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BRIEF REPORT

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Noninvasive ventilation in patients with "do-not-intubate" orders: medium-term efficacy depends critically on patient selection

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Abstract *Objective:* Randomized clinical trials demonstrating benefits of noninvasive ventilation (NIV) systematically exclude patients with "do-not-intubate" (DNI) orders, but in daily clinical practice these patients are frequently treated with NIV. A recent North American study found a 43% hospital survival rate in patients with DNI orders. Our hypothesis was that, due to the very different social and cultural setting, written DNI orders in a southern European country would be restricted to a population with a poor outcome, independently of whether they receive NIV, and we analyzed hospital survival in patients receiving NIV and the impact of DNI orders on survival. *Design and setting:* Retrospective cohort study in a general ICU in a university-affiliated hospital. *Patients and methods:* All 233 patients treated with NIV during 2002–2004. We recorded clinical characteristics on admission, mortality risk by APACHE II and ICU and hospital outcome, and 6-month outcome. *Results:* Hospital survival was 66%. Survival was better in the 199 patients without DNI orders than in the 36 with DNI orders both during hospitalization (74% vs. 26%, OR 7.9) and after 6 months (64% vs. 15%, OR 10.2). In both groups the presence of COPD was associated with better prognosis during hospitalization, but not in the medium-term. *Conclusion:* Our study suggests that NIV offers low expectations for medium-term survival in DNI patients.

Keywords Noninvasive ventilation · Ethics · Do-not-intubate orders · Hospital mortality · Chronic obstructive pulmonary disease

Introduction

Noninvasive ventilation (NIV) appeared more than a decade ago as an advantageous mode of ventilatory support for some patients. Several randomized controlled trials (RCT) have confirmed the benefit of NIV as first-line intervention in patients with chronic obstructive pulmonary disease (COPD) exacerbation [1] in patients with acute cardiogenic pulmonary edema [2] and in some groups of patients with acute hypoxemic respiratory failure, mainly immune compromised [3, 4] and following lung resection patients [5]. Nevertheless, as these RCT systematically exclude patients with "do-not-intubate" (DNI) orders [6, 7, 8], the efficacy of NIV in these patients is then supported only by nonrandomized clinical observations [9]. In a recent North American study [10] NIV was unrestrictedly offered to patients with DNI orders who developed respiratory failure of varied origin. This study showed 43% hospital survival, with better outcomes in heart failure and COPD.

Our hypothesis, however, was that due to the very different social and cultural approach [11], a formal statement of DNI status in a southern European country with low experience in advance directives would select a special population with a very poor outcome despite NIV. The objective of this study was to analyze hospital and medium-term

survival of both COPD and non-COPD patients receiving NIV, and the impact of DNI orders on survival.

Material and methods

We reviewed the clinical charts of all 3,150 patients admitted to our medical-surgical ICU between October 2002 and October 2004, 233 of whom (7.1%) were treated with NIV. Patients received NIV because of dyspnea, signs of respiratory distress including tachypnea (≥ 30 breaths/min) and increased accessory muscle use or abdominal paradox, or abnormal blood gases, either hypercapnic acidosis ($pH < 7.30$) or a PaO_2/FIO_2 ratio lower than 200 mmHg. As the data analyzed were taken from the ICU database, informed consent was waived. We prospectively added an item in the discharge chart about the DNI status of each patient. We recorded demographic variables, comorbidities, risk of death predicted by Acute Physiology and Chronic Health Evaluation (APACHE) II, length of ICU stay, complications, and outcome at ICU and hospital discharge. We analyzed patients, not NIV episodes or admissions, and then subsequent NIV episodes were ascribed to the medium-term survival analysis. Figure 1 presents the study flow chart.

Noninvasive ventilation was always supplied by oronasal mask connected to either conventional ICU ventilators (Servo 900C, Servo 300, and Servo-i from Siemens, Evita 2 and 4 from Draeger) or NIV ventilators (Vision Respironics). NIV was continuously applied as long as tolerated by patients, with a target of tidal volume above 6 ml/kg, SpO_2 of 88–92%, and a reduction in respiratory rate and subjective work of breathing to a level sustainable in the long term. Because of the observational nature of this study criteria for intubation remained at the discretion of the attending intensivist, based on commonly accepted medical knowledge. In some DNI patients NIV was maintained even when the target objectives were not achieved if the patient's subjective perception improved. Comfort was assured by the administration of sedatives and opiates, when appropriate. A survey was performed after 6 months through a search of hospital and public health databases, and phone calls when information was not available elsewhere.

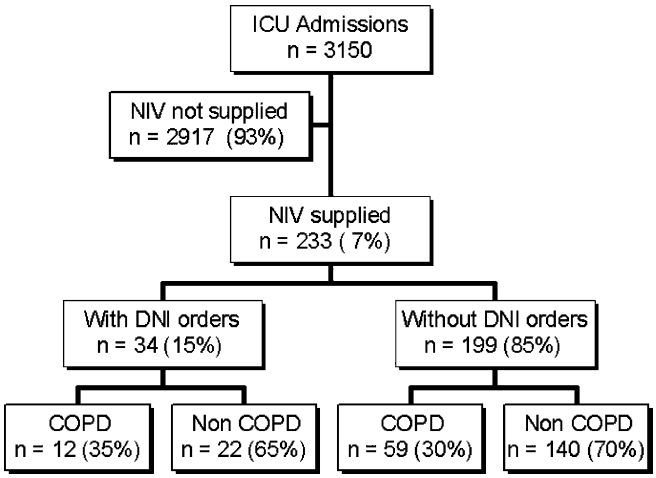

Fig. 1 Flow chart of the study for patients admitted to the ICU during 2002–2004

Analysis of variance was used to compare values on quantitative variables and Fisher's exact test for qualitative variables. Statistical significance was set at a $p \leq 0.05$. Multivariate analysis by conditional backward logistic regression was used to evaluate the relationship of clinical variables with hospital mortality. Six-month survival was assessed by Kaplan–Meier analysis.

Results

The rate of DNI orders was not particularly high (15%) and was similar in COPD and non-COPD patients. As expected, DNI patients were older and more frequently had cancer than did non-DNI patients (Table 1). Their predicted mortality was higher by Mortality Prediction Model (MPM), but failed to reach statistical significance by APACHE II. The incidence of major medical problems, nosocomial infection and acute renal failure, did not differ between groups. ICU length of stay was shorter

Table 1 Patients' clinical data on ICU admission and during ICU stay in the two groups

	With DNI orders ($n = 34$)	Without DNI orders ($n = 199$)	p
At ICU admission			
Age (years)	73.8 ± 9.4	67.1 ± 14.6	0.01
Female sex	8 (23%)	52 (26%)	0.8
Cancer	6 (18%)	10 (5%)	0.02
Chronic renal failure	4 (12%)	18 (9%)	0.5
APACHE score	20 ± 7.9	18 ± 7.1	0.3
APACHE II risk of death (%)	32 ± 22.5	29 ± 21.6	0.6
MPM risk of death (%)	38 ± 23.8	28 ± 21.1	0.04
Main indication for NIV			
COPD exacerbation	12 (35%)	65 (33%)	0.8
Cardiac failure	6 (18%)	44 (22%)	0.7
Pneumonia	7 (21%)	52 (26%)	0.7
Other	9 (26%)	38 (19%)	0.4
During ICU stay			
Nosocomial infection	3 (9%)	33 (17%)	0.3
Acute renal failure	5 (15%)	29 (15%)	0.9
ICU length of stay (days)	6.3 ± 4.8	12.0 ± 16.2	0.04
ICU mortality	20 (59%)	35 (18%)	0.001
Causes of death			
Cardiac failure	7 (35%)	8 (23%)	0.4
Respiratory failure	3 (15%)	7 (20%)	0.7
COPD exacerbation	7 (35%)	2 (5%)	0.008
Multiorgan failure	3 (15%)	10 (29%)	0.3
Other	0	8 (23%)	0.04

Table 2 Major therapeutic interventions during ICU stay in the two groups

	With DNI orders ($n = 34$)		Without DNI orders ($n = 199$)		p
	n	%	n	%	
Vasoactive drugs	12	35	71	35	0.9
Blood transfusion	3	9	49	25	0.04
Swan-Ganz catheter	2	6	38	19	0.08
Total parenteral nutrition	2	6	13	6	0.9
Pleural drainage	2	6	11	5	0.9
Hemodialysis	1	3	6	3	0.9

in DNI patients while ICU mortality was higher. The major therapeutic measures during the ICU stay are presented in Table 2. Interestingly, only blood transfusion and Swan–Ganz catheterization showed a tendency to be applied less in DNI patients whereas vasoactive drugs, hemodialysis, and total parenteral nutrition appeared unrestricted. Hospital survival was lower in DNI patients than in non-DNI patients (26% vs. 74%, $p = \leq 0.001$; OR = 7.9, 3.2–19.7). Regarding the role of COPD the impact of DNI orders on survival was similar, despite a slightly better survival for COPD patients (33% vs. 90%, $p = \leq 0.001$; OR = 18) than for non-COPD patients (23% vs. 67%, $p = \leq 0.001$; OR = 7). Multivariate analysis identified four variables associated with hospital and 6-month mortality: need for vasoactive drugs, acute renal failure, age, and DNI orders, the latter being the variable with the highest impact (Table 3). All patients were reached in the 6-month survey, where a progressive decay in survival was found in all groups except in non-DNI, non-COPD patients (Fig. 2). DNI patients had only a 15% 6-month survival, either with or without COPD.

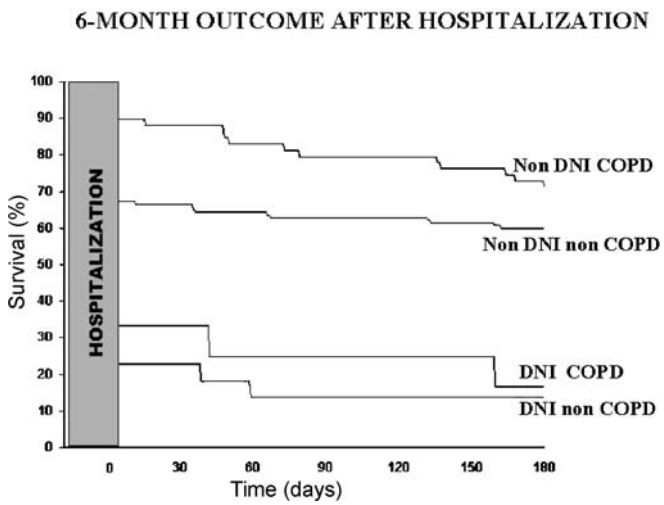

Fig. 2 Survival curves for the four predefined groups. Kaplan–Meier analysis reached statistical significance between DNI and non-DNI patients but not between COPD and non-COPD patients

Table 3 Multivariate analysis of factors associated with hospital mortality and at 6-months by binary logistic regression model (*OR* odds ratio, *CI* confidence interval)

	OR	95% CI	p
Hospital mortality			
DNI orders	11.4	4.4–29.4	0.001
Vasoactive drugs	6.2	3.0–12.5	0.001
Acute renal failure	3.3	1.3– 8.0	0.009
Age (by year)	1.02	0.99–1.05	0.06
6-month mortality			
DNI orders	9.2	2.4–35.1	0.001
Vasoactive drugs	3.2	1.5– 6.8	0.002
Acute renal failure	3.2	1.2– 8.4	0.02
Age (by year)	1.04	1.02–1.07	0.002

Discussion

The main finding of our study is that NIV support in our patients with DNI orders may "buy time" or even help them to survive their ICU and/or hospital stay, but it offers very little in medium-term survival. The usefulness of NIV to reverse respiratory failure has been clearly established in patients with COPD exacerbations or cardiogenic pulmonary edema [1, 2]. The advantage in hypoxemic failure is still controversial; whereas NIV is a definite indication in immunosuppressed patients [3, 4], its role in pneumonia is debatable [6, 8]. A systematic review [7] suggested a direct relationship between survival improvement with NIV and baseline severity of illness. Accordingly, the indication of a trial of NIV in our patients, who have a predicted mortality about 30%, was a widely accepted alternative in the clinical scenario. Patients may perceive ICU survival, and even hospital survival, as misleading because they may be transferred to chronic facilities, or returned home for a peaceful death. We therefore consider our 6-month survey gives a better picture of clinically significant prognosis for the decision process, despite the lack of specific quality of life indicators.

In patients without DNI orders we found an almost flat survival curve for acute respiratory failure, whereas those with COPD suffered a progressive survival reduction. This is in accordance with previous epidemiological studies on the progression of severe COPD after hospital admission [12]. In the DNI group the low hospital survival (26%) went down to 15% at 6 months, i. e., 42% of DNI patients discharged from hospital died in the next 6 months. This may mitigate the optimistic results of previous reports [10, 13].

Another source of differences with previous studies may be the criteria leading to DNI declaration in the given patient. Despite the progress made over the past few decades patients even in developed countries evidently play quite different roles in the decision process. In southern Europe the use of advance directives remains low [11] not only in acute severe illnesses such as cancer

and multiple organ failure but also in chronic conditions such as COPD. Accordingly, patients and families accept DNI labeling only at the very end of life. In this case NIV in DNI patients can be offered as part of the palliative portfolio, and physicians should consequently be aware of the real symptomatic relief that NIV offers in given patients [14, 15] as a reduction in morphine dose [16].

Limitations of the study

The fact that this was a single-center scenario reduces the extent to which our findings can be extrapolated, and multicenter or multinational studies should be conducted to clearly establish the usefulness of NIV in DNI patients. The retrospective condition of our study was not hampered by loss of patients during follow-up. Additionally, our retrospective approach reduces the likelihood of more intense treatment as described in prospective clinical trials [17], and it therefore gives a better description of NIV effectiveness in daily routine. One very specific issue of our study was the labeling of a patient with DNI orders. Our hospital mandates that a special DNI document be completed in advance according to the patient's and/or family's directives. Nevertheless, as only a minority of our patients were transferred to our ICU from the ward, very few patients signed advance directives. Furthermore, the decision about DNI orders was most commonly made inside the ICU within only hours or days of admission. In this scenario one can anticipate that DNI orders would probably only be given in cases of patients with a very poor quality of life or very low expectations of recovery. These conditions probably selected a specific population with very advanced diseases whereas in other studies [10, 13] the DNI order was decided in a less advanced state of progression. The lack of accuracy of APACHE II in predicting death in this group is probably attributable to the lack of this specific issue into any prediction score.

We conclude that the use of NIV in our setting offers very low expectations in medium-term survival in DNI patients. The main reason may be that, in a country with little experience in advanced directives, the DNI statement coincides with the final stages of disease progression.

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