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ORIGINAL

Impact of sedation and analgesia during noninvasive positive pressure ventilation on outcome: a marginal structural model causal analysis

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Take-home message: The simultaneous administration of sedative and analgesic drugs in patients with acute respiratory failure managed with noninvasive positive pressure ventilation may be associated with higher rate of failure.

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Abstract *Purpose:* There are limited data available about the role of sedation and analgesia during noninvasive positive pressure ventilation (NPPV). The objective of study was to estimate the effect of analgesic or sedative drugs on the failure of NPPV. *Methods:* We studied patients who received at least 2 h of NPPV as first-line therapy in a prospective observational study carried out in 322 intensive care units from 30 countries. A marginal structural model (MSM) was used to analyze the association between the use of analgesic or sedative drugs and NPPV failure (defined as need for invasive mechanical ventilation). *Results:* 842 patients were included in the analysis. Of these, 165 patients (19.6 %) received analgesic or sedative drugs at some time during NPPV; 33 of them received both. In the adjusted analysis, the use of analgesics (odds ratio 1.8, 95 % confidence interval 0.6–5.4) or sedatives (odds ratio 2.8, 95 % CI 0.85–9.4) alone was not associated with NPPV failure, but their combined use was associated with failure (odds ratio 5.7, 95 % CI 1.8–18.4). *Conclusions:* Slightly less than 20 % of patients received analgesic or sedative drugs during NPPV, with no apparent effect on outcome when used alone. However, the simultaneous use of analgesics and sedatives may be associated with failure of NPPV.

Keywords Noninvasive positive pressure ventilation · Acute respiratory failure Sedation · Analgesia · Mortality

Introduction

Noninvasive positive pressure ventilation (NPPV) is an effective technique that can avert side effects and complications associated with endotracheal intubation [1]. The tolerance of NPPV is crucial for its success. Mask intolerance because of pain or discomfort, or claustrophobia, may lead the patient to refuse ongoing NPPV prompting its discontinuation. In one trial, mask intolerance or inadequate patient cooperation led to intubation in 9 % of patients with acute respiratory failure [2]. Thille et al. [3] found that up to 13 % of patients with acute respiratory failure had poor tolerance to NPPV from the beginning of ventilatory support. In a survey of 70 intensive care units (ICUs) [4] to evaluate the use of NPPV, multiple regression analysis revealed that the severity (estimated by Simplified Acute Physiology Score, SAPS II) and de novo respiratory failure were two

independent predictors of the need for mechanical ventilation, whereas good tolerance to NPPV and high body mass index were associated with success. On the other hand, delirium and agitation are serious complications in critically ill patients and, even if it is indicated, NPPV is sometimes unsuccessful under these conditions [5].

For those reasons, after considering other factors known to improve adaptation of the patient to NPPV, the use of sedation during NPPV can be part of a strategy designed to optimize its use. An international survey regarding current sedation practices during NPPV in patients with acute respiratory failure showed that among physicians, 41 % used sedation and 48 % analgesic therapy for NPPV in the USA, whilst 24 % used sedation and 35 % used analgesic therapy in Europe [6]. Pilot studies suggest that continuous infusion of a single sedative agent may decrease patient discomfort, with no significant effects on respiratory drive, respiratory pattern, or hemodynamics [7]. While the current limited data available suggests that sedation during NPPV is safe and feasible, more widespread application should await the results of larger observational studies or randomized clinical trials.

Therefore, the purpose of this analysis was to assess the effect of analgesic and/or sedative drug therapy on NPPV failure.

Materials and methods

Patients

We used data from a prospective, international, multicenter, observational study of mechanically ventilated patients in 322 ICUs from 30 countries (see "Appendix 1") throughout March 2010 (Clinicaltrials.gov identifier NCT01093482) [8]. The research ethics board of each participating institution approved the protocol and need for informed consent was according to local rules. From this data set we included patients who received more than 2 h of NPPV as first-line ventilatory support at ICU admission. We excluded those with short duration of NPPV ($N = 327$, of whom 72 patients failed and were intubated) to guard against reverse causality; we felt that in this short time frame it would be impossible to separate patients given sedation or analgesia because they were already failing NPPV from those given sedation or analgesia to improve comfort of ongoing NPPV.

Protocol

We collected the following baseline characteristics: age, sex, severity at ICU admission estimated by SAPS II, use of NPPV at home, application of NPPV in the hospital previous to admission in the ICU; reason for NPPV [chronic obstructive pulmonary disease (COPD), asthma, other chronic pulmonary disease non-COPD, postoperative acute respiratory failure, acute respiratory distress syndrome, community-acquired pneumonia, hospital-acquired pneumonia, congestive heart failure, aspiration, neurologic disease, trauma, sepsis, do-not-intubate order, other reason] that, for the purpose of the analysis, was grouped into three categories: hypercapnic respiratory failure, hypoxemic respiratory failure, and other; arterial blood gases prior to NPPV commencement; interface and ventilator used to apply the NPPV. At NPPV commencement we registered the following variables: mode of ventilation, inspiratory positive airway pressure, expiratory positive airway pressure, tidal volume, respiratory rate, inspired fraction of oxygen, arterial blood gases and level of consciousness-sedation by Richmond Agitation Sedation Scale (RASS) [9]. At each change of ventilator settings we registered the same variables and the administration of sedatives (midazolam, propofol, lorazepam, dexmedotimidine) or analgesics (morphine, fentanyl, remifentanyl, sufentanyl) at this moment. Monitoring was continued until NPPV was considered failed or the patient was discharged from the ICU.

The failure of NPPV was defined as the need for intubation and invasive mechanical ventilation.

Statistical analysis

Data are expressed as mean (standard deviation), median (interquartile range), absolute and relative frequencies as appropriate. Student's t, Mann–Whitney, ANOVA, and Kruskal–Wallis tests were used to compare continuous variables and Chi-squared tests were used for categorical variables.

To assess the relationship between the use of analgesics or sedatives drugs with the failure of NPPV and to avoid time-dependent confounders, we performed a marginal structural model (MSM) by inverse probability treatment weight (IPTW) introducing analgesics, sedatives, or both as a dummy variable using non-sedoanalgesia as the reference, and adjusted by baseline variables (age, SAPS II, reason for starting NPPV, interface for NPPV), and time-dependent confounders (RASS score, pH, and PaCO2). A full description of this statistical analysis is available in the electronic supplementary material.

To account for patients clustering, the effect of analgesics or sedatives drugs on 28-day mortality was analyzed using logistic regression model with generalized estimating equations methods [10]. In the multivariable analysis for risk of mortality, we adjusted only for baseline variables related to mortality (age, SAPS II, reason for NPPV).

Statistical tests were two-sided, and $p < 0.05$ was considered to be statistically significant. These analyses

were performed using Stata/IC 13.1 (STATA Corp, Texas, USA).

Results

At admission in the ICU, 1169 patients received NPPV. For the purpose of the current analysis we excluded 327 patients (27.9 %) because they underwent less than 2 h of NPPV.

From the remaining 842 patients, 165 patients (19.6 %) received some kind of analgesic and/or sedative drugs at any time during NPPV: 88 patients received analgesia, 44 patients received sedation, and 33 patients received both analgesics and sedatives drugs (Fig. 1). Midazolam and morphine were the most commonly used sedative and analgesic drugs. Table 1 displays the differences between patients who received analgesic and/or sedative drugs and patients who did not.

Relationship between sedation–analgesia and failure of NPPV

Patients who received analgesic or sedative drugs had similar duration of NPPV—analgesics [median 24 h (interquartile range 13–85)], sedatives [median 29 h (interquartile range 11–77)], and analgesics and sedatives [median 39 h (interquartile range 7–58)]—to those who received neither [median 26 h (interquartile range 12–59)] ($p = 0.938$).

Overall, 269 of 842 patients (32 %) failed NPPV. Table 2 shows the differences between patients with successful NPPV and NPPV failure. Patients who failed NPPV had higher severity of illness at ICU admission, and more commonly had hypoxemic respiratory failure.

In the unadjusted analysis analgesia was not significantly associated with failure of NPPV (Table 3). After adjusting for confounders, the marginal structural model by IPTW analysis showed that neither analgesia (odds ratio 1.8, 95 % confidence interval 0.6–5.4) nor sedation (odds ratio 2.8, 95 % CI 0.85–9.4) was significantly associated with NPPV failure. However, the simultaneous use of analgesics and sedatives was significantly associated with failure of NPPV: odds ratio 5.7, 95 % CI 1.8–18.4 (Table 3). A full description of the development of the model is showed in ESM.

Clinical outcomes

ICU length of stay was longer in patients who received sedative drugs with analgesics [median 6 days (interquartile range 3.5–10 days)] or without analgesics [median 7 days (interquartile range 4–18 days)] vs. those who did not receive drugs [median 5 days (interquartile range 3–10 days)]. Patients who received only analgesia had a length of stay in the ICU [median 6 days, interquartile range 3–10 days) similar to patients who did not receive any drug.

Crude 28-day mortality was higher in patients who received analgesic or sedative drugs compared with those who did not (34 vs. 23 %, $p = 0.014$). The combination of analgesics and sedative drugs during NPPV remained significantly associated with 28-day mortality after adjustment for confounders: odds ratio 4.6, 95 % CI 2.1–9.9 (Table 4). Also, crude ICU mortality was higher (31 vs. 21 %, $p = 0.007$).

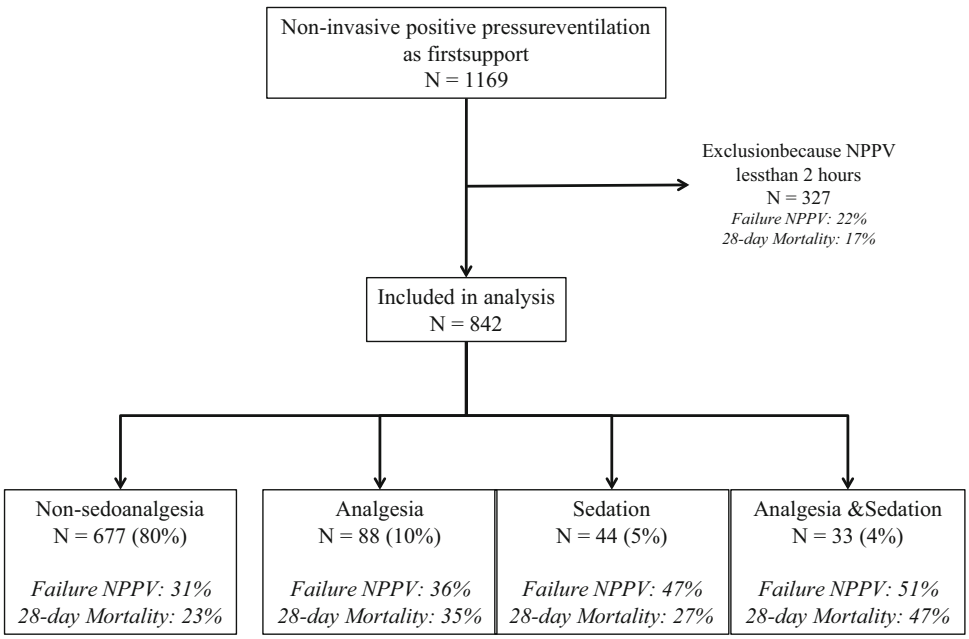

Fig. 1 Flowchart of outcome according to sedoanalgesia status. *NPPV* Non-invasive positive pressure ventilation

Discussion

In this study, we did not find any evidence suggesting a benefit of sedation or analgesia during NPPV. Almost 20 % of patients received analgesic or sedative drugs.

A cross-sectional Web-based survey [6] carried out by American and European physicians concluded that most physicians infrequently use sedation and analgesic therapy for acute respiratory failure patients receiving NPPV, but practices differ widely within and among specialties and geographic regions. According to this survey, sedation was usually administered as an intermittent intravenous bolus, outside of a protocol. A benzodiazepine alone was the most preferred (33 %), followed by an opioid alone (29 %). Europeans were less likely to report using a benzodiazepine alone (25 vs. 39 %, $p < 0.001$) but more likely to report using an opioid alone (37 vs. 26 %, $p < 0.009$). In our study, which examined recorded actual practice, rather than stated practice patterns, we did not observe significant differences between regions.

Aside from that survey, a few clinical trials, mostly with small sample sizes and varying results, have

Table 1 Baseline characteristics of patients according to sedoanalgesia status during ventilatory support

	Non sedoanalgesia ($N = 677$)	Analgesia ($N = 88$)	Sedation ($N = 44$)	Analgesia and sedation ($N = 33$)
Geographic region, *n* (%)				
Africa	88 (13)	8 (9)	10 (23)	6 (18)
Asia	38 (6)	1 (1)	1 (2)	0
Europe	307 (45)	46 (52)	21 (48)	15 (45.5)
Latin America	108 (16)	19 (22)	6 (14)	4 (12)
Oceania	66 (10)	4 (4.5)	2 (4.5)	1 (3)
USA–Canada	70 (10)	10 (11)	4 (9)	7 (21)
Age, mean (SD), years	65 (16)	64.5 (15)	61 (16)	66 (15)
Female, *n* (%)	296 (44)	37 (42)	21 (48)	15 (45.5)
SAPS II, mean (SD), points	38 (14)	41 (15)	39 (14)	40 (13)
Noninvasive ventilation at home, *n* (%)	57 (8)	7 (8)	2 (4.5)	1 (3)
NPPV prior to admission to ICU, *n* (%)	104 (15)	10 (11)	7 (16)	4 (12)
Reason for NPPV, *n* (%)				
Hypercapnia	306 (45)	23 (26)	18 (41)	12 (36)
Hypoxemia	331 (49)	61 (69)	23 (52)	18 (55)
Other	40 (6)	4 (5)	3 (7)	3 (9)
Arterial blood gases prior to start NPPV				
pH, mean (SD)	7.32 (0.10)	7.35 (0.10)	7.35 (0.14)	7.33 (0.11)
$PaCO_2$, mmHg, mean (SD)	55 (25)	43 (15)	50 (27)	51 (19)
PaO_2/FiO_2 ratio, mean (SD)	193 (121)	153 (80)	174 (87)	221 (190)
Specific ventilator for NPPV, *n* (%)	341 (55)	46 (58)	26 (65)	16 (57)
Interface, *n* (%)				
Oral-nasal mask	337 (50)	46 (52)	24 (55)	16 (48.5)
Facial mask	290 (43)	36 (41)	19 (43)	16 (48.5)
Nasal mask	38 (6)	3 (3)	1 (2)	0
Helmet	12 (2)	3 (3)	0	1 (3)
Ventilator settings at start NPPV				
Mode of ventilation, *n* (%)				
BIPAP	487 (72)	60 (68)	36 (82)	25 (76)
CPAP	47 (7)	12 (14)	0	5 (15)
Pressure support	134 (20)	13 (15)	6 (14)	3 (9)
Other	9 (1)	3 (3)	2 (4)	0
Parameter of ventilator				
IPAP, mean (SD), cmH_2O	14 (4)	13.5 (5)	15 (5)	13.5 (5)
EPAP, mean(SD), cmH_2O	6 (2)	7 (2)	7 (2)	7 (2)
Respiratory rate, bpm, mean (SD)	24 (7)	23 (7)	25 (8)	26 (8)
RASS at start NPPV, *n* (%)				
−5 to −3 points	19 (3)	2 (2)	4 (9)	1 (3)
−2 to 0 points	355 (52)	50 (57)	15 (34)	16 (48.5)
1 to 4 points	166 (25)	24 (27)	18 (41)	8 (24)

Missing data: pH in 85 patients, $PaCO_2$ in 87 patients, ratio PaO_2 to FiO_2 in 334 patients, IPAP in 70 patients, EPAP in 17 patients, respiratory rate in 46 patients, and RASS in 164 patients

IPAP inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *BIPAP* bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *RASS* Richmond Agitation Sedation Scale, *NPPV* noninvasive positive pressure ventilation, *bpm* breaths per minute

Table 2 Comparison between patients with success of noninvasive positive pressure ventilation and patients with noninvasive positive pressure ventilation failure

	Successful NPPV ($N = 573$)	Failure NPPV ($N = 269$)	p value
Age, mean (SD), years	66 (16)	63 (16)	0.014
Male, *n* (%)	317 (55)	156 (58)	0.570
SAPS II, mean (SD), points	37 (14)	42 (16)	<0.001
NPPV at home, *n* (%)	77 (10)	16 (5)	0.008
NPPV prior to admission to ICU, *n* (%)	123 (16)	38 (12)	0.090
Reason for NPPV, *n* (%)			
Hypercapnia	265 (46)	94 (35)	0.007
Hypoxemia	277 (48)	156 (58)	0.003
Other	31 (5)	19 (7)	0.083
Arterial blood gases prior to start NPPV, mean (SD)			
pH, mean (SD)	7.34 (0.10)	7.39 (0.11)	0.189
$PaCO_2$, mmHg, mean (SD)	53 (22)	47 (21)	<0.001
PaO_2/FiO_2 ratio, mean (SD)	190 (97)	164 (95)	0.002
Duration of NPPV, hours, median (IQR)	37 (18, 80)	18 (9, 45)	0.001
Specific ventilator for NPPV, *n* (%)	392 (57)	148 (50)	0.065
Interface, *n* (%)			
Oral-nasal mask	286 (50)	137 (51)	0.027
Facial mask	238 (41.5)	123 (46)	0.215
Nasal mask	36 (6)	6 (2)	0.013
Helmet	13 (2)	3 (1)	0.618
Ventilator settings during noninvasive positive pressure ventilation			
Highest IPAP, cmH_2O, mean (SD)	14 (4)	14 (5)	0.515
Highest EPAP, cmH_2O, mean (SD)	6 (2)	6 (2)	0.426
Highest respiratory rate, bpm, mean (SD)	23 (7)	26.5 (8)	<0.001
Worst arterial blood gases during NPPV			
pH, mean (SD)	7.32 (0.09)	7.30 (0.11)	0.001
$PaCO_2$, mmHg, mean (SD)	55 (21)	54 (24)	0.390
PaO_2/FiO_2 ratio, mean (SD)	194 (90)	157 (97)	<0.001
RASS			
−2 to 0 points, *n* (%)	307 (67)	129 (57)	0.010
−5 to −3 points, *n* (%)	12 (3)	14 (6)	0.012
1 to 4 points, *n* (%)	139 (30)	84 (37)	0.036

NPPV noninvasive positive pressure ventilation, *bpm* breaths per minute, *RASS* Richmond Agitation Sedation Scale, *IPAP* inspiratory airway pressure, *EPAP* expiratory airway pressure

evaluated the efficacy of analgesic or sedative drugs during NPPV [11]. Several studies [7, 12–16] have reported the evolution of a few patients—with acute respiratory failure [7, 12, 13] or failure of NPPV due to agitation [13], discomfort [14], or interface intolerance [15]—who were sedated with sufentanyl [7], morphine and/or midazolam [12], remifentanyl [13, 16], dexmedetomidine [14], or propofol [15] to obtain a level of sedation to improve the tolerance to NPPV. In these studies, the rate of intubation ranged between 0 and 39 %. Only three studies [17–19] were randomized controlled trials that compared sedation with two different drugs: midazolam vs. dexmedetomidine. Senoglu et al. [17] did not report any failure of 40 uncooperative patients sedated that received NPPV. Huang et al. [18] included 62 patients with acute cardiogenic pulmonary edema who refused NPPV and reported an overall rate of failure of 32 %, and the group assigned to midazolam had a higher rate of NPPV failure (45 vs. 21 % in the dexmedetomidine group). Devlin et al. [19] randomized 36 adults with acute respiratory failure within 8 h after starting NPPV to receive dexmedetomidine, to maintain a Sedation-Agitation Scale score of 3–4, or placebo up to 72 h. They found that initiating dexmedetomidine soon after NPPV initiation did not improve NPPV tolerance: odds ratio 1.44, 95 % CI 0.44–4.70 ($p = 0.54$).

Our study represents the largest observational study in patients in NPPV receiving analgesic and/or sedative drugs. We observed a rate of unsuccessful NPPV in patients who received analgesic or sedative drugs in the range of previous reports (39 %). Using a marginal structural model, we showed an independent association between the use of combined sedation or analgesia during NPPV and NPPV failure. This potentially deleterious effect of simultaneous use of analgesic and sedative drugs on outcome of critically ill patients receiving NPPV has not previously been reported [20]. Nevertheless, randomized clinical trials are encouraged to further address this question.

Our study has several limitations. First, we cannot know if the administration of sedoanalgesia drugs was used as an attempt to improve the tolerance to NPPV, or to avoid the failure of NPPV when first signs of poor tolerance appeared. Nevertheless, we think that our

Table 3 Effect of sedoanalgesia on failure of noninvasive positive pressure ventilation

	Failure NPPV (%)	Crude (GEE model)		Adjusted by age, SAPS II, interface for NPPV, reason for NPPV, RASS, pH and $PaCO_2$	
		Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value
Non-sedoanalgesia	31	1		1	
Analgesia	36	1.5 (1.0–2.3)	0.063	1.8 (0.6–5.4)	0.266
Sedation	47	2.3 (1.3–3.9)	0.003	2.8 (0.8–9.4)	0.095
Sedation and Analgesia	51	6.6 (3.3–12.8)	<0.001	5.7 (1.8–18.4)	0.004

NPPV noninvasive positive pressure ventilation, *GEE* generalized estimating equation, *CI* confidence interval, *SAPS* Simplified Acute Physiology Score, *RASS* Richmond Agitation Sedation Scale

Table 4 Relationship between sedoanalgesia and 28-day mortality in patients with noninvasive positive pressure ventilation

	28-day mortality (%)	Crude (GEE model)		Adjusted by age, SAPS II, reason for NPPV	
		Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value
Non-sedoanalgesia	23	1		1	
Analgesia	35	1.8 (1.0–2.3)	0.013	1.5 (0.9–2.4)	0.101
Sedation	27	1.7 (0.9–3.3)	0.134	1.8 (0.9–3.6)	0.085
Sedation and analgesia	47	4.8 (2.3–10.3)	<0.001	4.6 (2.1–9.9)	<0.001

NPPV noninvasive positive pressure ventilation, *GEE* generalized estimating equation, *CI* confidence interval, *SAPS* Simplified Acute Physiology Score

findings support the conclusion that the administration of sedoanalgesia, whatever the indication, did not improve the outcome of NPPV. Second, as a result of the design of the study, we did not register any variable related to the assessment of the tolerance to NPPV or to patient–ventilator interaction. Third, owing to the characteristics of this observational and non-interventional study, there was no protocol for analgesic or sedation drug dosing and we only collected the drugs administered but not their dosage. Four, the decision to start and finish NPPV was based on the clinical judgment of the physician in charge of the patients; however, this study represents the routine clinical practices in the use of NPPV in the ICU. Last, there are probably remaining unmeasured confounders. In observational studies, the control of confounding is a fundamental problem in analyzing data and interpreting results. A confounder variable is associated with both the occurrence of the outcome event (failure of NPPV) and the treatment (sedation and/or analgesia). Use of standard regression models for the analysis of cohort studies with time-updated measurements may result in biased estimates of treatment effects if time-dependent confounders affected by prior treatment are present. If past treatment predicts the current covariate value (e.g., if the covariate is on the causal pathway between treatment and the outcome), standard survival analyses with time-updated treatment effects will give biased treatment effect estimates. We have performed a marginal structural model to analyze the results of this observational study to avert time-dependent confounders. The results evaluated by the MSM are valid only under the assumption that all covariates influencing the use of NPPV were introduced in the analysis [21]. However, we included numerous measured covariates but the assumption of positivity would have not been fulfilled. The use of truncated weight would attenuate this limitation [22].

In conclusion, we observed no benefit of the use of sedation or analgesia in patients receiving noninvasive positive pressure ventilation. The association of sedation and analgesia may be related to NPPV failure.

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Conflicts of interest The authors declare that they have no conflict of interest.

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