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Mechanical ventilation of patients on long-term oxygen therapy with acute exacerbations of chronic obstructive pulmonary disease: prognosis and cost-utility analysis

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Abstract *Objective:* To analyze the prognosis and costs of mechanical ventilation in patients with exacerbations of chronic obstructive pulmonary disease (COPD) treated with long-term oxygen therapy.
Design: A prospective cohort study. Follow-up at 1 and 5 years. Cost utility analysis.
Setting: A medical-surgical intensive care unit (ICU) in a university hospital.
Patients: 20 patients with previous COPD treated with long-term oxygen therapy and needing mechanical ventilation due to acute respiratory failure.
Measurements and main results: Mortality in the ICU, in-hospital mortality (ICU plus ward), and mortality at 1 and 5 years, and factors associated with prognosis and cost–utility were assessed. The mean Acute Physiology and Chronic Health Evaluation II score was 20 (median 20 range 12–36). Cumulative mortality was 35 % in the ICU, 50 % in hospital, 75 % at 1 year, and 85 % at 5 years. Factors significantly associated with mortality in the ICU were low levels of albumin ($p = 0.05$) and sodium ($p = 0.01$) at admission. Patients who died in hospital and in the first year after discharge had a lower forced expiratory volume in 1 s (FEV_1) than survivors ($p = 0.03$ and $p = 0.05$, respectively). The cost per Quality Adjusted Life Year (QALY) was U. S. $26283 and U. S. $44602 in a "best" (cost/QALY calculated for the life expectancy in Spain) and a "worst case scenario" (cost/QALY calculated for a 68-year life expectancy), respectively.
Conclusions: Applying mechanical ventilation to COPD patients treated with long-term oxygen therapy carries a high mortality and cost. Factors significantly associated with mortality in the ICU were albumin and sodium concentrations and FEV_1 in hospital and in the first year after discharge.

Key words Lung disease, obstructive · Long-term oxygen therapy · Prognosis · Quality of life · Cost analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the United States and Europe [1, 2]. Acute respiratory failure (ARF) is a common and often fatal complication of COPD, requiring mechanical ventilation on some occasions. It is known that weaning can be difficult in patients with COPD, with the risk of converting them into ventilator-dependents. Therefore, the decision to implement mechanical ventilation is difficult, controversial, and based on subjective impressions due to the poor outcomes classically attributed to COPD, which has an ICU mortality ranging from 16 to 51 % [3–17]

Table 1 Mortality of COPD patients requiring mechanical ventilation for acute respiratory failure in the ICU, in hospital, and long term

Study	Year	ICU mortality (%)	In-hospital mortality (%)	1-year mortality (%)	2-year mortality (%)	5-year mortality (%)
Vandenbergh et al. [3]	1968	50				
Sluiter et al. [4]	1972	35		46		
Burk and George [5]	1973		42			
Kettel [6]	1974				80[b]	
Bone et al. [7]	1978		31			
Petheram and Branthwaite [8]	1980		44			
Gillespie et al. [9]	1986	25		50		
Spicher and White [10]	1987	51	61	72	78	
Kaelin et al. [11]	1987			36[a]		
Menzies et al. [12]	1989	21		62		
Shachor et al. [13]	1989					84
Ludwigs et al. [14]	1991	50	53	58		
Rieves et al. [15]	1993	43				
Nava et al. [16]	1994				60	
Seneff et al. [17]	1995	16	32			

[a] Six-month mortality
[b] Thirty-month mortality

and up to 80% at 30 months (Table 1). Patients previously treated with long-term oxygen therapy present clinical characteristics that make the decision to use mechanical ventilation even more difficult because of a greater severity of their disease. Furthermore, critical care is expensive. The rise in health care costs and expensive high-tech services, such as those provided in ICUs, have caused many experts to investigate the efficiency of services related to expenditure and outcome [18]. Little is known about the prognosis and cost of COPD patients on long-term oxygen therapy requiring mechanical ventilation following severe exacerbations. Thus, the objectives of this study were to study mortality in the acute phase and at 1 and at 5 years of follow-up in patients with COPD, previously treated with long-term oxygen therapy, who needed mechanical ventilation in the ICU due to ARF, and to establish those variables associated with the prognosis and perform a cost-utility analysis.

Patients and methods

A prospective cohort study was carried out during a 2-year period (between 1 February 1992 and 31 January 1994) in a 26-bed medical-surgical ICU in a university hospital. This investigation was approved by the Hospital Ethics Committee and informed consent was obtained from each patient or from his/her legal representative for participation in the study.

The inclusion criterion was patients with COPD, previously treated with long-term oxygen needing mechanical ventilation due to ARF. Patients were being treated with long-term oxygen therapy as prescribed by a pneumologist according to the criteria established by the Spanish Society of Pneumology and Thoracic Society [19]: patients with COPD in a stable phase, free of exacerbations for at least 3 months, with a partial pressure of oxygen (PaO_2) of 55 mm Hg or less or between 55 and 60 mm Hg with evidence of tissue hypoxia such as cor pulmonale, polycythemia (hematocrit > 55%), congestive heart failure, arrhythmias, or impaired mental status.

ARF was defined by clinical and blood gas criteria. The clinical criteria were respiratory arrest or dyspnea, tachypnea, signs of respiratory muscle failure defined by prominent use of accessory respiratory muscles or paradoxical inward inspiratory motion of the abdomen, and impairment of consciousness defined by obtundation, agitation, or coma. Blood gas criteria were hypoxemia defined as a drop in the baseline PaO_2 (below 10 mm Hg when the previous baseline was known) and a rise in the partial pressure of carbondioxide ($PaCO_2$) with a drop in serum pH (< 7.30).

The criteria required for mechanical ventilation were clinical, and biochemical when possible (this was not possible in three patients, one due to respiratory arrest and two due to extreme signs of respiratory muscle failure and coma). The exclusion criteria were ARF secondary to trauma, surgery, neurological disease, anoxic encephalopathy after cardiopulmonary arrest, and cancer.

Data were collected on the following: age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II, previous ARF episodes resulting in mechanical ventilation, comorbid illnesses, length of stay in the ICU and in hospital (ICU plus ward), mortality in the ICU and in hospital and at 1 and at 5 years after discharge, arterial blood gas readings prior to endotracheal intubation, serum levels of albumin, sodium, phosphorus, creatinine, and urea at admission to the ICU, and forced expiratory volume in 1 s (FEV_1) in a stable phase. The total cost in the ICU, the total hospital cost (costs in ICU plus ward), and the cost per patient were determined.

To calculate costs, we used the Weighted Health Care Unit [20], a unit for measuring intermediate hospital products used by the Spanish National Health Institute to calculate hospital budgeting. The results have been expressed in dollars for the period 1992–1994. The cost per day of the stay in different areas was U.S. $1485 in the ICU, U.S. $256 in the medical ward, and U.S. $384 in the surgical ward. We calculated the number of life-years gained with the procedure and the quality of life obtained in each of these years expressed as the Quality Adjusted Life Year (QALY) [21].

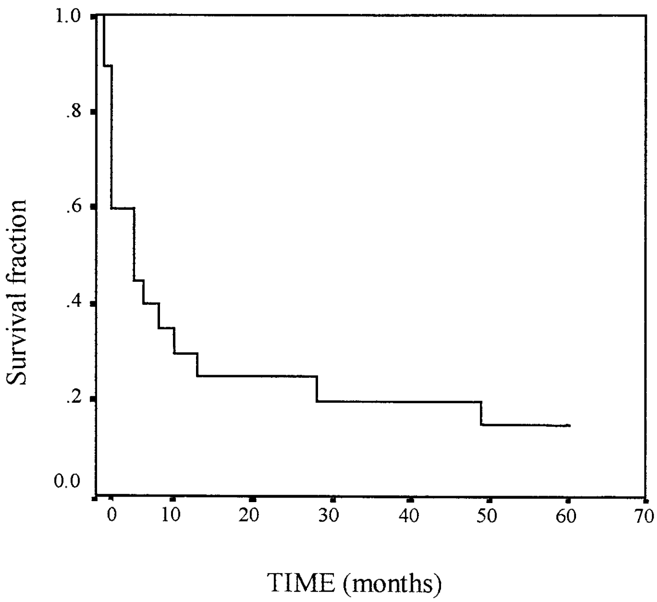

Fig. 1 Survival curve (Kaplan-Meier) for COPD patients treated with long-term oxygen and mechanically ventilated for acute respiratory failure. Time 0 represents the time of admission to the ICU

Table 2 Clinical and laboratory data on admission for 20 COPD patients with ARF. Values are median and range

Variable	Value	No.
Age (years)	64 (44–77)	20
APACHE II (points)[a]	20 (12–36)	20
FEV_1 (ml · s^{-1})	830 (480–1070)	17
pH	7.2 (7–7.34)	17
PaO_2 (mm Hg)	43 (26–61)	17
$PaCO_2$ (mm Hg)	85 (44–133)	17
Serum albumin (g/l)	29.5 (23–38)	20
Serum sodium (mmol/l)	134 (111–145)	20
Urea nitrogen (mmol/l)	9.49 (1.14–6.63)	20
Serum creatinine (µmol/l)	100.77 (44.2–291.7)	20
Serum phosphate (mmol/l)	0.64 (0.19–1.29)	20

[a] Data collected during the first 24 h after admission

To calculate the QALYs, the theoretical number of life-years available after the use of mechanical ventilation was multiplied by the Rosser Index Score, an estimate of the quality of life [22]. Quality of life was assessed at 1 and at 5 years after discharge. This assessment was conducted over the telephone by the principal investigator. The Rosser Index Score describes a two-dimensional state of health; disability and pain are used to classify the different states of health on a scale of 0 (death) to 1 (perfect health). For example, a patient with a 5-year life expectancy after mechanical ventilation and a Rosser Index of 0.946 would have 4.73 QALYs assigned to him or her. The patients who died in the hospital had a computed QALY of 0 because they obtained no benefit from the procedure. The life expectancy in Spain in the period of the study was 75 years for men and 78 years for women. In patients surpassing this age, 1 more year was computed. Since this life expectancy may overestimate survival for patients without a known date of death, we calculated a cost/QALY for a 68-year life expectancy (mean age of patients who died in the ICU) as a "worst case scenario" and a cost/QALY for the life expectancy in Spain as a "best case scenario". The ratio between the total cost of the complete hospitalization and the total number of QALYs achieved equals the cost per QALY.

The quantitative variables are expressed as median and range. A Student's *t*-test was used to demonstrate differences among means of quantitative variables. The Mann-Whitney test was used for those variables that did not meet a normal distribution criteria. These variables were serum levels of sodium, urea, and creatinine. Fisher's exact test was used to demonstrate differences between qualitative variables. The statistical significance of the presence of comorbid illness and previous mechanical ventilation on survival was determined by this test. Survival rates were estimated by the Kaplan-Meier method. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software (version 7.5) for Windows.

Results

We evaluated 206 admissions due to COPD; 22 admissions in 20 patients met the inclusion criteria. The mean age was 64 years (median 64, range 44–77), 90% ($n = 18$) were men and 10% ($n = 2$) women. Location before ICU admission was the emergency room for 59%, a hospital ward for 27%, and another hospital for 14%. The mean length of time on long-term oxygen therapy was 2.8 years (median 3, range 1–5). The mean APACHE II score was 20 (median 20, range 12–36). The mean duration of mechanical ventilation was 36 days (median 16.5, range 2–171). The mean length of stay in the ICU was 41 days (median 20.5, range 5–182) and in the hospital, 65 days (median 43, range 16–237). Cumulative mortality was 35% ($n = 7$) in the ICU, 50% ($n = 10$) in the hospital, 75% ($n = 15$) at 1 year, and 85% ($n = 17$) at 5 years (Fig. 1). Prior to the current admission, 45% of the patients had required mechanical ventilation. Of these, 1 patient died in the ICU, 3 in hospital, and 5 at 1 year (NS). Comorbid conditions were present in 8 patients: 2 patients had hypertension and chronic atrial fibrillation, 2 had hypertension and diabetes, and 4 had ischemic heart disease. Moreover, 12 patients had electrocardiographic signs of right ventricular hypertrophy. Of these, 7 died in the ICU (NS). The results of the biochemical variables are shown in Table 2. Although not statistically significant, the mean age was greater ($p = 0.06$) and the FEV_1 lower ($p = 0.08$) in the patients who died in the ICU compared to survivors. Levels of serum albumin and sodium were diminished in the nonsurvivors ($p = 0.05$ and $p = 0.01$, respectively). No relation was found with other variables studied (Table 3). Patients who died in hospital and in the first year after discharge had a lower FEV_1 than survivors ($p = 0.03$ and $p = 0.05$, respectively). The total cost in the ICU was U.S. $1359061, with a mean cost per patient of U.S. $67953 (median 34943,

Table 3 Relationship between variables and mortality in the ICU[a]

	Alive	Dead	*p*
Age (years)	61 ± 8.9	68 ± 7.1	0.06
APACHE II (points)	20 ± 7.2	19 ± 4.9	0.6
FEV_1 ($ml \cdot s^{-1}$)	1005 ± 340	678 ± 302	0.08
Serum albumin (g/l)	30.6 ± 0.34	27.8 ± 0.18	0.05
Serum sodium (mmol/l)	139 (118–145)	133 (111–137)	0.01
Urea nitrogen (mmol/l)	6.78 (3.21–19.9)	7.14 (3.21–24.2)	0.83
Serum creatinine (µmol/l)	70.72 (61.8–291.7)	79.56 (44.2–238.6)	0.94
Serum phosphate (mmol/l)	0.65 ± 0.22	0.61 ± 0.35	0.8

[a] Mean ± standard deviation differences between variables for different outcomes in the ICU. A Student's *t*-test was used for data with normal distribution. Median values and range are shown for variables with an abnormal distribution criteria of variables. The Mann-Whitney test was used in this instance

range 7231–263 340). The total hospital cost (ICU plus ward) was U. S. $ 1 471 864, with a mean per patient cost of U. S. $ 73 593 (median $ 43 531, range $ 8757–278 063).

Of the 5 survivors at 1 year, 2 had previously had a good functional level and both were able to carry out paid work after discharge. The functional capacity of the rest of the survivors was characterized by an absence of pain but with total disability demonstrated by a marked limitation defined as domiciliary confinement except for short assisted walks. At 5 years only 3 patients were alive with a mean age of 63.3 years, and only 1 of them had a good functional level.

In the "best case scenario" the QALYs gained were 56. The total cost was U. S. $ 1 471 864; therefore the cost per QALY was U. S. 26 283. In the "worst case scenario" QALYs gained were 33, and therefore the cost/QALY was U. S. $ 44 602.

Discussion

We found a high mortality in hospital, at 1 year, and at 5 years in our group of patients. Factors significantly associated with mortality in the ICU were low levels of albumin and sodium at admission. Patients who died in hospital and in the first year after discharge had a lower FEV_1 than survivors. The cost/QALY analysis showed a high cost but little benefit from mechanical ventilation. Previous studies of outcomes for patients on long-term oxygen therapy have been performed on stable patients [23–27]. Therefore, we believe that our study is a useful addition because we identified a group of patients with a severe baseline disease who are often treated in the ICU.

The mean length of stay in the ICU and the cumulative mortality in our study was greater than the ICU stay and mortality reported by other authors who have researched outcomes for COPD patients after mechanical ventilation [5, 7–9, 11–13, 17]. This can be explained by the probable greater severity of illness of our study group. Other authors have reported factors that determine survival after an acute exacerbation of COPD. Classically, pH [28, 29] has been related to mortality; other factors more recently documented include FEV_1 [12, 30], age [17, 30, 31], albumin [12, 31, 32], serum sodium [32], PaO_2/fractional inspired oxygen, body mass index, cor pulmonale [31], functional status [3–5, 12, 29, 31], pulmonary infiltrates on initial chest radiography [15], and comorbid illness [30]. Conversely, others [11, 16] have found that no independent variables are related to prognosis.

In our study, the population investigated was small because the inclusion criteria limited the sample available for study. Furthermore, pulmonary function tests could not be evaluated in 3 patients. This precluded meaningful comparisons of some variables (i. e., the relation between age and FEV_1 to mortality in the ICU, the prognostic value of comorbidity). Arterial blood gas samples were obtained before endotracheal intubation, although in 3 patients, due to respiratory arrest or to the extreme severity of illness, endotracheal intubation was performed without an arterial blood gas sample being taken first. Therefore, the analysis of arterial blood gas readings as a predictor of outcome is not possible in our group because we lost 15 % of date, primarily in the more severely ill patients.

We also found that low levels of serum sodium and albumin were related to prognosis [12, 31, 32]. It has been suggested that stimulation of the renin-aldosterone and plasma arginine-vasopressin systems in conjunction with a hypoxia-hypercapnia mediated disturbance in renal function contributes to edema and hyponatremia in advanced COPD [33]. The association between serum albumin levels and outcome underlines the importance of the nutritional status in these patients, as demonstrated by Laaban et al. [34].

The APACHE II score did not correctly predict mortality in our study. Other authors have not found a powerful relation between acute illness scoring systems and mortality in small subgroups of patients [32].

The need to improve health care services and the progressive increase in hospital expenditure constitute a challenge for all developed countries. Concerns about critical care costs have been discussed for several decades [35–37]. Today, one of the more widely applied methods to evaluate the allocation of health care resources is the cost-utility analysis, which compares the costs of different procedures with their results determined in units based on quality of life parameters. Cost-effectiveness analyses have been applied to the utility of mechanical ventilation of patients over the age of 80 where the cost per year of life saved was estimated at between U. S. $ 51 854 and $ 75 090 in 1985–1987 dollars [38].

In our study, the Spanish life expectancy data may lead to an overestimation of the actual survival for patients without a known date of death and consequently may decrease the cost/QALY. Therefore, we have also calculated the cost/QALY for a 68-year life expectancy corresponding to the mean age of the nonsurvivors in the ICU. We found that the cost/QALY in this so-called "worst case scenario" was U. S. $ 44 602, which may be a less optimistic but more realistic approach than the cost/QALY obtained in the "best case scenario".

Comparisons between health care interventions in terms of their relative cost-effectiveness, cost per life-year or per QALY gained have recently become popular. The principal motivation is to help in the decision-making process about the allocation of health care resources. With information about the obtainable QALYs and the cost of medical procedures, it is possible to classify the procedures in terms of their respective costs per QALY gained. Association tables of QALYs [39] have been published; however, the interpretation of such tables is difficult because individual studies presented in a table are not often comparable for two important reasons: the analyses have been completed at different times, and consequently methods and relative prices differ, and the approaches used to determine the state of health often differ [40].

In conclusion, patients with COPD treated with long-term oxygen therapy needing mechanical ventilation for acute exacerbations had a high mortality in the acute phase, at 1 year and at 5 years. The cost of treatment was high and the benefits obtained in terms of quality of life were poor. The patients who died in the ICU were generally older and had lower FEV_1 measured during a stable phase (NS) and had significantly lower levels of serum sodium and albumin during the acute illness. Patients who died during admission and in the first year postdischarge had a lower FEV_1 than survivors.

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