Original Article

Non-Invasive Ventilation in Emergency Patients with Respiratory Distress: A Randomized Controlled Trial

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Background: Benefits of non-invasive ventilation [NIV] has been proven as a modality of treatment for acute respiratory failure patients. However, there are few studies about the benefit of early use of NIV in dyspnea and hypoxemic patients.

Objective: To investigate the benefit of NIV in emergency patients with respiratory distress.

Materials and Methods: A prospective randomized controlled trial was conducted at the Emergency Department of Siriraj Hospital, to compare NIV and standard oxygen therapy [SOT] in patients with respiratory distress. The primary outcome was respiratory rate at 120 minutes after intervention.

Results: One hundred fourteen patients were randomized to receive SOT (57 patients) and NIV (57 patients). NIV could provide a significant decrease in respiratory rate at 120 minutes compared to SOT (p = 0.042). NIV was also associated with a significant improvement in pulse rate at 120 minutes (p = 0.001). No statistically significant differences were found in respiratory rate at 60 minutes, intubation, short-term mortality rate, and length of hospital stay between the two groups. Overall success rate of NIV was 86%.

Conclusion: NIV could rapidly reduce respiratory rate and pulse rate at 120 minutes compared to SOT in emergency patients with acute respiratory distress. However, there was no benefit of NIV in the reduction of length of hospital stay, intubation, and short-term mortality rate.

Keywords: Acute respiratory distress, Emergency, Non-invasive ventilation, Respiratory rate

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Respiratory distress is a common presenting symptom of emergency patients. The treatment of respiratory distress is emphasized on reversing the specific underlying causes. Management is otherwise supportive and directed at improving oxygenation and ventilation. All is aimed to prevent consequential acute respiratory failure [ARF] and intubation, which lead to increased length of stay [LOS] and mortality.

Non-invasive ventilation [NIV] has been widely used in ARF to avoid intubation, especially in acute exacerbation of chronic obstructive pulmonary disease [AECOPD] and acute cardiogenic pulmonary edema [CPE][1-3]. Early use of NIV in ARF has been proven to increase chances of successful NIV. In contrast, the risk of NIV failure is increased if the NIV was delayed[2]. Early use of NIV in patients with respiratory distress has been shown to prevent ARF. In adult patients with respiratory distress, NIV could be used as a respiratory supporting device to help prevent intubation[4]. It has also been shown to improve physiologic parameters such as respiratory rate, heart rate, and arterial pH[5]. NIV could also reduce heart rate and respiratory rate in pediatric patients with acute respiratory distress [ARD], defined as increased respiratory rate for age, accessory muscle use, and a requirement of oxygen support to maintain oxygen saturation above 94%[6].

However, previous trials were non-randomized with inclusion criteria not clearly defined or small randomized controlled trial [RCT]. Furthermore, there was no use of physiologic parameters as outcomes of NIV use in emergency patients with respiratory distress. The authors hypothesized that NIV could improve physiologic parameters in respiratory distress patients. Therefore, the present study aimed to compare respiratory rate between the patients who received NIV and those received standard oxygen therapy [SOT].

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Materials and Methods

Study design

A prospective randomized parallel controlled trial (Thai Clinical Trials Registry number TCTR 20150325002) was conducted at the Emergency Department [ED] of Siriraj Hospital, a tertiary care university hospital with 2,200 inpatients beds, between May 2014 and December 2015. The present study was approved by the Siriraj Institutional Review Board. Written informed consent was obtained from all patients or surrogate decision makers.

Participants

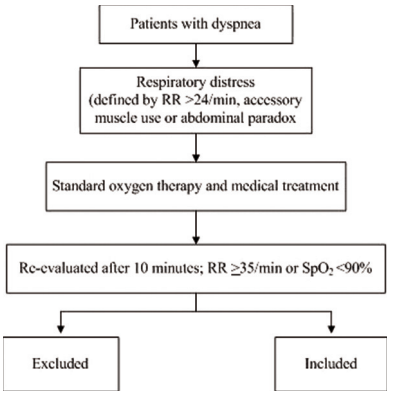
Adult patients with respiratory distress were included. Inclusion criteria were age over 18 years, respiratory rate greater than 24 breaths per minute, accessory muscle use or abdominal paradox, and room air oxygen saturation by pulse oximetry [SpO_2] of less than 95%. Patients with cardiac arrest, a requirement of immediate intubation, unstable medical conditions (shock, acute myocardial infarction, and ventricular arrhythmia), high risk of aspiration, Glasgow coma scale of less than 13, untreated pneumothorax, recent esophagus and upper airway surgery, pregnancy, inability to fit mask, respiratory rate greater than 35 breaths per minute, or pulse oximetry of less than 90% after receiving oxygen supplement for 10 minutes were excluded.

Intervention

After ED arrival, patients with dyspnea would receive initial oxygen supplement and standard medical treatment. They were then re-evaluated at 10 minutes. If, they had respiratory rate of less than 35 breaths per minute and SpO_2 greater than 90% after receiving initial oxygen supplement, they were included and randomly assigned to receive either SOT or NIV (Figure 1).

SOT: Patients received oxygen therapy via nasal cannula or face mask with reservoir bag, with oxygen flow adjusted to maintain SpO_2 above 94% or 90% to 92% in patients with chronic respiratory failure.

NIV: Bi-level positive airway pressure [BiPAP] or pressure support ventilation [PSV] or continuous positive airway pressure [CPAP] was delivered through oronasal mask by Carina, Dräger® or Trilogy 202, Respironic®. Initial inspiratory positive airway pressure [IPAP] was started at 5 to 7 cmH_2O or pressure support at 3 to 4 cmH_2O and expiratory positive airway pressure [EPAP] at 2 to 3 cmH_2O, while CPAP was initially set at 2 to 3 cmH_2O. Either could be increased to achieve targeted tidal volume of 5 to 7 ml/kg and total airway pressure below 25 cmH_2O. Fraction of inspired of oxygen [FiO_2] was commenced at 0.5 and adjusted to maintain SpO_2 above 94%.



RR, respiratory rate

Figure 1. Flow diagram of the patients inclusion process.

All patients would receive the allocated intervention within one hour after ED arrival and for at least two hours. In the NIV group, NIV was discontinued when the symptoms improved or under the decision of the primary physician. Standard medical treatment was prescribed in all patients. Termination criteria were NIV intolerance, respiratory rate of more than 34 breaths per minute or SpO_2 less than 90% for 10 minutes, major complications of NIV (hypotension or pneumothorax), or at the primary physician discretion. If any of the termination criteria was met, the patients were discontinued from each intervention. In the NIV group, the patients who met termination criteria were considered as NIV failure. After the intervention period, further management in both groups continued according to the decision of the primary physician.

Outcomes

The primary outcome was the comparison of the respiratory rate at 120 minutes [RR_{120}] between NIV and SOT groups. The respiratory rate was measured for one minute by nurse or research assistant. The secondary outcomes were respiratory rate at 60 minutes [RR_{60}], pulse rate at 120 minutes [PR_{120}], intubation rate within 24 hours, 7-day mortality rate, LOS, complications and success rate of NIV, defined as no termination criteria and no requirement of intubation within 24 hours after the start of NIV use.

Sample size calculation

From the previous study in children[6], the mean of respiratory rate was 28±6 breaths per minute in the

NIV group and 32±12 breaths per minute in the SOT group. With 80% of power and two-sided significance level of 0.05, the sample size was 57 in each arm. The data were analyzed according to an intention-to-treat analysis.

Randomization

Patients were randomly assigned in a 1:1 ratio by block of 10 using sealed opaque envelope. If there were eligible patients in the ED, the primary physician would notify the project researchers to obtain written informed consent and randomize the patients.

Data collection

Demographic data including age, sex, underlying diseases, and diagnosis at discharge were recorded. Non-invasive blood pressure, PR, RR, and SpO_2 were recorded at initial presentation, before commencing allocated intervention and at 5, 10, 30, 60, 90, and 120 minutes after intervention.

Statistical analysis

Descriptive data were presented as number, percentage or mean ± standard deviation [SD] for normal distributed data and median (min, max) for non-normal distributed variables. Continuous data was analyzed using student t-test or Mann-Whitney U test while Chi-square or Fisher's exact test was employed to analyze categorical data. The primary outcome (RR_{120}) was analyzed using Analysis of Covariance [ANCOVA] with respiratory rate at initial presentation at ED [RR_{ED}] as a covariate. Variables with 2-sided p-value of less than 0.05 were considered statistically significant. All statistical analyze were performed using SPSS 18 (SPSS Inc., Chicago, Illinois).

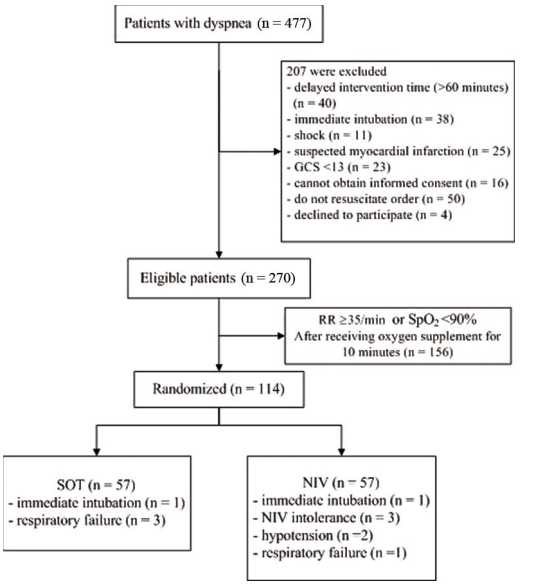
Results

During the study period, 477 patients with dyspnea were eligible for inclusion. Two hundred seven patients were excluded. Two hundred seventy patients were enrolled. After receiving oxygen supplement for 10 minutes, 156 patients were further excluded, and 114 patients underwent randomization, 57 in the SOT group and 57 in the NIV group (Figure 2).

Patients' mean age was 69±15 years and 54.4% were female. The most common diagnosis was AECOPD followed by CPE and asthma with acute exacerbation. The RR_{ED} was 31.6±4.6 breaths per minute in the SOT and 32.1±5.6 breaths per minute in the NIV group. There were no statistically significant differences of baseline characteristics between the two groups except for the treatment with antibiotics and systemic corticosteroids (Table 1).

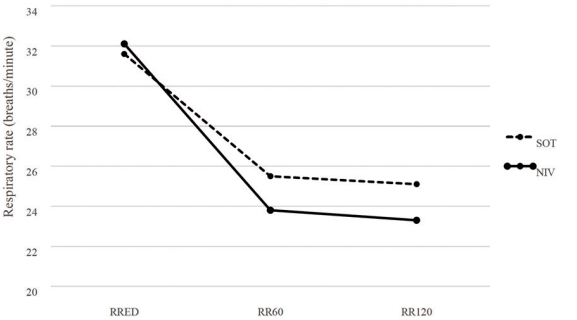
RR_{120} in the NIV group was statistically significantly lower than the SOT group (23.3±5.1 versus 25.1±5.1, $p = 0.042$) (Figure 3).

For the secondary outcome, PR_{120} in the NIV group was also statistically significantly lower than the SOT group (91±21 versus 104±20, $p = 0.001$). There were no significant differences in RR_{60}, intubation rate within 24-hour, LOS and 7-day mortality rate between the two groups (Table 2). Eleven patients were early



SOT, standard oxygen therapy; NIV, non-invasive ventilation; RR, respiratory rate; SpO_2, oxygen saturation by pulse oximetry; respiratory failure, RR ≥35 breaths/min or SpO_2 <90%; GCS, Glasgow coma scale

Figure 2. Flow diagram of the eligible patients.



	RR_{ED}	RR_{60}	RR_{120}
SOT	31.6	25.5	25.1
NIV	32.1	23.8	23.3
p value	0.623	0.111	0.042

SOT, standard oxygen therapy; NIV, non-invasive ventilation

Figure 3. Comparing of initial respiratory rate at Emergency Department [RR_{ED}], 60 minutes [RR_{60}], and 120 minutes [RR_{120}] after between SOT and NIV group.

Table 1. Baseline characteristics of patients

Variable	SOT (n = 57)	NIV (n = 57)	*p*-value
Age (years), mean ± SD	67.2±14.9	71.0±13.1	0.152
Female, n (%)	34 (59.6)	28 (49.1)	0.259
ER arrival vital signs, mean ± SD			
Systolic blood pressure (mmHg)	153.3±29.7	148.7±29.5	0.418
Diastolic blood pressure (mmHg)	87.0±19.4	81.9±19.2	0.157
Heart rate (beats/minute)	104.8±21.7	99.6±24.4	0.234
Respiratory rate (breaths/minute)	31.6+4.6	32.1+5.6	0.623
Oxygen saturation (%)	87.4±7.6	86.9±8.4	0.745
Underlying disease, n (%)			
Hypertension	31 (54.4)	34 (59.6)	0.570
COPD	23 (40.4)	19 (33.3)	0.437
Dyslipidemia	15 (26.3)	18 (31.6)	0.536
Asthma	14 (24.6)	11 (19.3)	0.497
Cardiovascular disease	16 (28.1)	16 (28.1)	1.000
Diabetes	14 (24.6)	14 (24.6)	1.000
Diagnosis, n (%)			
AECOPD	21 (36.8)	15 (26.3)	0.230
Cardiogenic pulmonary edema	8 (14.0)	11 (19.3)	0.448
Asthma with acute exacerbation	11 (19.3)	8 (14.0)	0.448
Pneumonia	5 (8.8)	12 (21.1)	0.068
Other	12 (21.1)	11 (19.3)	0.821
Co-treatment, n (%)	56 (98.2)	56 (98.2)	1.000
Diuretic	15 (26.3)	19 (33.3)	0.413
Bronchodilator	44 (77.2)	41 (71.9)	0.519
Dexamethasone	29 (50.9)	18 (31.6)	0.038
Antibiotics	17 (29.8)	28 (49.1)	0.040

SOT = standard oxygen therapy; NIV = non-invasive ventilation; AECOPD = acute exacerbation of chronic obstructive pulmonary disease

Table 2. Secondary outcomes

Variables	SOT	NIV	*p*-value
RR_{60} (breaths/minute)	25.5±5.8	23.8±6.1	0.111
PR_{120} (beats/minute)	104.1±19.8	91.2±20.7	0.001
Length of hospital stay (hours), median (min, max)	59 (1.65, 2,192.9)	61.3 (23, 748.3)	0.438
7-day mortality, n (%)	0 (0.0)	1 (1.8)	1.000
Intubation within 24-hour, n (%)	3 (5.3)	2 (3.5)	1.000

SOT = standard oxygen therapy; NIV = non-invasive ventilation

Table 3. Complications of NIV

Complications	n (%)
Minor complications	26 (45.6)
Mask related	18 (31.6)
• Mask discomfort	17 (29.8)
• Facial erythema	9 (15.8)
Flow related	9 (15.8)
• Nasal congestion	2 (3.5)
• Nasal - oral dryness	3 (5.3)
• Eye irritation	3 (5.3)
• Gas insufflation	1 (1.8)
Major complications	2 (3.5)
Hypotension	2 (3.5)
Pneumothorax	0 (0.0)
Aspiration	0 (0.0)

NIV = non-invasive ventilation

terminated from the study and included four from the SOT and seven from the NIV group. Of all the patients who had met termination criteria, two patients required immediate intubation. One patient in the NIV group that did not meet termination criteria within 2-hour period of intervention was intubated within 24 hours. Therefore, success rate of NIV in the present study was 86% (49/57). One patient in NIV group died due to sepsis.

Most of NIV complications were minor such as mask discomfort (29.8%) and facial skin erythema (15.8%). As for major complications, two patients had hypotension, but the blood pressure returned to normal after intravenous fluid bolus (Table 3).

Discussion

This was a large RCT that demonstrated a statistically significantly lower RR_{120} in emergency patients with respiratory distress who received NIV compared to those who received SOT. The previous RCT by Wood et al was conducted in a small number of emergency patients with respiratory distress[5]. The primary outcome was intubation rate, which was not statistically significantly different between NIV and conventional medical therapy group (43.8% versus 45.5%, $p = 0.930$). However, there were significant improvement of 1-hour and 24-hour respiratory rate and mean arterial blood pressure compared to baseline among patients receiving NIV, which was similar to the primary outcome of the present study. Another prospective study by Pollack et al was conducted in non-traumatic ARD emergency patients[4]. They reported a comparable NIV success rate of 86%, though they did not have a clearly defined inclusion criteria for ARD patients, which may have caused selection bias. A retrospective study by Popnick et al, performed in emergency patients with ARF, reported the success rate of NIV at 74%, which could be predicted by an improvement in pH and $PaCO_2$ during the 30-minute trial[11].

NIV has been proven to improve physiologic parameters, and reduce intubation and mortality rate in patients with ARF due to AECOPD[2,3,7,8] and CPE[2,3,9]. About 50% of patients in the present study were diagnosed as AECOPD and CPE, which was similar to the previous studies[4,5]. They were, thereby, more likely to be successfully treated with NIV. An improvement of physiologic parameter, such as respiratory rate and pulse rate, was usually seen at one to two hours after using NIV. The success rate of NIV was increased in mild to moderate ARF patients from AECOPD, which

corresponded to the inclusion criteria in the present study.

Intubation rate within 24 hours and 7-day mortality did not differ between the two groups in the present study. This might be due to the short duration of NIV use. The required time of NIV use to prevent endotracheal intubation was commonly 6 to 10 hours per day. Furthermore, NIV should also be continued for a few days[10]. The mortality rate in the present study was in contrast to the study by Wood et al, which was seen to be increased among patients receiving NIV. The increased mortality rate in that study might be explained by the prolonged interval between ED arrival and endotracheal intubation in the NIV group compared to SOT group[5]. Therefore, the termination criteria in our study was created for patient safety to prevent such consequences.

Overall success rate of NIV in the present study was about 86%, which was similar to a previous study in emergency patients with respiratory distress[4]. For ARF patients in the ED, NIV success rate was about 60% to 74%, which was less than in patient with respiratory distress[11-13]. Therefore, early use of NIV in mild degree of respiratory distress could give more chance of success. Two patients in the NIV group required intubation within 24 hours as both were diagnosed as pneumonia, which was proven to be a predictor of NIV failure[14,15].

From literature review, the rate of minor NIV complications, which are mask discomfort and facial skin erythema, occurred in about 30% to 50% and 20% to 34%, respectively. Major NIV complication, such as hypotension, presented at less than 5%. Accordingly, the rate of minor and major NIV complications in the present study were similar to the previous study[16].

The present study had several limitations. First, the authors only studied short-term physiologic parameters without arterial blood gas results. Second, the short duration of NIV used might not demonstrate a statistically significant difference in intubation and mortality rate.

Conclusion

NIV could rapidly reduce respiratory rate and pulse rate compared to SOT in emergency patients with ARD. However, no benefit of NIV was shown in the reduction of length of hospital stay, intubation, and short-term mortality rate.

What is already known on this topic?

NIV has been a proven benefit in ARF from COPD and CPE patients. Early use of NIV reduces chance of intubation and mortality rate. However, roles of NIV in ARD patients is still controversial.

What this study adds?

When comparing with standard oxygen therapy, NIV was associated with rapidly reduced respiratory rate and pulse rate in ARD patients. However, early use of NIV was not associated with reducing intubation rate, short term mortality, and length of hospital stay in these population.

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Potential conflicts of interest

The authors declare no conflict of interest.

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