Extended Utilization of Noninvasive Ventilation for Acute Respiratory Failure and Its Clinical Outcomes

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BACKGROUND: Noninvasive ventilation (NIV) has increasingly been used for the treatment of acute respiratory failure. Despite recommendations supporting its utilization in a limited group of patients, NIV is frequently relied on as a first line treatment. We conducted a retrospective study to assess whether the extended use of NIV is associated with worse clinical outcomes. METHODS: This was a retrospective review of a data set consisting of patients admitted with respiratory failure and treated with NIV. Based on guidelines, we grouped the patients on whether they had indications and/or contraindications for NIV: NIV indicated and not contraindicated; NIV indicated and contraindicated; NIV not indicated and not contraindicated; NIV not indicated and contraindicated. The need for endotracheal intubation, hospital mortality, and stay were compared between these 4 groups. RESULTS: Demographic data were not significantly different between the groups. Within the group of subjects with no contraindication for NIV, those with indication and with no indication intubation rates were 28% and 17%, respectively ($P = .39$). Among the group of subjects with indications for NIV, the rate of intubation was 28% for those with no contraindication and 56% in those with it ($P = .13$). In the group of subjects with no indication for NIV, the presence of contraindications was associated with higher rate of intubation, compared with those without contraindications (70% vs 17%, $P = .002$). CONCLUSIONS: This study supports the extended utilization of NIV for subjects without contraindications, and for subjects with indications despite the presence or absence of contraindications. *Key words: noninvasive ventilation; NIV; acute respiratory failure.* [Respir Care 2013;58(5):778–784. © 2013 Daedalus Enterprises]

Introduction

The use of noninvasive ventilation (NIV) for the treatment of acute respiratory failure has been growing over the last 2 decades. Several studies have evaluated the impact of implementing NIV in different hospital settings and diseases. Specifically, treatment with NIV for patients with hypercapnic COPD and cardiogenic pulmonary edema (CPE) was extensively studied, obtaining successful results.[1-4] In fact, improvements in important clinical outcomes, such as the rate of endotracheal intubation and mortality, were replicated on multiple occasions.[5-7] Lately, NIV was assessed in other clinical conditions such as asthma,[8,9] acute lung injury (ALI),[10] pneumonia,[11] and postoperative respiratory failure.[12] In these scenarios the evidence supporting NIV use has been less robust, with some studies favoring and others not favoring it. Based on the aforementioned data, clinical practice guidelines were developed by medical societies recommending indications and contraindications for NIV.[13-15] Despite the large body of evidence supporting the utilization of NIV for a very limited group of patients, NIV is frequently used by practitioners as a first line treatment for acute respiratory failure, independently of its cause. Whether the utilization of NIV beyond guideline recommendations presents any impact on patient outcomes remains unknown. Therefore, we conducted a retrospective study to assess whether the ex-

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tended utilization of NIV for the treatment of acute respiratory failure beyond known recommendations is associated with worse clinical outcomes. Specifically, we attempted to answer the following questions: In patients with respiratory failure and no contraindications for NIV, how do the presence of indications compare with their absence in terms of intubation rate, mortality, and hospital stay? In patients with indications for NIV, how does the presence of contraindications compare with their absence in terms of those outcomes? The present study addresses these questions based on a consecutive series of patients admitted with acute respiratory failure and treated with NIV.

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) is a standard of care for exacerbations of COPD and hypercapnic respiratory failure in patients with neuromuscular disease. NIV for hypoxemia remains controversial, and contraindications to NIV are well described, including intolerance of the face mask, medical instability, and excessive secretions.

What this paper contributes to our knowledge

Patients with an accepted indication for NIV and no contraindications had a low intubation rate. In the presence of both an indication and a contraindication, the NIV failure rate doubled. When there was no clear indication for NIV, the failure rate exceeded two thirds.

Methods

The study was approved by the investigational review board of the Creighton University School of Medicine (12–16316). We conducted a retrospective review of a data set consisting of 91 patients admitted to Creighton University Medical Center from July 2011 to January 2012, with diagnosis of respiratory failure and subsequently treated with NIV. As our institutional policy authorizes the use of NIV only in the critical care setting and the emergency department, our data set included patients with respiratory failure admitted in the ICU and coronary care unit. Patients with chronic use of NIV at home, those who had a tracheostomy, and patients who received NIV as a palliative treatment were excluded from this study. In order to maintain homogeneity in terms of therapeutic interventions used in patients presenting with acute respiratory failure, only subjects treated with NIV were considered. Patients treated with CPAP were excluded from the study. Only adult ($\geq$ 18 y old) non-pregnant patients were eligible. The causes of respiratory failure were categorized as follows: COPD exacerbation, CPE, ALI/ARDS, pneumonia, asthma exacerbation, postoperative (post-thoracotomy), immunosuppression with hypoxemia, and other. Based on recommendations of previously published guidelines,[13] we assessed whether subjects had indications and/or contraindications for NIV upon admission. Therefore, the subjects were classified in 4 groups: NIV indicated and not contraindicated, NIV indicated and contraindicated, NIV not indicated and not contraindicated, NIV not indicated and contraindicated. Table 1 shows indications and contraindications for NIV. The use of NIV in circumstances not listed in the indication or contraindication criteria was deemed not indicated and/or not contraindicated.

Demographic and physiologic data such as heart rate, breathing frequency, mean arterial blood pressure, P_{aO_2}/F_{IO_2}, P_{aCO_2}, pH, and Glasgow Coma Scale (GCS) score were collected. The aforementioned data were assessed pre and post implementation of NIV, which was considered finished once the subject was either intubated and mechanically ventilated, completely weaned from NIV, or pronounced dead. Outcome data, specifically the need for intubation and mechanical ventilation, hospital mortality, and hospital stay, were collected and compared between the previously described 4 groups. The need for intubation was our primary outcome, whereas hospital stay and mortality were secondary ones. Importantly, advance directives of do-not-intubate that arose during the hospitalization were also documented, as they could have affected outcomes by increasing mortality, and/or decreasing need for mechanical ventilation and hospital stay.

Statistical Methods

Continuous measures are described as means and standard deviations. These variables were compared between groups using 1-way analysis of variance, as Gaussian distributions were observed. In order to verify and confirm true differences between 2 groups, the unpaired *t* test was utilized. Categorical measures were summarized using frequencies and percentages. These variables were compared with the Fisher exact test. Statistics software (SAS 9.1.3, SAS Institute, Cary, North Carolina) was used for all analyses.

Results

Out of 91 subjects admitted with respiratory failure and treated with NIV, 36 (39%) were included in group 1 (indicated and not contraindicated), 9 (11%) in group 2 (indicated and contraindicated), 36 (39%) in group 3 (not indicated and not contraindicated), and 10 (11%) in group 4 (not indicated and contraindicated), respectively. Table 2 shows demographic data and diagnoses of respiratory fail-

Table 1. Indications and Contraindications for Noninvasive Ventilation

Indications
Hypercapnic COPD exacerbation with pH < 7.35
Cardiogenic pulmonary edema
Hypoxemic respiratory failure in immunosuppressed patients
Hypoxemic respiratory failure in postoperative (post-thoracotomy) patients
Contraindications
Unable to fit mask
Medically unstable
Agitated or uncooperative
Unable to protect the airway
Swallowing impairment
Excessive secretions not managed by clearance techniques
Recent upper airway or upper gastrointestinal surgery

ure in each group. Notably, there was a statistically significant difference in terms of patient severity upon admission between 2 groups. Specifically, the Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores revealed higher scores (sicker patients) in group 4, compared with group 3. There were no differences among the other groups.

As expected, the causes of respiratory failure on admission were imbalanced between groups. Nevertheless, when comparing diagnoses among groups with indications (group 1 vs group 2) and no indications (group 3 vs group 4) for NIV, no statistically significant differences were seen (see Table 2). Group 1 had a higher percentage of subjects with COPD, compared with group 2, whereas group 2 had a higher proportion of subjects with immunosuppression and hypoxemia. Among subjects with no indications for NIV, group 3 was composed of a higher percentage of subjects with ALI/ARDS, while group 4 had a higher proportion of subjects with pneumonia.

Contraindications for NIV in groups 2 and 4 were: unable to fit the mask in 4 (44%) and 1 (10%) subjects, respectively ($P = .11$); unable to protect the airway in 3 (33%) subjects in group 2, and 5 (50%) in group 4 ($P = .28$); and medical instability in 2 (22%) and 4 (40%), respectively ($P = .24$). Physiologic parameters, including vital signs, GCS, and values obtained from the arterial blood gas analysis on admission, are shown in Table 3. Furthermore, the range of changes in vital signs and gasometric values pre and post implementation of NIV (eg, Δheart rate, Δbreathing frequency, ΔP_{CO_2}, ΔpH.) are also shown in Table 3. Importantly, there were no differences in vital signs on admission and post utilization of NIV between the 4 groups. Nevertheless, values of pH and P_{CO_2} on admission, and their change pre and post NIV (ΔpH and ΔP_{CO_2}) revealed statistically significant difference between groups.

Specifically, group 1 had lower pH on admission (mean of 7.25) and the highest P_{CO_2} (mean of 69 mm Hg), compared with the other 3 groups. Also, ΔpH and ΔP_{CO_2} were higher in group 1, compared with the other groups. Notably, even though all 4 groups presented with acidosis and hypercapnia (see Table 3), only groups 1, 2, and 3 changed their pH values toward normalization, whereas P_{CO_2} corrected toward normalization only in group 1 and 3. Gasometric values in group 4 changed toward more acidosis and hypercapnia post NIV. Treatment duration with NIV was similar between groups, with a mean of 9.4 ± 4.6 h. Level of consciousness on admission, as assessed by the GCS, showed significant differences between groups. Group 1 had a mean GCS of 14, whereas groups 2, 3, and 4 had GCS of 12, 13, and 11, respectively. Statistical significance was seen between group pairs 1 and 2, 1 and 4, and 3 and 4.

Outcome data are shown in Table 4. Interestingly, when comparing groups of subjects with no contraindication for NIV, those subjects with indications (group 1) had higher rate of intubation (28%), compared with those with no indications (group 3) (17%). Nevertheless, this difference did not reach statistical significance ($P = .39$). Among subjects with indications for NIV, which included groups 1 and 2, the rates of intubation were 28% and 56%, respectively. This difference was not statistically significant ($P = .13$), even though group 1 included subjects with no contraindications and group 2 did include subjects with contraindications. Notably, within the groups of subjects with no indications for NIV (groups 3 and 4), the presence of contraindications (group 4) was associated with higher rate of intubation (70% vs 17%, $P = .002$). As expected, the rate of intubation in subjects with indications and no contraindications (group 1) was significantly lower, compared with the group with no indication and contraindication (group 4) (28% vs 70%, respectively, $P = .02$).

Mortality rate ranged between 3% and 20%, with the highest number seen in group 4. Hospital stay ranged between 7 and 13 days, with the longest hospital stay seen in group 4, as well. Strikingly, the lowest rate of intubation, mortality, and stay in the hospital was observed in group 3, which included subjects with no indications and no contraindications for NIV. Nevertheless, no statistical significance was observed in terms of mortality and hospital stay between all 4 groups.

Discussion

This retrospective study presents the following results:

- When NIV is used in subjects admitted with acute respiratory failure and no contraindications for NIV, the presence or absence of indications for this treatment does not affect clinical outcomes such as rate of intuba-

Table 2. Demographic Data and Diagnoses of Respiratory Failure

	Group 1 (indicated/not contraindicated) $n = 36$	Group 2 (indicated/ contraindicated) $n = 9$	Group 3 (not indicated/not contraindicated) $n = 36$	Group 4 (not indicated/ contraindicated) $n = 10$	P*
Age, mean y	64	66	60	65	.52
Male, no. (%)	16 (43)	5 (55)	15 (42)	6 (60)	.70
BMI, mean kg/m^2	28	27	29	31	.77
APACHE II score, mean	18	21	16	22	.01
SOFA score, mean	3	5	4	8	.01
Diagnoses, no. (%)					
COPD	20 (55)	3 (33)	0	0	.15
CPE	10 (28)	3 (33)	0	0	.29
ALI/ARDS	0 (0)	0	14 (39)	2 (20)	.17
Postoperative	1 (3)	0	0	0	
Immunosuppressed	5 (14)	3 (33)	0	0	.15
Pneumonia	0	0	11 (31)	5 (50)	.15
Asthma	0	0	7 (19)	2 (20)	.34
Other	0	0	4 (11)	1 (10)	.43

* P values for diagnoses are based on comparisons between group 1 versus group 2, and group 3 versus group 4.
BMI = body-mass index
APACHE = Acute Physiology and Chronic Health Evaluation
SOFA = Sequential Organ Failure Assessment
CPE = cardiogenic pulmonary edema
ALI = acute lung injury

Table 3. Physiologic Parameters on Admission and Changes After Noninvasive Ventilation

	Group 1 (indicated/not contraindicated), mean ± SD	Group 2 (indicated/ contraindicated), mean ± SD	Group 3 (not indicated/not contraindicated), mean ± SD	Group 4 (not indicated/ contraindicated), mean ± SD	P
Heart rate, beats/min	109 ± 25	109 ± 18	109 ± 26	102 ± 36	.86
Breathing frequency, breaths/min	27 ± 8	28 ± 5	27 ± 10	28 ± 8	.92
Mean arterial pressure, mm Hg	96 ± 24	85 ± 19	88 ± 25	85 ± 32	.38
pH	7.25 ± 0.09	7.28 ± 0.08	7.33 ± 0.09	7.32 ± 0.06	.01
P_{CO_2}, mm Hg	69 ± 22	60 ± 18	53 ± 16	51 ± 18	.01
P_{aO_2}/F_{IO_2}, mm Hg	193 ± 90	170 ± 76	200 ± 123	170 ± 90	.78
Glasgow Coma Scale score	14 ± 1	12 ± 2	13 ± 2	11 ± 3	.01
Changes after NIV					
Δ Heart rate (beats/min)	−17 ± 18	−14 ± 17	−11 ± 14	−6 ± 17	.19
Δ Breathing frequency, breaths/min	−5 ± 6	−2 ± 4	−6 ± 9	−2 ± 9	.44
Δ pH	0.07 ± 0.11	0.06 ± 0.11	0.04 ± 0.05	−0.05 ± 0.07	.01
Δ P_{CO_2}, mm Hg	−9 ± 14	2 ± 31	−5 ± 11	6 ± 10	.04
Δ P_{aO_2}/F_{IO_2}, mm Hg	41 ± 96	14 ± 41	33 ± 100	1 ± 71	.65

tion, hospital mortality or hospital stay.

- In subjects with indications for NIV, the presence or absence of contraindications for this treatment is not associated with differences in clinical outcomes.
- In subjects with no indications for NIV, the presence of contraindications is associated with higher rate of NIV failure (more intubations), but no differences in terms of mortality and hospital stay.

The indication of NIV in the context of exacerbation of COPD is based on 16 published randomized control studies that compared this ventilation modality versus standard of care, including oxygen therapy, bronchodilators, and corticosteroids[1-3,5-7,16,17] Overall, these trials revealed a lower incidence of endotracheal intubation and hospital mortality in the NIV group. However, most of these studies included patients with severe exacerbations, defined by admission pH lower than 7.35. Among the group of pa-

Table 4. Clinical Outcomes According to the Presence or Absence of Indications and/or Contraindications for Noninvasive Ventilation

Outcome	Group 1 (indicated/not contraindicated) $n = 36$	Group 2 (indicated/ contraindicated) $n = 9$	Group 3 (not indicated/not contraindicated) $n = 36$	Group 4 (not indicated/ contraindicated) $n = 10$	P
Intubation, no. (%)	10 (28)	5 (56)	6 (17)	7 (70)	.004*
Hospital mortality, no. (%)	6 (17)	1 (11)	1 (3)	2 (20)	.12
Hospital stay, mean ± SD d	7 ± 6	11 ± 10	7 ± 5	13 ± 17	.12

* $P = .002$ for group 3 versus group 4.

tients with mild exacerbations (higher pH values), no benefits in clinical outcomes were observed with NIV.[18] Treatment of CPE with CPAP and NIV has also been extensively studied. Particularly, a large study that accounted for 70% of all patients with CPE who have been studied in randomized controlled trials of NIV,[19] plus 5 systematic reviews addressing this treatment,[4,20-23] demonstrated a trend toward reduction in endotracheal intubation and hospital mortality. Among subjects with immunosuppression, 2 randomized controlled trials evaluated NIV in patients with respiratory failure and immunosuppressive therapy due to solid organ or bone marrow transplant, or chemotherapy.[24,25] Both studies, which included a total of 92 patients, showed a reduction in endotracheal intubation and hospital mortality. Finally, the application of NIV in postoperative patients has been evaluated in one trial, which included subjects post lung resection complicated with hypoxemia and increased work of breathing.[12] This study found a reduction in rate of endotracheal intubation. The aforementioned evidence constituted the framework for the development of guidelines supporting indications for NIV use. The utilization of NIV for other diseases or syndromes, such as asthma exacerbation, pneumonia, and ALI/ARDS, is not indicated based on current evidence.[13]

Other studies have focused on physiologic parameters to predict NIV failure (need for intubation and mechanical ventilation) in hypercapnic or hypoxemic patients. Among hypercapnic patients, lack of improvement or a fall in pH, no change or an increase in the breathing frequency after 1–2 hours of treatment, high acuity of illness on admission (defined by Simplified Acute Physiology Score II > 34), and lack of cooperation were associated with higher rate of intubation.[26,27] In subjects with hypoxemic respiratory failure, the lack of improvement in P_{aO_2}/F_{IO_2} after 1–2 hours of treatment, age older than 40 years, high acuity of illness, presence of community-acquired pneumonia with or without sepsis, and development of multi-organ system failure were all associated with NIV failure.[10,28,29]

In our study we collected etiology of respiratory failure and physiologic parameters. Not surprisingly, group 4 presented the highest rate of intubation, as it included subjects with no indications but contraindications for NIV, and also physiologic predictors of failure, such as worsening of pH and P_{CO_2}, and high acuity of illness, defined in our study by the APACHE II and SOFA scores. The analysis of subjects with no contraindications (group 1 and group 3) presented interesting results. Despite the fact that group 1 (indications/no contraindications) included subjects with COPD and CPE (both groups with highest evidence of NIV success), greater improvements in pH and P_{CO_2}, and better mental status (GCS), this group did not show better outcomes than group 3 (no indication/no contraindication). These unexpected findings may be due to the small number of subjects included in the study, obscuring a real difference in outcomes. Nevertheless, it is also possible that within subjects with acute respiratory failure and no contraindications for NIV, outcomes may not be affected by the presence or absence of NIV indications. Similarly, in subjects with indication for NIV (groups 1 and 2), the presence of contraindications was associated with a trend toward a higher rate of endotracheal intubation, but it did not reach statistical significance. Again, the small number of subjects may have accounted for this lack of difference. Strikingly, the rate of intubations in the group of subjects with no indications for NIV (groups 3 and 4) was strongly associated with the presence or absence of contraindications. These results might be associated with the presence of contraindications, as well as the fact that group 4 (with contraindications) had higher APACHE II and SOFA scores, and worsening of pH and P_{CO_2} after NIV use.

In our opinion, this study presented several strengths, such as the inclusion of subjects with acute respiratory failure due to multiple diagnoses, the evaluation and comparison of physiologic parameters, and the assessment of relevant clinical outcomes. The study also confirms prior findings such as the importance of physiologic parameters (ie, ΔP_{CO_2} and ΔpH) in predicting NIV failure. Nevertheless, there were also several limitations. First, as this was a retrospective cohort study, selection and information biases were probably present. It is likely that many subjects did not receive NIV upon admission based on lack of indications and/or presence of contraindications, introducing selection bias. It is also possible that subjects were admitted with more than one diagnosis (ie, COPD and

pneumonia), but only one of them was documented, introducing information bias. Second, we included a small number of subjects, which may have affected the statistical significance of our results. Also, these subjects presented a variety of diagnoses, creating heterogeneity within and between each group. Third, we considered immunosuppression and postoperative respiratory failure as indications for NIV. However, current guidelines give recommendations graded 2B and 2C to each one of these conditions, respectively. Fourthly, specific criteria that providers utilized to decide the need for tracheal intubation were unavailable in our data set. Therefore, it is possible that some subjects could have been intubated or not intubated without clear reasons, affecting our final results. Last, other factors not accounted for in this study, such as lack of tolerance to NIV interface, provider experience in terms of NIV management, and factors unrelated to respiratory problems (eg, need of sedation for agitation, elective surgery), could have affected clinical outcomes.

Conclusions

In summary, our study supports the extended utilization of NIV for subjects without contraindications for it, and for subjects with indications despite the presence or absence of contraindications. Healthcare providers should consider very carefully those subjects with no indications for NIV, as the presence of contraindications is associated with higher NIV failure rate.

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