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Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey

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Abstract *Objective*: To observe the nosocomial infection (NI) distribution in ventilated patients of a single intensive care unit (ICU) according to the kind of control of the upper airways: noninvasive positive pressure ventilation (NPPV) versus endotracheal intubation (ETI).
Setting: ICU of a general hospital.
Design: Prospective clinical and epidemiologic survey.
Patients: In the period December 1994–March 1997, 761 patients were included who needed mechanical ventilation for more than 48 h: 129 were ventilated by NPPV (NPPV group), 607 were intubated (ETI group) and 25 required intubation after a period of NPPV (NPPV-ETI group).
Measurements and results: The data used were prospectively collected according to the NI epidemiologic surveillance protocol of "C. CLIN Sud Est, Réa Sud Est", France. NI included a ventilator-associated pneumonia (VAP), catheter-related infection, urinary tract infection and bacteremia. Occurrence of NI was estimated by the density of incidence. Covariate-adjusted NI and VAP risk factors were assessed by the Cox model. The incidence density of total NI was lower for NPPV than for ETI (14.2 versus 30.3 per 1000 patient-days, $p < 0.01$). The Cox model showed that the use of noninvasive ventilation, adjusted to the severity of illness (SAPS II), reduced not only the VAP risk (hazard ratio (HR) = 4.07) but also the NI risk (HR = 1.95).
Conclusion: The use of NPPV reduces the risk of VAP and NI, compared to ETI, irrespective of the severity of the patient's illness.

Key words Noninvasive ventilation · Nosocomial infection · Ventilator-associated pneumonia · Prospective survey · Intensive care unit

Introduction

Although the indications are limited, the frequency of complications in patients with acute respiratory failure treated by NPPV is significantly lower than in those patients invasively ventilated with endotracheal intubation (ETI) [1]. Furthermore, Confalonieri et al. [2] have reported an improvement of immediate and long-term outcome in patients treated by NPPV.

In addition to severity of illness, which is a well known risk factor for nosocomial infection (NI), there is a relationship between the use of any invasive device (endotracheal tube, central venous catheter, arterial line and urinary tract catheter) and NI [3, 4]. These infections are also reported to increase with the duration of use of the invasive device [5, 6]. Thus, the 6 % risk of acquiring NI in a general ward rises to 18 % in an intensive care unit (ICU) [7]. Other NPPV benefits are no sedative use, improved nutrition, better communication and a reduction of the complications attendant on ETI. Therefore the occurrence of NI is expected to decrease in ICU patients treated with NPPV for an acute

Table 1 Initial characteristics of 761 patients according to the type of ventilatory support

Variables	NPPV (n = 129) m (SD)	ETI (n = 607) m (SD)	NPPV-ETI (n = 25) m (SD)	p
Age (years)	65 (14)	59 (18)	60 (14)	0.01
Male sex (%)	68	63	72	0.39
SAPS II	31 (12)	40 (15)	31 (14)	< 0.01
Admission motive in ICU				
Traumatism (%)	19	13	20	0.20
Medical (%)	74	54	76	< 0.01
Surgical (%)	7	33	4	< 0.01
Days of ventilation	5 (4)	10 (12)	19 (13)	< 0.01
Days of ICU stay	6 (5)	12 (16)	21 (13)	< 0.01
Days of hospitalization, before ICU admission	12 (23)	11 (17)	5 (6)	0.19
Hospitalization < 48 h, before ICU admission (%)	85	74	88	0.01
Repeat ICU admission (%)	26	17	44	< 0.01
CVC (%)	24	69	80	< 0.01
Days of CVC	5 (3)	10 (9)	11 (6)	< 0.01
UTC (%)	44	94	92	< 0.01
Days of UTC	5 (3)	10 (11)	10 (7)	< 0.01
Mortality (%)	10	26	12	< 0.01

(*NPPV* noninvasive positive pressure ventilation, *ETI* endotracheal intubation, *SAPS* simplified acute physiologic score, *ICU* intensive care unit, *CVC* central venous catheter, *UTC* urinary tract catheter, *m (SD)* mean (standard deviation)

respiratory failure in comparison with intubated patients.

This work reports a prospective clinical survey in a ICU over a 2 1/2-year period. NI distribution in ventilated patients according to the method of control of the upper airways has been studied, adjusting the respective risks to the severity of illness and pathology.

Methods

Population

From December 1994 to March 1997, all patients admitted to a 20-bed ICU at the 1,000-bed general hospital of Roanne (Loire, France) and needing assisted ventilation for more than 48 h were included in the study (761 patients). Patients characteristics are displayed in Table 1. The NI criteria were defined by the ICU nosocomial infection epidemiologic surveillance protocol of "C. CLIN Sud-Est, Réa Sud-Est", France (version 1:

November 1994). The ventilation and NI data used in this analysis were prospectively collected according to this surveillance protocol. An infection was considered nosocomial when its onset occurred after 48 h of ICU stay.

Noninvasive positive pressure ventilation and/or endotracheal intubation criteria

For obvious ethical reasons, randomization between NPPV and ETI was not allowed. NPPV was indicated when patients presented chronic obstructive pulmonary disease (COPD) or chronic restrictive respiratory failure (CRRF) exacerbation, symptoms of acute hypoventilation (particularly in cases of thoracic trauma), acute respiratory failure as a result of cardiogenic pulmonary edema or acute pneumonia. Patients who were not candidates for intubation with poor physiologic status or terminal illness and a reversible cause of acute respiratory failure were also considered for NPPV [1]. Patients were intubated if they were unconscious or showed rapid deterioration in neurologic status, hemodynamic instability, acute cardiac ischemia, cardiorespiratory arrest, risk of inhalation and inability to cooperate sufficiently. The medical team, nurses and respiratory therapists concentrated particularly on the correct choice of size and type of facial mask, good position and fitting of the mask with frequent changes of the patient's position. Patients were mechanically ventilated with NPPV using one of the following ventilators : Servo (Siemens-Elema, Sweden) or Cesar (Taema, Antony, France). The mode of mechanical ventilation using NPPV was an inspiratory pressure support (12–16 cm H_2O). The main goal was to provide a PaO_2 of 8.5 kPa or more or percutaneous oxygen saturation of 90 % or more, which was measured by a pulse oximeter (Siemens), with a FIO_2 less or equal to 0.6. If required, a 4–5 cm H_2O positive end-expiratory pressure (PEEP) was used to achieve these parameters.

If necessary, patients admitted because of thoracic trauma, particularly, were treated with morphine chlorhydrate intravenous bolus up to 1 mg/10 kg, to relieve the pain and then improve NPPV tolerance. Intermittent ventilation was regularly delivered and patients were encouraged to use NPPV for more than 6 h per 24 h. Continuous NPPV was applied if necessary, according to the patient's tolerance. In order to achieve mechanical ventilation weaning, the NPPV rate was gradually reduced, at first at night and then during the day. NPPV was discontinued according to the following criteria: patient conscious and cooperative, stable hemodynamics, disappearance of dyspnea with respiratory frequency less than 25/min, correction of the initial event that caused the need to ventilate the patient and stable arterial blood gases when breathing room air or

oxygen supplementation. ETI was needed when patients met the previous exclusion criteria for NPPV or if respiratory distress signs were observed under NPPV (use of accessory muscles, abdominal paradox, severe hypercapnia more than 9.3 kPa, acute decreasing pH, persistent hypoxemia ($SaO_2 < 90\%$ or $PaO_2 < 8.5$ kPa).

Nosocomial infection criteria

The diagnosis of ventilator-associated pneumonia (VAP) was considered as recommended by Pingleton et al. [8]. The diagnosis of central venous catheter (Swan-Ganz, dialysis and arterial catheters) colonization was defined by semi-quantitative bacterial cultures of 15 cfu or more after removal of the catheter. The diagnosis of catheter-associated urinary tract infection required bacteriuria 10^5 cfu or more/ml (with only one or two pathogens) with leukocyturia 10^4 or more/ml. Without urinary tract catheter, the diagnosis of urinary tract infection required one of the following symptoms (fever > 38 °C, imperious miction, pollakiuria, dysuria) and bacteriuria 10^5 cfu or more/ml (with only one or two pathogens) or bacteriuria 10^3 cfu or more/ml with leukocyturia 10^4 or more/ml. Bacteremia based on a positive blood culture for a pathogen germ (with or without clinical signs) or at least two positive blood cultures (in a period of 48 h) for the following germs: coagulase negative *Staphylococcus*, *Acinetobacter* sp., *Corynebacterium* sp., *Bacillus* sp., *Propionibacterium* sp., oxidase-negative and anaerobic *Bacillus* spp., *Pseudomonas* other than *P. aeruginosa* or other cutaneous germs.

Covariate analysis

The following variables were recorded: sex, duration of hospital stay before ICU admission, duration of ICU stay, type of ICU admission (medical, postsurgical and polytraumatism), repeat ICU admissions, simplified acute physiologic score II (SAPS II) [9], length of ventilation and intubation, type of airway control (NPPV and/or ETI), type and duration of invasive devices use.

Statistical analysis

The incidence density of each type of NI was determined taking into account the total number of NI of the site in the numerator and the total number of days of exposure to the device from the period of either NPPV or ETI in the denominator. For the patients of the NPPV-ETI group, we allocated any episode of NI, whatever its site, from the ETI period if it had occurred 2 or more days after intubation and from the NPPV pe-riod if it had occurred less than 2 days after intubation [10]. In NPPV-ETI patients, the length of exposure to the device was recorded before and after intubation.

Statistical analysis was performed using the Stata program. Comparisons between groups were made using the chi-square test for categorical variables, and Mann-Whitney U and Kruskal-Wallis tests for continuous variables by means. The densities of incidence were compared between NPPV and ETI with the Mantel Haenszel test [11] and the Yates test [12]. The data permitting analysis of the factors influencing NI probability occurrence were studied using the Cox semi-parametric model with respect to the multiple-record survival data. The hypothesis of proportionality was verified in a graphic manner for each categorical variable by the graphic log-minus-log method. Probability values equal to or less than 0.05 were considered significant.

Results

The main characteristics of the population studied are reported in Table 1. Among that population, 129 patients (20%) were ventilated by NPPV alone (NPPV group) and 607 directly intubated patients constituted the ETI group. The values throughout are means with the standard deviations in brackets. Twenty-five patients were treated with NPPV and subsequently intubated. The duration of NPPV was 2.5 (3.6) days. The reasons for ETI in this NPPV-ETI group are reported in Table 2. Among these, 56% were intubated after NPPV failure with a NPPV duration of 1.4 (0.9) days.

The three groups differed in age, SAPS II, surgery and medical conditions as indications for admission to the ICU and repeat ICU admissions. The NPPV-ETI patients had the shortest hospitalization (< 48 h) before ICU admission and the higher frequency of patients with a hospital stay less than 48 h before ICU admission. The length of ventilation and length of ICU stay were significantly different among the three groups. Central venous catheter (CVC) and urinary tract catheter (UTC) frequency and durations of use were lower in the NPPV group ($p < 0.02$).

One hundred sixty-four patients (22%) developed NI. Among them, 51 developed repeated NI at the same site (with one or two isolated pathogens) or NI at different sites, during the same ICU stay. No arterial catheter was colonized. We therefore identified 245 ICU-acquired NI. Sixteen percent of the germs isolated were *Staphylococcus aureus (SA)*. The incidence rate of methicillin-resistant *SA* was 5.3%. On average, the first NI was diagnosed 7 (4) days after ICU admission among the nine infected patients of the NPPV group, 9 (9) days among the 155 infected patients of the ETI group and 12 (7) days among the 12 infected patients of the NPPV-ETI group ($p = 0.25$). The ICU mortality

Table 2 Characteristics of 25 patients treated by NPPV and subsequently intubated

Patient	Age	History	Cause of ARF	Days of NPPV	Cause of intubation	Outcome
1	81	No	TT	1	NPPV failure	Dead
2	64	Bronchectasia	Bronch inf	14	VAP	
3	64	Bronchectasia	Bronch inf	1	VAP	
4	66	No	TT	3	VAP	
5	70	COPD	Bronch inf	4	NPPV failure	
6	40	unknown	Acute pneumonia	1	NPPV failure	Dead
7	49	CRRF	Congestive HF	1	Acute HF	
8	47	COPD	Bronch inf	2	Cereb isch	
9	69	No	Acute pneumonia	3	Pneumothorax	
10	68	COPD	Bronchosp	1	NPPV failure	
11	50	O and R CRF	Congestive HF	14	Hemorrhagic ulcer	
12	81	Chronic HF	Congestive HF	1	Hemodynamic instability	
13	77	CRRF	Bronc inf	1	NPPV failure	
14	76	Unknown	Atelectasia	1	NPPV failure	Dead
15	59	COPD	Bronch inf	1	NPPV failure	
16	61	No	Aspiration pneumonia	2	NPPV failure	
17	38	No	Acute pneumonia (Legionella)	1	NPPV failure	
18	41	Post surgery	Atelectasia	1	NPPV failure	
19	64	COPD	Bronchosp	1	NPPV failure	
20	71	No	TT	1	Pneumothorax	
21	34	No	TT	1	Orthopedic surgery	
22	45	No	Pneumonia, sepsis	1	Septic shock	
23	54	COPD	Bronch inf	1	NPPV failure	
24	48	No	TT	2	NPPV failure	
25	61	No	Aspiration pneumonia	2	NPPV failure	

(*NPPV* noninvasive positive pressure ventilation, *SAPS* simplified acute physiologic score, *ARF* acute respiratory failure, *TT* thoracic traumatism, *Bronch inf* bronchial infection, *VAP* ventilator-associated pneumonia, *COPD* chronic obstructive pneumonia disease, *CRRF* chronic restrictive respiratory failure, *HF* heart failure, *Cereb isch* cerebral ischemia, *Bronchosp* bronchospasm, *O* obstructive, *R* restrictive)

Table 3 Distribution of nosocomial infection by site in the NPPV, ETI and NPPV-ETI groups

	NPPV	NPPV-ETI	ETI
VAP	0	4	80
CRC	1	7	42
UTI	7	7	82
B	1	0	14

(*NPPV* noninvasive positive pressure ventilation, *ETI* endotracheal intubation, *VAP* ventilator-associated pneumonia, *CRC* catheter-related colonization, *UTI* urinary tract infection, *B* bacteremia)

rate for the patients with NI was 24 % (40/164) versus 22 % in those without NI ($p = 0.54$).

Among the 25 patients intubated after receiving NPPV, the four cases of VAP occurred after intubation (0, 1, 1 and 9 days) and then three of them were attributed to the NPPV period. Seven venous catheter colonizations and seven urinary tract infections were recorded in these patients. The delay occurring after intubation was 13 (4) days for the first venous catheter colonization and 11 (6) days for the first urinary tract infection. Then they were allocated to the ETI period. There was one case of bacteremia in the NPPV group, 14 in the ETI group and none in the NPPV-ETI group. The incidence density of total NI (including pulmonary, urinary tract, CVC and bloodstream) in this study was 14.2 versus 30.3 per 1000 patient-days for the NPPV and ETI periods, respectively ($p < 0.01$). For VAP, the incidence density difference was also significant (4.4 versus 13.2 per 1000 patient-days, $p < 0.05$).

The incidences of infected patients according to the type of ICU admission (trauma, medical and surgical) were 29, 22 and 16 %, respectively. These NI were pulmonary in 50 % of the traumatized, 30 % of the medical, and 31 % of the surgical, patients. Some differences in the distribution of NI at each of the sites in NPPV, ETI and NPPV-ETI patients are shown in Table 3. Infected patients in the NPPV group had a higher percentage of urinary tract infection (78 %). The incidence of gram-negative bacillus in infected NPPV, NPPV-ETI and ETI patients was 64, 53 and 53 %, respectively. *Staphylococcus spp.* among these made up 9, 37 and 27 %, respectively. This distribution of isolated pathogens in the three groups was not significant.

Using the univariate analysis, several factors were significantly associated with a higher NI occurrence. In

Table 4 Characteristics of ventilated patients with (NI +) versus without (NI-) nosocomial infections

| Variables	NI + (n = 164) m (SD)	NI– (n = 597) m (SD)	p
Age (years)	61 (17)	60 (17)	0.43
Male sex (%)	59	66	0.12
SAPS II	40 (14)	38 (15)	0.03
Admission motive in ICU:			
Traumatism (%)	20	13	0.03
Medical (%)	59	57	0.67
Surgical (%)	21	30	0.03
Days of ICU stay	26 (24)	7 (7)	< 0.01
Days of hospitalization, before ICU admission	6 (15)	4 (12)	0.01
Repeat ICU admission (%)	17	20	0.44
Days of ventilation	21 (17)	6 (6)	< 0.01
NPPV (%)	5.5	20	< 0.01
Days of NPPV	9 (5)	5 (4)	< 0.01
NPPV-ETI (%)	7	2	< 0.01
CVC (%)	83	56	< 0.01
Days of CVC	16 (11)	8 (6)	< 0.01
UTC (%)	100	81	< 0.01
Days of UTC	18 (16)	6 (5)	< 0.01

(*NI* nosocomial infection, *M* male sex, *F* female sex, *ICU* intensive care unit, *SAPS* simplified acute physiologic score, *NPPV* noninvasive positive pressure ventilation, *ETI* endotracheal intubation, *CVC* central venous catheter, *UTC* urinary tract catheter, *m (SD)* mean (standard deviation))

Table 5 Nosocomial infection (NI) and ventilator-associated pneumonia (VAP): hazard ratios (HR) and 95 % confidence intervals (CI) according to Cox

	NI		VAP	
	Hazard Ratio	95 % CI	Hazard Ratio	95 % CI
NPPV-ETI*	2.27	0.95–5.44	1.01	0.11–9.78
ETI*	1.95	1.06–3.58	4.07	1.25–13.24
Traumatism**	3.19	1.95–5.23	4.27	2.16–8.45
Medical**	2.11	1.41–3.14	2.01	1.08–3.72
SAPS II	1.01	0.99–1.02	1.00	0.99–1.02
Sex	0.69	0.50–0.95	1.25	0.75–2.11

(*NPPV* noninvasive positive pressure ventilation, *ETI* endotracheal intubation, *SAPS* simplified acute physiologic score) NPPV* and surgical admission** groups have been considered as group references in the hazard ratio calculation. NI : Chi^2, 5 df = 34.26 ($p < 0.01$) and VAP : Chi^2, 5 df = 26.10 ($p < 0.01$), where df means degrees of freedom. Sex code: 1 for men

this patient population, NPPV patients were significantly associated with a lower NI rate (Table 4). The NI and VAP adjusted hazard ratios (HR), according to ventilator mode, are reported in Table 5 with the survival curves (Figs. 1, 2).
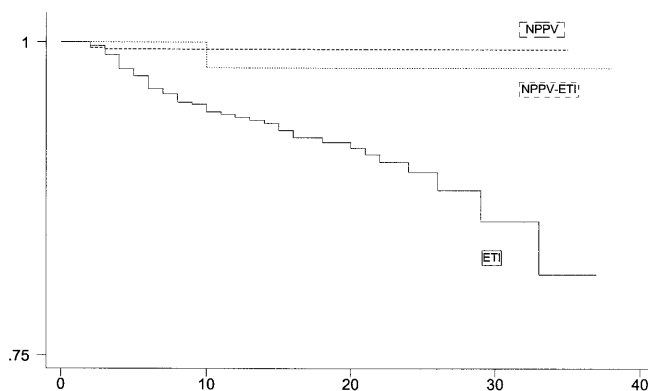
Fig. 1 Survival curves for ventilator-associated pneumonia (VAP) adjusted to SAPS II, type of ICU admission and sex (*NPPV* noninvasive positive pressure ventilation, *ETI* endotracheal intubation, *SAPS* simplified acute physiologic score, *ICU* intensive care unit)
x axis : Admission to VAP (days)
y axis : Cumulative survival
Footnote: Cox model. The lines represent the probability of remaining free of VAP during the ICU stay
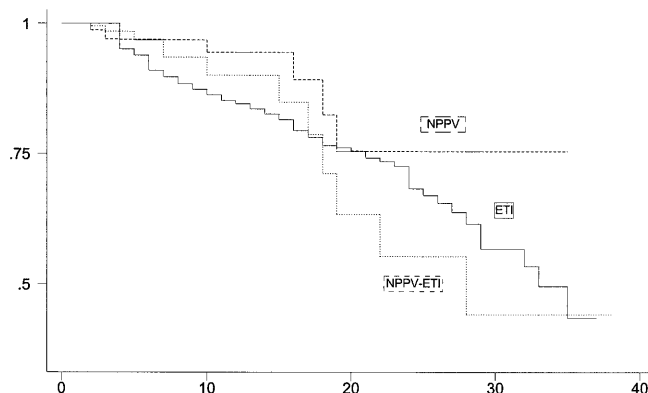
Fig. 2 Survival curves for nosocomial infection (NI) adjusted to SAPS II, type of ICU admission and sex (*NPPV* noninvasive positive pressure ventilation, *ETI* endotracheal intubation, *SAPS* simplified acute physiologic score, *ICU* intensive care unit)
x axis : Admission to NI (days)
y axis : Cumulative survival
Footnote: Cox model. The lines represent the probability of remaining free of NI during the ICU stay

Discussion

This study confirms the efficacy of NPPV in acute respiratory failure with indications similar to those reported in previous works [13, 14, 15, 16, 17, 18, 19, 20]. Furthermore, this prospective clinical survey based on a large patient population showed a lower risk of NI and VAP associated with NPPV.

Clinical team training had been concentrated on preventing imperfect reproducibility of criteria for the use of NPPV and clinical decisions for intubation. Indeed, many of the exclusion criteria for NPPV depend on phy-

sician experience, but they are undoubtedly crucial for the success and safety of the technique [21]. Among the 154 NPPV patients, only 16% were afterwards intubated and three of these died. Among the 129 patients treated with NPPV alone during the ICU stay, 13 patients with poor physiologic status died. Thus, 138 out of 154 patients were successfully treated with NPPV (75%). This result is similar to other authors' experience with success rates ranging from 60 to 92% [13, 16, 17, 18, 20, 22, 23].

Among NPPV-ETI patients, four cases of VAP occurred. Three were attributed to NPPV because of the short delay before their occurrence after intubation. Two of them were diagnosed in patients with thoracic trauma. No argument for a depression of airway reflexes due to morphine treatment was noted.

This observation study lacked a control group. However, the results were in accordance with a prospective, randomized trial of NPPV compared to ETI reported by Antonelli et al. [23]. In that study, avoiding intubation was associated with a lower incidence of septic complications ($p = 0.006$), pneumonia and sinusitis ($p = 0.003$) and ten NPPV randomized patients subsequently requiring ETI had a higher SAPS I than that of other NPPV patients ($p = 0.009$). In the present study, SAPS II of the 14 patients intubated after NPPV failure was 34 (16). This score did not show any significant difference with that of the NPPV group. The present study was also in accordance with the results of Guérin et al. [10], with a significant reduction in VAP density of incidence associated with NPPV.

The cofactors studied have been extensively documented in the literature. Severity of illness has long been recognized as one of the highest risk factors for NI [24, 25, 26, 27]. Moreover, specific types of ICU populations may possess certain properties that increase VAP [28, 29, 30] and NI risks [5]. Sex has been reported as a risk factor for NI [31], its incidence rate being higher for men [5]. However, in that study, the HR increased with female sex. This might be due to the high percentage of UTI (78%) observed in infected NPPV patients. Indeed, Haley et al. [5] reported an incidence of UTI 1.45 times higher in women. Female sex was also a risk factor for UTI in our study ($p = 0.003$).

These results suggest that the risk of NI is characterized by other parameters, including the initial diagnosis, as shown by patients admitted because of trauma. The risk of NI and VAP in this traumatic population might reflect its heterogeneous composition (head injury, unconsciousness, various fractures), its hemodynamic instability (inflammatory response, hemorrhage) and its large variety of treatment (transfusion, surgery, morphine, antibiotherapy).

Multivariate analysis allowed the measurement of the HR of NI and VAP, other cofactors being equal. Thus, the adjusted risk of NI increased by 2 times with ETI in comparison to NPPV. Moreover, the adjusted risk of VAP was multiplied by four in the ETI group. These results, achieved in a single ICU, were in accordance with previous studies and might be considered as an encouraging argument for others studies on the expected benefits of noninvasive ventilation.

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