding or not high flow, when using NIV.

	This should appear clearly in the conclusion of the manuscript. On page 4, line 48, authors state that NIV is used by many teams for preoxygenation, please provide a reference to substantiate this assertion or qualify the sentence.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I read with interest the study planned by Jaber et al. The protocol is clear and well written
However, I have 2 potential concerns:

Q1. First, if the authors consider NIV as the reference treatment, the SHAM group is not exactly the standard. Indeed, the nasal cannula linked to the circuit is located under the NIV mask and may therefore generate leaks during NIV and decrease its efficacy. However, the 2 groups are treated similarly and the assessment will be preoxygenation with or without apnoeic oxygenation.

R1: We agree with the reviewer on that comment. The NIV is indeed considered as the reference treatment, but a nasal cannula is added under the NIV mask in the reference group, which could generate leaks. However, the operator holds directly the NIV mask, which limits the leaks. As underlined by the reviewer, the aim was to make the two groups comparable and to assure blinding. This is now added in the limits section, as follows (Page 17): "Adding a nasal cannula under the NIV mask may generate leaks during NIV and decrease its efficacy. However, the operator performing intubation holds the mask, which limits the leaks, and the two groups are treated similarly."

Q2: Second, the number of patients needed to include is based to detect a 5% difference in the lowest SpO2. However, the same authors have defined in their previous studies that a profound desaturation occurred when SpO2 dropped below 80%. We can imagine reaching the 5% difference expected with a SpO2 markedly above 80%. For example, the authors may detect a difference from 95% to 90% and it is not sure that such difference has a real clinical impact.

R2: Again, we understand the reviewer comment. Indeed, the number of patients needed to include is based to detect a 5% difference in the lowest SpO2, and not to detect a difference in the percentage of severe desaturation, defined in previous published studies when SpO2 drops below 80%. However, severe desaturation is a rare event when preoxygenation is done with NIV alone (2 of 27 in a previous study, 7% (Baillard et al, AJRCCM 2006)) and expected to be even rarer in the NIV more HFNC group (interventional group). To detect a difference from 7% of severe desaturation in the reference group to 4% in the interventional group, with an alpha risk of 5% and a power of 80%, the number of subjects needed would be 1780 overall (890 per group). We think that the lowest saturation per procedure is a good alternative to detect the efficacy of apnoeic oxygenation, and could be interesting even if a difference from 95% to 90% is detected. This difference, without apparent clinical impact, could reflect the existence of apnoeic oxygenation, allowing to save some patients in case of severe desaturation, for example if a difficult intubation occurs.

Reviewer: 2

Q1. Jaber and colleagues present the protocol for a prospective randomized controlled trial of the benefit of adding high flow nasal cannula and apneic oxygenation to non- invasive ventilation in

patients requiring intubation for hypoxic respiratory failure.

The study is well thought out with a plausible hypothesis. Adequate explanation of the rationale, methods and analysis plan for the study is presented. I look forward to seeing the results of the study.

R1. We really thank the reviewer for his careful reading and these nice and positive comments.

Reviewer: 3

Q1. The topic explored by this study is original and there are only publications in the area of ICU. The authors have experience in this topic with well known publications. The authors want to assess in this new study high flow oxygen therapy, which use is growing in ICU. No study compared so far NIV to the association of NIV with high flow during preoxygenation. The rationale is strong to allow such a comparison. I have only minor comments or concerns about this study protocol:
- primary outcome: it should be more interesting, in clinical point of view, to compare severe desaturation between groups (defined by a SPO2 drop under 80%) than the lowest SPO2; however as this variable is included in the secondary outcomes, this information will be assessed.

R1. We understand and agree with the reviewer comment. This point was also raised by other reviewers. However, severe desaturation (defined by a SpO2 drop under 80%) is a rare event when preoxygenation is done with NIV alone (2 of 27 in a previous study, 7% (Baillard et al, AJRCCM 2006)) and expected to be even rarer in the NIV more HFNC group (interventional group). To detect a difference from 7% of severe desaturation in the reference group to 4% in the interventional group, with an alpha risk of 5% and a power of 80%, the number of subjects needed would be 1780 overall (890 per group). We think that the lowest saturation per procedure is a good alternative to detect the efficacy of apnoeic oxygenation, and could be interesting even if a difference from 95% to 90% is detected. This difference, without apparent clinical impact, could reflect the existence of apnoeic oxygenation, allowing to save some patients in case of severe desaturation, for example if a difficult intubation occurs. Moreover, ad underlined by the reviewer, severe desaturation is included in the secondary outcomes.

Q2. - as concerned the strategy with the association of NIV with high flow: its application should cautious as many leaks may happen and challenge the potential beneficial effect of NIV; however as this device will be applied in the control group (but not operating) results will be interpretable.

R2. We understand the reviewer comment, as also underlined by Reviewer 1. The NIV is indeed considered as the reference treatment, but a nasal cannula is added under the NIV mask, which could generate leaks. However, the operator holds directly the NIV mask, which limits the leaks. As underlined by the reviewer, the aim was to make the two groups comparable and to assure blinding. This is now added in the limits section, as follows (Page 17): "Adding a nasal cannula under the NIV mask may generate leaks during NIV and decrease its efficacy. However, the operator performing intubation holds the mask, which limits the leaks, and the two groups are treated similarly."

Reviewer: 4

Q1. Authors must be commended for planning this interesting and well designed study. Nonetheless, I have a concern regarding the sample size calculation. Authors state they plan to detect a 5%

difference in SpO2 with a SD of 6%. In the only study in the literature on the subject (performed by the authors), the lowest saturation in the NIV group was 93% with a SD of 8%.
I'm concerned that the SD they chose may be too small.

R1. We understand the reviewer on that comment, also raised by other reviewers. Indeed, the number of patients needed to include is based to detect a 5% difference in the lowest SpO2, and not to detect a difference in the percentage of severe desaturation, defined in previous published studies when SpO2 drops below 80%. However, severe desaturation is a rare event when preoxygenation is done with NIV alone (2 of 27 in a previous study, 7% (Baillard et al, AJRCCM 2006)) and expected to be even rarer in the NIV more HFNC group (interventional group). To detect a difference from 7% of severe desaturation in the reference group to 4% in the interventional group, with an alpha risk of 5% and a power of 80%, the number of subjects needed would be 1780 overall (890 per group). We think that the lowest saturation per procedure is a good alternative to detect the efficacy of apnoeic oxygenation, and could be interesting even if a difference from 95% to 90% is detected. This difference, without apparent clinical impact, could reflect the existence of apnoeic oxygenation, allowing to save some patients in case of severe desaturation, for example if a difficult intubation occurs.

Q2. In addition, given the error of measure associated with SpO2 monitors (usually around 2%) and the error associated with the oxygen blender (again, around 2%) one could argue that in fact, difference in SpO2 could be solely due to devices' imprecision. This could be added in the limitation.

R2. We thank the reviewer for this comment. We added this comment in the limitation (Page 17-18): "Given the error of measure associated with SpO2 monitors (usually around 2%) and the error associated with the oxygen blender (around 2%), one could argue that in fact, difference in SpO2 could be solely due to devices' imprecision. However, given the randomized design of the study, this imprecision should be evenly distributed in each group".

Q3. Finally, authors should also acknowledge that their study does not answer the question of the best mode of preoxygenation in critically ill patients, i.e., use of high flow or of NIV. Their study will only answer the question of adding or not high flow, when using NIV. This should appear clearly in the conclusion of the manuscript.

R3. We agree with the reviewer on this comment. This study will only answer the question of adding or not high flow, when using NIV. This was added in the conclusion of the manuscript as follows (Page 18): " In conclusion, the OPTINIV trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that NIV combined to HFNC adding HFNC in combination with NIV in comparison to NIV alone allows to decrease severe hypoxemia during the intubation procedure of hypoxemic ICU patients requiring mechanical ventilation for acute respiratory failure."

Q4. On page 4, line 48, authors state that NIV is used by many teams for preoxygenation, please provide a reference to substantiate this assertion or qualify the sentence.

R4. We thank the reviewer for this comment. In a previous study performed on 1400 intubation procedures in 60 French ICU, NIV was used for preoxygenation in 40% of intubation procedures (De

Jong et al., AJRCCM 2013). This reference was added on page 4, line 48 (reference 2), as follows (Page 4): " Incidence of severe hypoxemia defined by a pulse oxymetry (SpO2) of less than 80% can be decreased by applying NIV preoxygenation, a method which is now used by many teams for preoxygenation of patients with hypoxemic acute respiratory failure.2"

VERSION 2 – REVIEW

REVIEWER	Arnaud W. Thille CHU de Poitiers, Medical ICU, France
REVIEW RETURNED	29-Apr-2016

GENERAL COMMENTS	The authors have well answered to my comments

REVIEWER	Daniel Talmor Beth Israel Deaconess Medical Center Boston MA
REVIEW RETURNED	14-Apr-2016

GENERAL COMMENTS	I have no further comments

REVIEWER	Jean-Pierre FRAT CHU de Poitiers, Réanimation Médicale, Poitiers France
REVIEW RETURNED	26-Apr-2016

GENERAL COMMENTS	The authors have answered properly to all the comments.

REVIEWER	Jean-Damien Ricard Université Paris Diderot, Paris, France Fisher&Paykel have covered travel expenses for me to attend scientific meetings
REVIEW RETURNED	15-Apr-2016

GENERAL COMMENTS	The authors have answered part, but not all of my concerns. 1) there is no answer provided to concern regarding the number of subjects needed given the different data used from the publication on which is based the present protocol 2) the mention that this study will not conclude on the superiority or not of NIV over high flow, and therefore on the best means to ensure preoxygenation is still missing.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

The authors have answered part, but not all of my concerns.

1) there is no answer provided to concern regarding the number of subjects needed given the different data used from the publication on which is based the present protocol
2) the mention that this study will not conclude on the superiority or not of NIV over high flow, and therefore on the best means to ensure preoxygenation is still missing.

We understand the reviewer concerns.

R1) We now tried to be more clear in which way our senior statistician provided the number needed to treat for the present study. We used our large data base of the FRIDA REA study including 1400 ICU intubation procedures (De Jong et al AJRCCM 2013) added with another data base from 244 ICU intubation procedures from our group (Jaber et al ICM 2010) and a third data base from our princeps study including 53 ICU intubation procedures (Baillard et al CCM 2006). Pooling all these three data base in which the lowest saturation per intubation procedure was collected prospectively, we obtained a set of 1697 ICU intubation procedures.
Then, the main hypothesis is that the lowest oxygen saturation observed in the reference group (NIV alone) will increase of 5% in the interventional group (NIV combined to HFNC), with a standard deviation of 6%, at a two-sided α level of 0.05 and a statistical power of 80%. To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement before intubation, 25 patients will be included in each group. In the revised version, we update the references of the papers which allowed to obtain the large data base. We focused mainly on the oxygen saturation increase (+5%) in the interventional group (NIV combined to HFNC) compared to the reference group (NIV alone), given a standard deviation of 6% (obtained from the large data base), instead of the hypothetic and speculative exact expected lowest value.

R2) We agree with the reviewer that further studies are need to better evaluated the superiority or not of NIV alone over high flow alone.

On the previous version, we changed the conclusion as follows: " In conclusion, the OPTINIV trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that NIV combined to HFNC adding HFNC in combination with NIV in comparison to NIV alone allows to decrease severe hypoxemia during the intubation procedure of hypoxemic ICU patients requiring mechanical ventilation for acute respiratory failure."

We added in the revised version of the manuscript the following sentences (Page 17 Line 30-34): " Moreover, the design of these studies differ from the design of the current study, which allows to specifically study apnoeic oxygenation by HFNC simultaneously combined with NIV preoxygenation. However, the current study will not conclude on the superiority or not of NIV over HFNC alone, and therefore on the best means to ensure preoxygenation."