Appendix I. Post-hoc Subgroup Analysis

Post-hoc subgroup analysis of PaCO2 levels for starting NIPPV in patients with COPD

Background

In patients with chronic obstructive pulmonary disease (COPD), there is variability regarding the level of hypercapnia (PaCO2) that is considered as a prerequisite for initiation of noninvasive positive pressure ventilation (NIPPV). This variability exists in clinical practice, guideline recommendations, and patient enrollment criteria for comparative effectiveness studies.

For example, guidelines included in this review used the following criteria to consider initiation of NIPPV in patients with COPD: stable daytime PaCO2 >50mmHg, ≥ 50mmHg, and >55mmHg. Some guidelines used lower thresholds (i.e. PaCO2 46-50mmHg or PaCO2 50-54mmHg) when other characteristics were present (such as nocturnal hypercapnia, nocturnal hypoxia, recurrent exacerbations, or severe exacerbations requiring ventilatory support). Other guidelines did not specify which PaCO2 levels constituted "hypercapnia." In clinical practice, for example, the United States Centers for Medicare and Medicaid Services (CMS), uses a PaCO2 ≥ 52mmHg for initiation of BPAP for patients with COPD.[84] In this systematic review, we identified eleven studies (most of which were published in the past 10 years) that used PaCO2 levels of >45mmHg as inclusion criteria for initiating NIPPV, somewhat lower than was considered in many guidelines and clinical practices.

To evaluate the impact of PaCO2 initiation threshold on clinical outcomes, we searched for, but ultimately found no included studies which directly assessed this association. Based on reviewers' comments, we performed a post-hoc subgroup analysis of individual included studies to indirectly assess if higher PaCO2 thresholds to initiate NIPPV were associated with larger effect sizes for the 4 primary clinical outcomes (mortality, need for intubation, quality of life and all-cause hospital admissions).

Methods

We included studies which enrolled patients with COPD, reported one of the 4 primary outcomes (mortality, need for intubation, quality of life, and all-cause hospital admissions), and reported a daytime stable PaCO2 threshold for initiation of NIPPV. We excluded studies that did not report a PaCO2 threshold or that reported a PaCO2 threshold during an episode of acute respiratory failure. To evaluate if there was a dose response (higher cutoffs associated with increasingly better outcomes), and in the setting of PaCO2 ≥ 52mmHg threshold commonly used in the United States, we defined the PaCO2 threshold categories as: 1) PaCO2 ≥45 to 49 mmHg, 2) PaCO2 ≥50 to 51 mmHg, and 3) PaCO2 ≥52 mmHg or greater. The other methods and analysis were identical to the methods used in the main report.

Results

The post-hoc subgroup analysis was only possible for studies comparing BPAP use with no device use. When compared BPAP use to no device use in patients with COPD, 16 studies,[8, 10, 14, 15, 23, 29, 46, 70, 85 16, 30, 38, 43, 49, 64, 66] 11 RCTs, and 6 observational studies reported at least one of the 4 primary outcomes (mortality, need for intubation, quality of life and all-cause hospital admissions). We excluded 4[10, 29 30, 70]of these 16 studies from the subgroup analyses as two studies[30, 70] did not report PaCO2 threshold cutoffs and two studies[10, 29] measured PaCO2 cutoff during episodes of acute respiratory failure. Twelve studies were included in the subgroup analyses. The risk of bias of these 12 studies was rated as moderate to high similar to those in the main analysis. Findings are presented in Figures 1-3. These findings suggested that higher PaCO2 levels may be associated with improved quality of life compared to lower levels (PaCO2 ≥52 mmHg: SMD 0.22; 95% CI: -0.05 to 0.50 vs. PaCO2 ≥50 to 51: 0.97; 95% CI: 0.36, 1.58 vs. PaCO2 ≥45 to 49: -0.05; 95% CI: -0.16 to 0.06). The effect size for quality of life for cutoff PaCO2 ≥50 to 51 mmHg was also higher than the overall effect size (SMD: 0.97; 95% CI: 0.36 to 1.58 vs. SMD: 0.15, 95% CI: -0.03 to 0.32); however, this was driven by a single nonrandomized study. Differences in mortality and hospital readmissions favored higher initiation criteria but were not statistically different. There were no other significant difference between the subgroups and overall pooled effect sizes.

Conclusions

No included studies directly evaluated the association between clinical outcomes with different levels of hypercapnia as a criterion to initiate NIPPV in patients with COPD. In this post-hoc subgroup analysis of RCTs and observational studies, which compared BPAP use to no device use, there were no differences in mortality or all-cause hospital admissions based on PaCO2 threshold initiation criteria. There was a statistically significant larger improvement in quality of life with higher PaCO2 threshold initiation criteria (PaCO2≥50 to 51compared to PaCO2 ≥45 to 49). These findings suffer a high risk of bias and do not warrant high strength of evidence.