Original Article

A change from high-flow to titrated oxygen therapy in the prehospital setting is associated with lower mortality in COPD patients with acute exacerbations: an observational cohort study

LP Bentsen, AT Lassen, IL Titlestad & M Brabrand

Abstract

Background: *The aim of this study was to investigate 30-day mortality for COPD patients treated by ambulances in the period before and after implementation of a pre-hospital oxygen protocol.*

Methods: *Prehospital High-flow oxygen was used from April to September 2012 and titrated oxygen from April to September 2013. Primary outcome was 30-day mortality.*

Results: *707 patients were included; 209 in the high-flow group and 498 in the titration group. Of these, 56 and 132 arrived with acute exacerbation (AE). Overall 30-day mortality was 11.5% vs. 9.4% (p=0.41), respectively. For patients with AE, it was 19.6% vs. 4.6% (p=0.001).*

Conclusion: *Change of treatment protocol is associated with a lower 30-day mortality for patients registered with acute exacerbation, but not for all COPD patients.*

Keywords

Oxygen, Pre-hospital, COPD, Exacerbation, Mortality

Key points

- COPD patients with acute exacerbations have higher mortality when oxygenated above 92%
- Many COPD patients received inappropriate oxygen therapy, most likely due to air-driven nebulization not being available in the pre-hospital setting

Lasse Paludan Bentsen
MD, Emergency Department, Odense University Hospital

Annmarie Touborg Lassen
MD DMSc, Emergency Department, Odense University Hospital and University of Southern Denmark.

Ingrid Louise Titlestad
MD PhD, Department of Respiratory Medicine, Odense University Hospital

Mikkel Brabrand
MD PhD, Emergency Department, Hospital of South West Jutland and Emergency Department, Odense University Hospital and University of Southern Denmark.

Correspondence
Lasse Paludan Bentsen
MD, Emergency Department, Odense University Hospital
Email: lasse.paludan.bentsen@rsyd.dk

Background

Mortality in chronic obstructive lung disease (COPD) patients with acute exacerbations (AEs) is high due to respiratory failure.[1] There has been an increased focus on the use of oxygen in the treatment of COPD patients in recent years, especially in the context of pre-hospital management.[2] Even though oxygen therapy is used in many protocols for critically ill patients, there is a lack of evidence supporting the use of high-flow oxygen.[3] Ringbaek et al.[4] reported that a substantial portion of COPD patients with AEs are transported to the hospital by ambulance. Although low-dose oxygen therapy has been shown to be effective in a hospital setting,[5] its generalizability to a pre-hospital setting is unclear, as patients in a pre-hospital setting may be less well-defined, and the personnel that attend to them may have a range of experience and qualifications. Austin et al.[6] showed that the pre-hospital use of titrated oxygen combined with air-driven nebulised delivery of bronchodilator agents can decrease mortality rates in COPD patients compared to treatment with high-flow oxygen.

Until September 26, 2012, when a new protocol was implemented, COPD patients received high-flow oxygen via a non-rebreather mask plus oxygen-driven nebulisation in the pre-hospital environment in most parts of Denmark. According to the new protocol, oxygen treatment was revised so that it was titrated to a measured saturation level of 88% to 92% and combined with oxygen-driven nebulisation bronchodilator delivery. The changes in the protocol aimed to decrease mortality in patients receiving high-flow oxygen during pre-hospital transit.

The aim of this study was to investigate and compare the 30-day mortality of COPD patients treated by ambulance paramedics in the period before and after implementation of a pre-hospital titrated oxygen protocol in Denmark. We hypothesized that the change in treatment protocol from high-flow to

© 2020 Rila Publications Ltd.

titrated therapy has lowered the mortality for COPD patients.

Methods

Study design

We conducted a retrospective register study of COPD patients treated by ambulance paramedics and emergency medical technicians (EMT) arriving at the emergency department (ED) of Odense University Hospital (OUH).

The ED of OUH is a 48-bed highly specialised emergency department which sees around 315 patients every day for many different specialities, totalling more than 100,000 patient contacts a year. Some aspects of the Danish pre-hospital emergency medical system (EMS) differ in the five regions of the country. In southern Denmark, ambulances are staffed by at least 2 EMTs and sometimes by a paramedic. Some areas in the southern Denmark region have a paramedic-staffed first response vehicle along with a medical emergency care unit (MECU), which is a vehicle staffed with a prehospital anaesthesiologist plus either an EMT or a paramedic who acts as an assistant to the physician. All ambulances and emergency vehicles are dispatched by the dispatch centre after either a call from a general practitioner or after a call to the nationwide emergency number (1-1-2). An ambulance is dispatched to all emergency calls; depending on the call type, the severity of the situation and the availability of the support units, the ambulance is supported to some extent by either a paramedic first response vehicle or by a MECU. A few patients are transported by helicopter if necessary, usually due to long travel distances for time-critical patients. A helicopter is dispatched if deemed necessary by the EMS personnel, who work under the supervision of a medical doctor who has primary responsibility for the protocols used for patient treatment.

Patient population and data sources

This study included data that were collected from patients admitted to the ED of OUH from April 2012 until the end of September 2012 (the high-flow period) and from April 2013 to the end of September 2013 (the titrated period). October 2012 to March 2013 was considered a fade-out period, and data from this period were not included in the study. For *inclusion, patients had to be adults* (≥18 years old), *previously discharged from a Danish hospital with a primary or secondary diagnosis of COPD (ICD10 code of J44-449) and admitted to the OUH during the study periods. Patients were excluded if they did not arrive at the ED by ambulance, were treated by a pre-hospital medical emergency care unit that was staffed by an anaesthesiologist and an EMT, did not receive pre-hospital oxygen therapy or if they had been* admitted to the ED within the previous 90 days.

Data collection and measurements

Clinical data for non-invasive ventilation [NIV] were extracted from electronic patient files. NIV use was recorded by the treating physician or supporting secretary by yes/no registration plus the time the procedure started. Comorbidities (Charlson Comorbidity Index) were recorded, ICU admittance, and the length of the hospital stay was identified from the Danish National Patient Registry.[7] The Charlson Comorbidity Index was calculated using data from the Danish National Patient registry—this index has been validated and shown to have a high positive predictive value for mortality.[8] Demographic data, including mortality data, were retrieved from the Danish Civil Registration System.[9] All data were linked using the personal identification number that all Danish citizens use in all contacts with the health care system.[7]

The following were determined from the ambulance case records: response time, time at the scene, transport time to hospital, whether the patient received salbutamol inhalations, the amount of oxygen therapy, the first ambulance-measured oxygen saturation level, blood pressure, pulse, Glasgow Coma Score and respiratory frequency. Ambulance data are described in detail in a previous publication.[10] The primary outcome was 30-day all-cause mortality. The secondary outcomes were 7- and 90-day mortality, length of hospital stay, direct discharge from the ED, ICU admittance, hospitalisation within the first 48 hours after arrival and the need for intubation or NIV. The overall cohort included all COPD patients in the study. Arterial gas analyses completed within the first 4 hours after arrival were extracted and analysed for pH, pCO2, pO2 and respiratory acidosis (Defined as pH <7.35 and pCO2 >5.99). We also conducted a subgroup analysis of patients with a discharge diagnosis of AE of COPD (the AECOPD subgroup); this diagnosis was defined as an ICD-10 code of J440 or J441.

Statistics and data analysis

Data are presented as medians (interquartile ranges, IQRs) or as proportions (95% confidence intervals, 95%CIs). To compare differences between groups, we used Pearson's chi-squared test to analyse binary outcomes and the Mann-Whitney test to analyse numerical data. Proportions and Odds ratios (ORs) with 95%CIs were calculated for 7-, 30- and 90-day mortality. A two-sided p value <0.05 was considered significant. Survival in subgroup analyses is presented using Kaplan-Meier plots. Patients with missing

© 2020 Rila Publications Ltd.

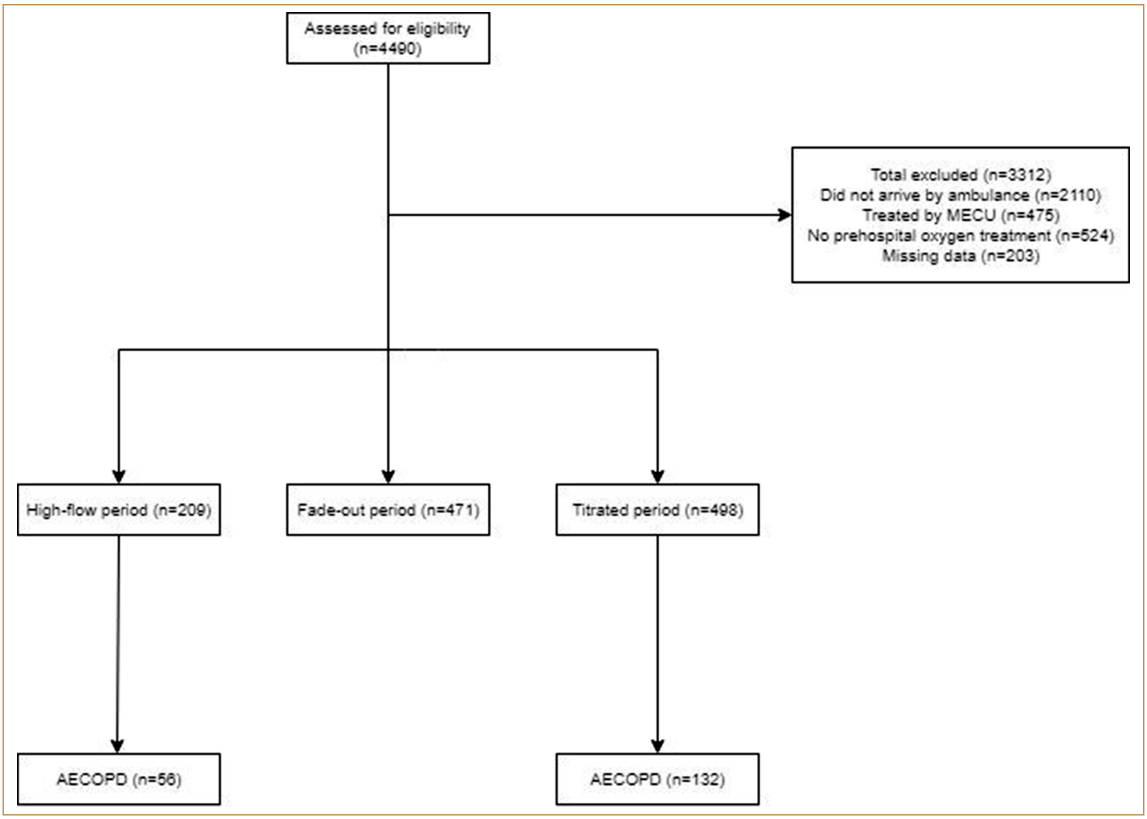

Figure 1. Flow diagram showing study inclusion and exclusion MECU: Medical emergency care unit

data were excluded from the study. Due to too few events, we did not perform multivariable analyses. Statistical analyses were performed using Stata 15.1 (StataCorp LP, Texas, USA).

Ethics

This study was approved by the Danish Data Protection Agency (file no. 15/43847) and by the National Board of Health (file no. 3-3013-355). Approval by the regional ethics committee was not required under Danish law. Consent from the included patients was not needed due to the approvals that were granted for this study.

Results

A total of 4,490 patients were admitted to the ED at OUH who had either a previous primary or secondary discharge diagnosis of COPD. A flow chart of patient inclusion and exclusion is shown in Figure 1. The study included 707 patients, 209 in the high-flow period and 498 in the titrated period. Of these, 188 patients, 56 in the high-flow period and 132 in the titrated period, had a discharge diagnosis related to AE. The baseline characteristics of the patients are shown in Table 1.

For the overall COPD group, the ambulance response time to the scene was 7 (5–11) min vs. 10 (6–15) min ($p<0.001$) in the high-flow period and the titrated period, respectively; for the AECOPD subgroup, the corresponding times were 7 (5–11) min vs. 10 (6–15) min ($p=0.047$). In the overall COPD group, 101 (48.3%) vs. 190 (38.2%) patients ($p=0.01$) received salbutamol inhalations in the high-flow period and the titrated period, respectively; for the AECOPD subgroup, the corresponding numbers were 40 (71.4%) vs. 91 (68.9%) ($p=0.73$).

For the overall COPD group, the 30-day mortality was 11.5% vs. 9.4% ($p=0.41$) in the high-flow period and in the titrated period, respectively; for the AECOPD subgroup, the corresponding figures were 19.6% vs. 4.6% ($p=0.001$). There was no significant difference in the 7-day or 90-day mortality in the two periods for the COPD group, but the AECOPD subgroup showed 7-day mortality of 12.5% vs. 2.3% ($p=0.004$) and 90-day mortality of 25.0% vs. 12.2% ($p=0.03$) in the high-flow period and the titrated period, respectively. The OR and 95%CI for 30-day mortality was significant in the AECOPD subgroup (0.44 [0.26–0.75]), and the OR and 95%CI values were 0.38 [0.19–0.76] for 7-day mortality and 0.64 [0.4–0.96] for 90-day mortality in these patients. No other OR findings were significant. We compared mortality to saturation levels of <88% to 88-92% and >92% using logistic regression. We found that was no significant difference in 30-day

© 2020 Rila Publications Ltd.

Table 1. Baseline data of the patients in this study

		High-flow n=209	Titrated n=498	Total n=707	p value	High-flow AECOPD n=56	Titrated AECOPD n=132	Total AECOPD n=188	p value
Age, years, median (IQR)		74 (66–81)	74 (67–82)	74 (67–82)	0.89	73 (68–80)	71 (66–78)	71 (66–79)	0.17
Male, n (%)		85 (40.7%)	234 (47.0%)	319 (45.1%)	0.12	18 (32.1%)	55 (41.7%)	73 (38.8%)	0.22
Charlson Comorbidity Index, n (%)									
Low = 0		13 (6.2%)	21 (4.2%)	34 (4.8%)	0.26	1 (1.8%)	9 (6.8%)	10 (5.3%)	0.16
Moderate = 1–2		100 (47.9%)	253 (50.8%)	353 (49.9%)	0.47	33 (58.9%)	77 (58.3%)	110 (58.5%)	0.94
High = 3+		96 (45.9%)	224 (45.0%)	320 (45.3%)	0.82	22 (39.3%)	46 (34.9%)	68 (36.2%)	0.56
Systolic blood pressure*		144 (126–165)	143 (125–165)	143 (125–165)	0.30	144 (125–163)	149 (136–170)	148 (133–169)	0.65
Diastolic blood pressure*		82 (71–96)	80 (69–94)	89 (70–94)	0.22	79 (71–91)	85 (74–98)	84 (72–97)	0.20
Pulse*		98 (82–113)	99 (84–111)	99 (83–112)	0.96	105 (91–118)	103 (94–115)	103 (93–115)	0.41
Glasgow Coma Score*		15 (15–15)	15 (15–15)	15 (15–15)	0.66	15 (15–15)	15 (15–15)	15 (15–15)	0.57
Respiratory rate*		24 (18–28)	24 (20–30)	24 (20–28)	0.09	24 (22–28)	28 (22–32)	27 (22–30)	0.06
Saturation by pulse oximetry*		93 (88–96)	93 (88–96)	93 (88–96)	0.53	92 (84–96)	91 (85–95)	91 (85–96)	0.36
Prehospital emergency call time	**Response time, min, median (IQR)**	7 (5–11)	10 (6–15)	9 (6–14)	<0.000**	7 (5–11)	10 (6–15)	9 (6–15)	0.047**
	Transit time, min, median (IQR)	34 (28–41)	35 (28–42)	34 (28–42)	0.24	33 (26—41)	34 (28–43)	34 (27–42)	0.74
Prehospital treatment	**Salbutamol inhalation, n (%)**	101 (48.3%)	190 (38.2%)	291 (41.2%)	0.01**	40 (71.4%)	91 (68.9%)	131 (69.7%)	0.73
	Oxygen therapy, L/min (SD, median, IQR)	12 (6–14)	12 (6–15)	12 (6–15)	0.11	13 (4–15)	14 (6–15)	14 (6–15)	0.75

*First ambulance measurement. **Significant (p value ≤0.05). 'Salbutamol inhalations' indicates the number of patients who received salbutamol. AECOPD: Acute exacerbations of COPD (known discharge diagnosis of J440 or J441).

mortality in the overall COPD cohort. For 7-day mortality there was a significant higher mortality in the group with >92% of OR 6.30 [2.73-14.54] and for 90-day mortality there was no significant difference. When comparing for AECOPD OR for 30-day mortality was 2.68 [1.51-4.77]. For 7-day and 90-day mortality for AECOPD it was 9.85 [1.18-82.42] and 2.49 [1.56-3.96] respectively. We did not find any significant difference in mortality levels comparing <88% to 88-92%.

In the COPD group, 9.1% vs. 11.7% (p=0.32) received NIV in the high-flow period versus in the titrated period; the corresponding figures were 21.4% vs. 22.0% (p=0.94) for the AECOPD subgroup. There were no significant differences between the two periods in terms of the number of patients discharged directly from the ED, hospital length of stay, hospitalization in the ICU or use of invasive ventilator therapy. The primary and secondary outcomes are shown in Table 2, and Kaplan-Meier survival plots for 30-day mortality are shown for both the overall COPD group (Figure 2) and the AECOPD subgroup (Figure 3).

© 2020 Rila Publications Ltd.

A change from high-flow to titrated oxygen therapy in the prehospital setting is associated with lower mortality in COPD patients with acute exacerbations: an observational cohort study

Table 2. Primary and secondary outcomes

	High-flow n=209	Titrated n=498	Total n=707	p-value	High-flow AECOPD n=56	Titrated AECOPD n=132	Total AECOPD n=188	p-value
30-day mortality, n (%)[1]	24 (11.5%)	47 (9.4%)	71 (10.0%)	0.41	11 (19.6%)	6 (4.6%)	17 (9.0%)	0.001**
7-day mortality, n (%)[2]	13 (6.2%)	25 (5.0%)	38 (5.4%)	0.39	7 (12.5%)	3 (2.3%)	10 (5.3%)	0.004**
90-day mortality, n (%)[3]	30 (14.4%)	87 (17.5%)	117(16.6%)	0.31	14 (25.0%)	16 (12.2%)	30 (16.0%)	0.03**
Hospitalization								
Discharged directly from the ED on day 0, n (%)	42 (20.1%)	127 (25.5%)	169 (23.9%)	0.12	8 (14.3%)	20 (15.2%)	28 (14.9%)	0.88
Length of stay in medical or surgical ward if not directly discharged, days, median, (IQR)	2 (1-5)	2 (1-6)	2 (1-6)	0.052	2 (1-5)	2 (1-5)	2 (1-5)	0.92
Referral to Intensive care unit within 48 hours, n (%)	7 (3.4%)	18 (3.6%)	25 (3.5%)	0.86	2 (3.6%)	4 (3.0%)	6 (3.2%)	0.85
Invasive ventilator therapy, n (%)	2 (1.0%)	3 (0.6%)	5 (0.7%)	0.61	0 (0.0%)	1 (0.8%)	1 (0.5%)	0.51
NIV, n (%)	19 (9.1%)	58 (11.7%)	77 (10.9%)	0.32	12 (21.4%)	29 (22.0%)	41 (21.8%)	0.94
Time to NIV, hours, median, (IQR)	12 (9-16)	7 (3-22)	10 (4-20)	0.39	13 (10-18)	7 (4-21)	12 (5-20)	0.14

**Significant with a p-value ≤0.05. AECOPD: Acute exacerbations of COPD (known discharge diagnosis of J440 or J441). The OR [95%CI] values for mortality were as follows: [1]0.90 [0.69-1.16] for COPD and 0.44 [0.26-0.75] for AECOPD; [2]0.89 [0.63-1.26] for COPD and 0.40 [0.20-0.81] for AECOPD; [3]1.12 [0.90-1.41] for COPD and 0.64 [0.43-0.96] for AECOPD.

We found no differences in pH, pO2, pCO2 or the amount of patients with respiratory acidosis within the first 4 hours after arrival (Table 3).

Discussion

This retrospective cohort study found that changing the oxygen treatment protocol from high-flow oxygen to titrated oxygen did not change the 30-day mortality for the overall group of COPD patients treated in ambulances in Denmark. However, patients who were discharged with diagnosed AECOPD had a significantly lower 30-day all-cause mortality when they were treated using the titrated oxygen therapy protocol. Notably, the levels of oxygen therapy given in the ambulance were not different in the overall COPD patient group than in the AECOPD patient subgroup.

The results in our study are not directly comparable to two previous studies on the same subject by Austin et al.[6] and Ringbaek et al.[4] Austin et al. included patients with breathlessness, age >35 years and a history or risk of COPD. Ringbaek et al. included patients with a discharge diagnosis of COPD exacerbation (ICD-10 diagnosis J440 or J441). Comparing our study to that of Austin et al. is difficult due to differences in the populations and treatments.

Surprisingly, the measured levels of oxygen delivery found, were not as high as expected using the high-flow protocol. There could be two reasons

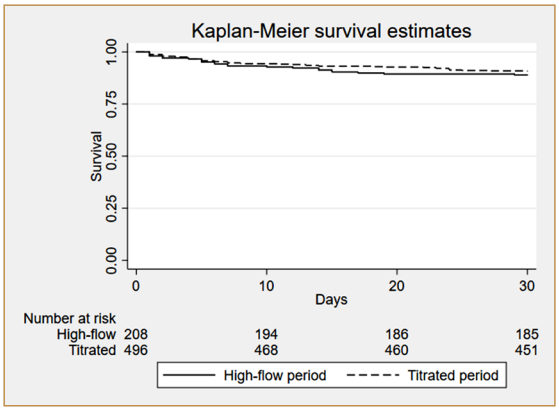

Figure 2. Kaplan-Meier plot for patients with COPD
COPD: Chronic obstructive pulmonary disease

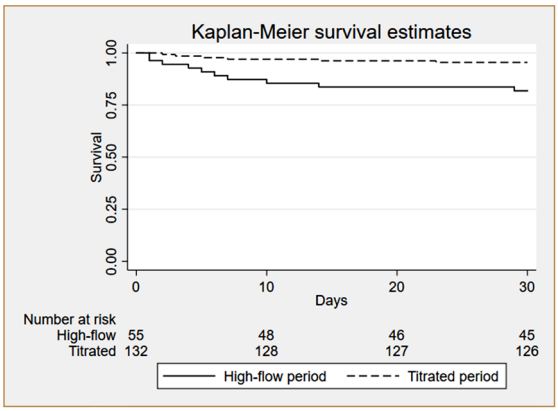

Figure 3. Kaplan-Meier plot for patients with AECOPD
AECOPD: Acute exacerbation of chronic obstructive pulmonary disease. AECOPD was defined as a diagnosis of J440 or J441.

© 2020 Rila Publications Ltd.

Table 3. Arterial gas analysis in the first 4 hours after arrival

	High-flow n=209	Titrated n=498	Total n=707	p value	High-flow AECOPD n=56	Titrated AECOPD n=132	Total AECOPD n=188	p value
pH	7.40 (7.33-7.45)	7.41 (7.36-7.45)	7.41 (7.35-7.45)	0.34	7.37 (7.30-7.43)	7.39 (7.33-7.42)	7.38 (7.32-7.42)	0.58
pCO2	5.79 (4.72-7.08)	5.77 (4.93-7.23)	5.77 (4.87-7.2)	0.98	6.15 (4.79-8.91)	6.59 (5.47-8.5)	6.53 (5.42-8.74)	0.73
pO2	10.7 (8.27-14.3)	10.1 (8.44-13.0)	10.2 (8.4-13.7)	0.36	11.1 (8.78-13.9)	10.6 (8.44-14.5)	10.65 (8.51-14.45)	0.48
Respiratory acidosis*	32 (15.31%)	78 (15.66%)	110 (15.56%)	0.91	17 (30.36%)	39 (29.55%)	56 (29.79%)	0.91

*defined as pH <7.35 and pCO2 >5.99. AECOPD: Acute exacerbations of COPD (known discharge diagnosis of J440 or J441).

for this. First, the ambulance personnel might already have initiated titrated oxygen delivery to more appropriate saturation levels, even though this was not the protocol at the time. Second, the time it took to provide nebulisation therapy may have used a larger proportion of the transit time, so that patients experienced a longer time with a lower oxygen flow compared to the use of regular supplementary oxygen

The difference in delivered oxygen therapy in the pre-hospital setting of our study did not differ in the two treatment groups. This could be due to registration of such therapy, as only one therapy level was recorded in the ambulance records, even though the patients might have received different levels of therapy, especially in the titrated period. This is a large confounder when it comes to baseline data, as patients may have had various SpO_2 levels during transit time to the ED.

When we compared mortality and saturation levels instead of periods, we found a significantly higher mortality for patients having a saturation of >92% when looking at 7-, 30- and 90-day mortality. We did not find this difference when comparing the overall COPD group, other than the 7-day mortality. This is in line with the findings of Ringbaek et al. However, we did not find any significant difference in the comparison between <88% compared to 88-92%. This could be due to few patients with a saturation level of less than 88% or simply that it is more problematic for this patient group to have high saturation levels than low compared to the currently recommended saturation goal of 88-92%.

Strengths and limitations

The main strength of this study was our use of data from Danish registers, which have been validated for clinical research.[7] However, we did not validate individual COPD diagnoses and therefore cannot say whether any patients received this diagnosis in error. We also used the registers for follow-up (in terms of outcome parameters), thus ensuring high validity.

This study has several limitations. It was a retrospective study, and there were 203 patients with missing data. Most of these missing data were from ambulance records, which were written on paper until September 1, 2015. Some data were lost either because of illegible writing or because the data was simply not noted or scanned. This creates a high risk of selection bias, as we cannot say if the most ill patients or the least ill patients were the ones with missing data. Registration of the COPD diagnosis in the Danish National Patient Registry in relation to respiratory insufficiency, pneumonia and AEs was validated in 2011.[11] Because of the positive predictive value of 92%, the patients included in the study were likely to have correct diagnoses. The issue is that patients who were not registered as having COPD might not have been included in our study; notably, Thomsen et al. found a negative predictive value of 81%. Thus, potential patients could have been left out of this study.

We can only speculate about possible reasons for the large difference in group size in the two periods. One explanation is coding practices. Specifically, the ED at OUH was reorganized during the study period, which may have affected documentation. More patients received salbutamol inhalations in the high-flow period compared to the titrated period (101 vs. 190 p=0.01), which could indicate that coding practices might have been an issue. If the coding practices were changed during this period, changes in the data could be biased in two ways. First, perhaps only the most ill patients were registered during this period, resulting in higher than normal mortality levels. Second, the number of patients included in the study could vary, as patients might have been diagnosed with pneumonia (J189) with addition of the COPD diagnosis (J449) instead of COPD with acute lower respiratory infection (J440). This could influence data and inclusion.

The use of salbutamol could also have skewed the numbers, especially in the overall COPD group. If patients did not receive inhalations in the titrated

© 2020 Rila Publications Ltd.

period, even though they might have benefitted from this treatment, one can speculate that their mortality would be higher than expected. This could explain why we did not find a significant difference in mortality in the overall COPD group in the high-flow period versus the titrated period.

If our results were affected by selection bias, this would also affect the generalizability of the findings. While this might be one of the larger studies of oxygen treatment in COPD in a pre-hospital setting, many questions remain. The evidence for oxygen treatment points in one direction, but studies differ on whether oxygen should be administered as high-flow oxygen or should be titrated towards a certain saturation level. The only way to answer this is with a prospective randomized trial.

Conclusion

Implementation of a new titrated oxygen therapy protocol in Denmark in the pre-hospital setting was associated with lower 30-day mortality for AECOPD patients but not for all COPD patients, even though the reported oxygen therapy levels were not significantly different between the groups. Due to several confounding factors, conclusions of this study should be evaluated and applied with caution.

List of abbreviations

AE: Acute exacerbation
AECOPD: Acute exacerbation of chronic obstructive pulmonary disease
COPD: Chronic obstructive pulmonary disease
CPAP: Continuous positive airway pressure
ED: Emergency department
EMS: Emergency medical services
EMT: Emergency medical technician
ICU: Intensive care unit
MECU: Medical emergency care unit
NIV: Non-invasive ventilation
OUH: Odense University Hospital
$PaCO_2$: Partial pressure of CO_2 in kPa
PaO_2: Partial pressure of O_2 in kPa
sO_2: Oxygen saturation as measured by pulse oximetry

Declarations

Approvals

Due to the study design, ethics approval from the regional ethics committee was not required according to Danish law. The study was approved (data access and analysis) by the Danish Data Protection Agency (file no. 15/43847) and from the National Board of Health (file no. 3-3013-355).

Competing interests

The authors declare that they have no competing interests.

Funding

This study was a substudy of the patient@home project (http://www.en.patientathome.dk). Patient@home received funding from the Innovation Fund Denmark and from Syddansk Vækstforum.

Author contributions

LPB and MB helped conceive and design the study, analyse and interpret the data, and write the manuscript. ATL and ILT helped design the study, interpret the data, and write the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Niels Ibsgaard Agerbek, who extracted and organised the data prior to its analysis.

References

1. Chenna PR, Mannino DM. Outcomes of severe COPD exacerbations requiring hospitalization. *Semin Respir Crit Care Med*. 2010;**31(3)**:286-294.
2. Cornet AD, Kooter AJ, Peters MJ, Smulders YM. The potential harm of oxygen therapy in medical emergencies. *Crit Care*. 2013;**17(2)**:313.
3. Meyhoff CS, Staehr AK, Rasmussen LS. Rational use of oxygen in medical disease and anesthesia. *Curr Opin Anaesthesiol*. 2012;25(3):363-370.
4. Ringbaek TJ, Terkelsen J, Lange P. Outcomes of acute exacerbations in COPD in relation to pre-hospital oxygen therapy. *Eur Clin Respir J*. 2015;**1**:1-6.
5. Brill SE, Wedzicha JA. Oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;**9(1)**:1241-1252.
6. Austin M a, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ*. 2010;**341**:c5462.
7. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;**7**:449.
8. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;**11(1)**:83.
9. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;**29(8)**:541-549.
10. Wedzicha W, Brill S. Oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;**25(5)**:1241.
11. Thomsen RW, Lange P, Hellquist B, *et al.* Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. *Respir Med*. 2011;**105(7)**:1063-1068.

© 2020 Rila Publications Ltd.