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CORRESPONDENCE

Effect of high flow nasal cannula therapy may be modified by PaO_2/FiO_2 ratio in acute hypoxemic respiratory failure

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Dear Editor,

Recently, Rochwerg et al. [1] published a meta-analysis reporting that high flow nasal cannula (HFNC) therapy may decrease intubation rates when compared to conventional oxygen support. Despite its rigorous design, this study suffers several limitations. Firstly, contrary to prior systematic reviews on this topic [2], Rochwerg et al. excluded studies investigating the efficacy of HFNC post-extubation. While this selection was intended to decrease case-mix heterogeneity, there is no proof that this was indeed necessary. Excluding these trials may have increased selection bias and, through sample size reduction, diminished the stability of their findings. Secondly, when testing the robustness of the results in sensitivity analysis by excluding one trial at a time, the seeming advantage of HFNC for decreasing the rate of intubation became non-significant without data from three trials shown in Fig. 3 in the original paper (Jones-2016, Frat-2015, Azoulay-2018). We, therefore, broadened the literature search to include trials evaluating the efficacy of HFNC post-extubation and reanalysed the data. Overall eleven studies were identified, with intubation rates ranging between 0% (Rittayamai-2015) and 42% (Frat-2015). Trials with high intubation rates (approximately $\geq 10\%$) reported significantly lower baseline PaO_2/FiO_2s, compared to those with low intubation rates (Frat-2015, Lemiale-2015, Azoulay-2018). Meta-regression [3] showed that baseline PaO_2/FiO_2 (>200 or ≤ 200 mmHg) was a significant contributor to heterogeneity ($p=0.017$). We, therefore, studied these subgroups separately and discovered that the advantage of HFNC was significantly greater and more stable in trials with high PaO_2/FiO_2s (>200 mmHg) compared to trials with low PaO_2/FiO_2s (≤ 200 mmHg), with no significant heterogeneity (Fig. 1). Thirdly, as patho-physiological mechanisms (e.g., inspiratory effort, lung volume) differ with hypoxemia and post-extubation, additional subgroup analysis was performed based on population type. For hypoxemic patients with $PaO_2/FiO_2 > 200$ mmHg, the pooled outcome was non-significant (RR 0.51, 95% CI 0.24–1.08). For patients post-extubation with $PaO_2/FiO_2 > 200$ mmHg the pooled benefit was significant (RR 0.37, 95% CI 0.16–0.91). For hypoxemic patients with a low PaO_2/FiO_2 the pooled benefit was non-significant (RR 0.87, 95% CI 0.75–1.01). Finally, since the benefit of HFNCs differed in patients with different PaO_2/FiO_2, the fragility index (FI) was calculated, i.e., the number of negative events that need to become positive to make the non-significant outcome become significant (Fig. 1). The FI was significantly lower in the subgroup of high PaO_2/FiO_2 than in that with low PaO_2/FiO_2 (3.4 ± 1.3 vs. 7.6 ± 2.3, $p=0.004$), which suggests that in studies with a high PaO_2/FiO_2, the conclusions are less stable due to under-powering. Further studies are needed to verify our findings.

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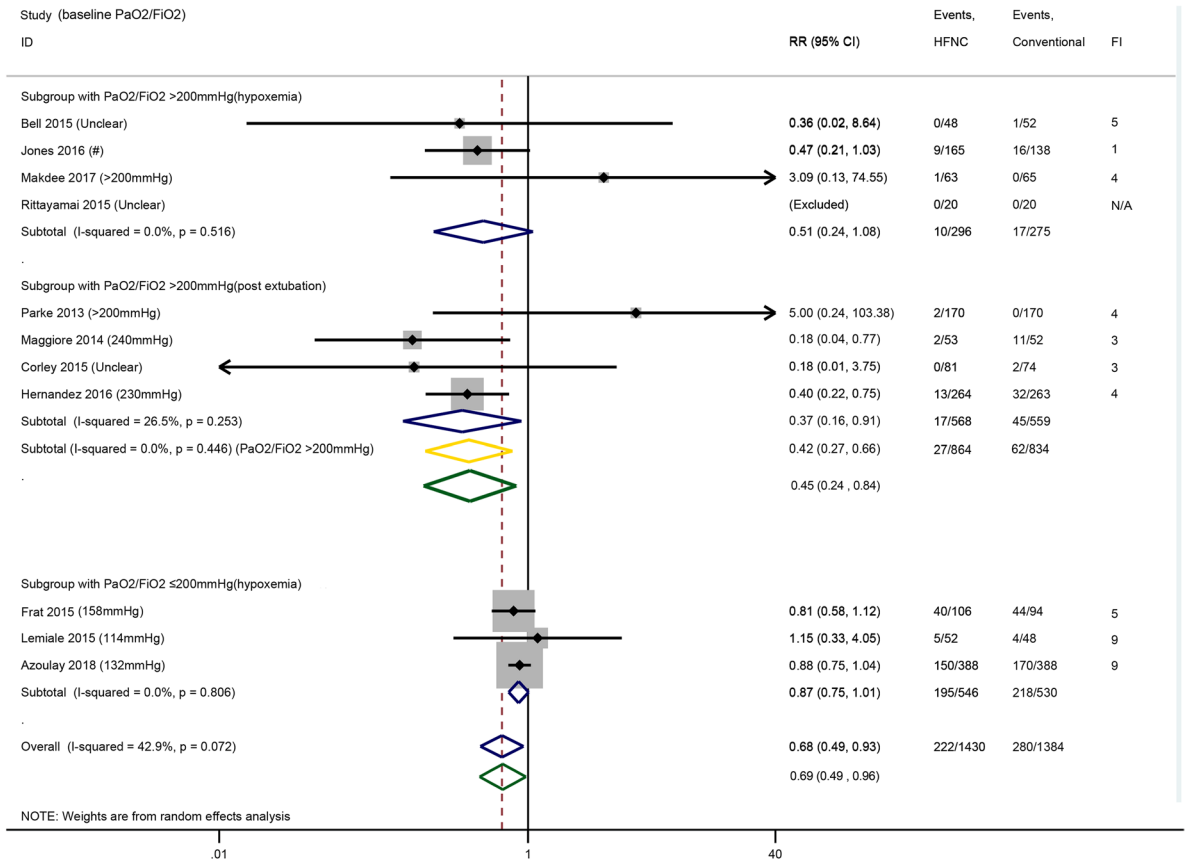

Fig. 1 Forest plot comparing the intubation rate of HFNC and conventional oxygen therapy in hypoxemic respiratory failure. The overall heterogeneity was significant ($I^2 = 42.9\%$) after including post-extubation trials. All the 11 trials were divided into two subgroups according the baseline PaO_2/FiO_2 (> 200 or ≤ 200 mmHg), and the heterogeneity of each subgroup was non-significant. For subgroup with high PaO_2/FiO_2, the pooled outcome was significant (yellow symbol) while for subgroup with low PaO_2/FiO_2 was non-significant. Meta-regression indicated that baseline PaO_2/FiO_2 was significant factor for heterogeneity ($p = 0.017$). # in trial of Jones-2016, the mean SpO_2 at study entry is 91.6%, and in trials of Bell-2015 and Corley-2015, the baseline oxygenation status was unclear. Thus, we also performed a sensitivity analysis by excluding trials of Bell-2015 and Corley-2015, the p value of PaO_2/FiO_2 in meta-regression remain significant ($p = 0.029$) and the conclusion remain stable (green symbol)

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Compliance with ethical standards

Conflicts of interest
No conflict of interest was involved in this study.

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