Critical Care

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Probing the efficacy of high-flow nasal cannula in the treatment of acute exacerbations of COPD with acute-moderate hypercapnic respiratory failure

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To the editor:

Dear Sir,

We have read with great interest the single-centre study by Tan, et al. [1], which concluded that high-flow nasal cannula (HFNC) was not non-inferior to non-invasive ventilation (NIV) and resulted in a higher incidence of treatment failure compared to NIV when used as the initial respiratory support for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and acute-moderate hypercapnic respiratory failure. We commend the authors on conducting this significant study and would like to offer some comments on their work and their findings.

First, although the authors report including 225 COPD patients in the two arms of the study, only 104 (46.2%) of them were current or former smokers. This raises the question: did the remaining patients develop COPD without being smokers? If so, what were the underlying causes of COPD in these patients? Did patients develop COPD due to biomass fuel use and air pollution, or was there another cause of lung obstruction? Given that smoking is the leading cause of COPD in developed countries, it is crucial for the authors to address this aspect of their manuscript. The inclusion of a non-homogeneous study population may significantly impact the validity and applicability of the study's results.

We would also like to pinpoint a discrepancy identified between the protocol of the study submitted to the Chinese Clinical Trials Registry [2] and the published paper. In the study protocol, it seems that the authors reported their intention to include 43 patients in each study arm, totaling 86 patients. How did they determine that number, and how do they explain the discrepancy with the power analysis presented in the "Materials and Methods" section of the published study [1]? An explanation addressing these differences would be valuable for clarifying the study's design and statistical considerations.

In addition, an obvious and widely accepted advantage of HFNC over a respiratory mask is the comfort it provides, allowing for easier daily activities and better compliance [3]. Patients using HFNC, unlike those on NIV interfaces, can eat, drink, cough, remove sputum, and converse with healthcare practitioners and family while undergoing therapy. Therefore, we are confounded as to why the overall duration of HFNC and NIV therapy appeared to be non-significantly different, indicating that patients on HFNC had to remain on conventional oxygen therapy (COT) for the same duration as those with NIV. Even in the first two days, some patients on HFNC continued with COT for over half of the day, something that might have affected the effectiveness of the intervention and the outcomes of the study.

This comment refers to the article available online at https://doi.org/10.1186/s13054-024-05040-9.

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Furthermore, we agree with the authors that the initial gas flow rate set at 40 L/min is indeed a limitation, as the authors themselves question whether higher flow rates might have been more effective in removing carbon dioxide. Previous studies [4] have indicated that higher flow rates exceeding the patient's peak inspiratory flow, can improve oxygenation, increase positive end-expiratory pressure, enhance carbon dioxide washout, and reduce the work of breathing. Although in some cases patients with expiratory flow limitations may have small tidal volumes and even 40 L/min could be enough to exceed their peak inspiratory flow, they would still benefit from higher airway pressures that can be achieved by higher NHF flow rates. Therefore, using lower flow rates might have influenced the study's outcomes. Additionally, in conjunction with the previous paragraph, there is also the question of whether the patients were on HFNC when the decision of treatment failure was made, and if so, at what flow rate.

Finally, although the authors mention that carbon dioxide retention was the most common reason for failure in the HFNC group, pH levels at all study points were similar to those observed with NIV. This finding is interesting and may indicate that physicians who are more familiar with NIV might be more likely to switch patients from HFNC to NIV, rather than the other way around. Moreover, the Kaplan–Meier graph in Fig. 2 shows that until day 3, failure rates were comparable between the study arms. From day 4 onwards, the gap between the curves widens, indicating a higher failure rate in the HFNC group. Given that the real difference between the two groups consisted of patients who were intubated, we would like to highlight that, based on our experience, intubating patients with moderate AECOPD more than 72 h after admission is extremely rare. It would be useful if the authors could provide a detailed explanation and breakdown of the patients who failed treatment to better understand this discrepancy.

In conclusion, all of the aforementioned factors may have contributed to the marginally statistically significant difference observed between the two groups in terms of treatment failure. Future well-designed studies are needed to better understand the role of HFNC in treating patients with AECOPD and acute-moderate hypercapnic respiratory failure.

Acknowledgements
None

Author contributions
I.P. and G.M. were involved in the conceptualisation and writing of the manuscript. I.P. was the supervisor of the work. All authors reviewed the manuscript.

Funding
None.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 July 2024 Accepted: 31 July 2024
Published online: 05 August 2024

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