The efficacy of non-invasive positive pressure ventilation in ARDS: a controlled cohort study

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ÖZET

ARDS'de noninvaziv pozitif basınçlı ventilasyonun etkinliği: Kontrollü kohort çalışması

Akut solunum sıkıntısı sendromu (ARDS)'nda noninvaziv pozitif basınçlı ventilasyon (NPPV)'un kullanımını inceleyen çalışmalar oldukça azdır. Bu kontrollü kohort çalışmasında amacımız; ARDS'de NPPV'nin etkinliğini belirlemektir. Solunum yoğun bakım ünitesinde iki yıl boyunca takip edilen 287 hasta çalışmaya dahil edildi. Yirmi iki hasta Avrupa-Amerika uzlaşı konferansı kriterlerine göre ARDS olarak kabul edildi ve çalışmaya dahil edildi. Hastalar sırayla "NPPV grubu" ve "standart tedavi grubu" olarak ikiye ayrıldı. Çalışma öncesi invaziv mekanik ventilasyon endikasyonları belirlendi. Her iki grupta da entübasyon endikasyonu olduğunda hastalar hemen entübe edildi. Standart tedavi grubunda acil entübasyon endikasyonu olmayan hastalara standart medikal destek tedavisi uygulandı. NPPV grubu ARDS hastalarında ise standart medikal tedaviye ek olarak NPPV uygulandı. Primer amacımız entübasyon sıklıkları, ikinci amacımız hastane mortalitesi idi. Hastaların 17 (%85)'si erkekti. Toplam 20 hastanın 18 (%90)'i primer ARDS idi. Ortalama yaş 45.2 ± 19.7 yıl, ortalama PaO_2/FiO_2 oranı 106.6. Standart tedavi grubunda sekiz hasta, NPPV grubunda ise üç hasta acil entübe edilerek invaziv mekanik ventilasyon uygulandı. NPPV grubundaki yedi hastaya yüz maskesi ile NPPV uygulandı. NPPV uygulanan hastaların 4 (%57)'ünde başarılı olundu, üçünde ise NPPV başarısızlığı nedeniyle entübasyon gerekti. Ortalama NPPV uygulama süresi 58.3 saatti. NPPV başarılı ve başarısız hastalar arasında "Acute Physiology Assessment and Chronic Health Evaluation (APACHE)" II skoru ve başlangıç PaO_2/FiO_2 değerleri açısından anlamlı bir fark yoktu. Yirmi dördüncü saatteki PaO_2/FiO_2 değerleri açısından fark istatistiksel olarak da anlamlı idi (sırasıyla 193 ve 93; p= 0.003). Sonuç olarak; ARDS'de NPPV uygulamasında ilk 24 saatte olumlu gelişme olmazsa gecikmeden invaziv mekanik ventilasyona başlanmalıdır.

Anahtar Kelimeler: ARDS, noninvaziv ventilasyon, entübasyon, mortalite, yoğun bakım.

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SUMMARY

The efficacy of non-invasive positive pressure ventilation in ARDS: a controlled cohort study

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Few studies have investigated non-invasive positive pressure ventilation (NPPV) in acute respiratory distress syndrome (ARDS). The aim of this controlled cohort study was to determine the efficacy of NPPV in ARDS. Two hundred and eighty-seven patients were monitored in the respiratory intensive care unit over two years. Twenty-two subjects met the American-European consensus criteria for ARDS and were included in the study. Patients were prospectively allocated into standard therapy group and NPPV group. Indications for invasive mechanical ventilation were determined before study commencement. Invasive ventilation was applied to those needing intubation. Those in the NPPV group showing no indications for urgent intubation received NPPV in addition to standard medical therapy. Subjects with indications for intubation were intubated. Primary outcome was intubation rate; secondary outcome was hospital mortality. Seventeen patients were males, 18 (90%) patients were treated for pulmonary ARDS. Mean age was 45.2 years; mean PaO_2/FiO_2 was 106.6. The need for intubation emerged for eight patients in the standard therapy group. Seven patients in the NPPV group received NPPV, and three patients in this group needed immediate intubation. NPPV was successful in 4 (57%) patients and the other three required intubation for high PEEP or NPPV intolerance. Mean duration of NPPV was 58.3 hours. There was no difference in Acute Physiology Assessment and Chronic Health Evaluation (APACHE) II scores and initial PaO_2/FiO_2 values between successful and unsuccessful NPPV groups; but the difference between PaO_2/FiO_2 ratios at 24 hours between these groups was statistically significant (193.0 and 93.3, respectively; p= 0.003). While using NPPV in ARDS patients, if improvement is not seen in the first day, invasive mechanical ventilation should be implemented immediately.

Key Words: *ARDS, non-invasive ventilation, intubation, mortality, intensive care.*

Non-invasive positive pressure ventilation (NPPV) is mainly used for patients with chronic obstructive pulmonary disease with hypercapnic respiratory failure (RF), immunocompromised hosts, and patients with cardiogenic pulmonary edema owing to its few adverse effects and high efficiency (1,2). Although many studies have shown that the use of NPPV in acute hypoxemic RF significantly reduces the prevalence of mortality and need for intubation, few studies have investigated its use in acute respiratory distress syndrome (ARDS) (1,3-10).

Resistant hypoxemia and decreased lung compliance are general characteristics of the ARDS. Mortality is mostly due to organ system failure or complications associated with intubation rather than hypoxemia (11,12). A few studies have reported that NPPV is suitable as initial therapy for cases of mild ARDS or for patients with acute lung injury who are conscious and who do not have contraindications for NPPV (5-10,13). In a recent study performed on patients with acute lung injury, NPPV reduced work of breathing (9). Other studies have reported that NPPV failure will be high owing to prolonged edema in ARDS and a need for high positive end expiratory pressure (PEEP) (1,14,15). In three randomized studies among patients with ARDS, NPPV avoided intubation in 46-60% (8,16,17).

Of ARDS patients, between 31% and 80% need mechanical ventilation (7,11,18). Use of the NPPV technique for artificial respiratory support is a new development for these patients. A multivariate analysis of patients with acute hypoxemic RF showed NPPV to be independently associated with a lower risk of invasive ventilation and a lower mortality rate (19). The incidences of adverse effects and hospital mortality of this technique are substantially low when compared to those of invasive ventilation (1,20).

The present study aims to determine the efficacy of NPPV and its effects upon intubation and

mortality in ARDS. We planned a controlled cohort study to demonstrate the efficacy of NPPV in ARDS patients without indications for urgent intubation.

MATERIALS and METHODS

Selection of the Study Group

This study was performed on patients with ARDS at or over 18 and who were treated in the respiratory intensive care unit within the department of chest diseases of the university hospital. Of the 287 patients monitored in the intensive care unit for two years between August 2003 and September 2005, 22 patients met the American-European consensus criteria for ARDS and were thus included in the study (18). One lung-cancer patient who had developed ARDS due to attempted suicide by hanging herself and one ARDS patient who developed severe hypoglycemia due to attempted suicide by injecting a lethal dose of insulin and subsequently diagnosed as brain dead were excluded from the study. As a result, the study group included 20 patients. The agreed ARDS criteria were partial arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) < 200 acute onset bilateral lung infiltration, < 18 mmHg of pulmonary capillary wedge pressure (PCWP) or no clinical and radiological diagnosis of the left ventricular failure. No PCWP measurements were taken for the patients if they had no indications of either clinical or radiological cardiogenic pulmonary edema.

Patients were successively divided into two groups (NPPV group and standard therapy group) to determine the efficiency of early use of NPPV in ARDS patients. Indications of invasive mechanical ventilation (IMV) were determined before the study (21,22). Patients in both groups were intubated immediately when indications of intubation were observed. Patients in the standard therapy group without indications for urgent intubation were only given standard medical therapy (such as oxygen, antibiotics, and bronchodilators), and IMV through an endotracheal tube was applied when intubation criteria were met. ARDS patients in the NPPV group showing no indications for urgent intubation received NPPV in addition to standard medical therapy, and those with indications were intubated. The study flow chart is presented in Figure 1. The process, the NPPV technique, its efficiency and adverse effects were explained to the patients and their relatives, and their consents were obtained. The study was also approved by the ethics committee of the university.

Arterial blood gases, electrocardiography, chest X-rays and other laboratory examinations were performed before the study was started and arterial blood gases analysis were repeated at 1, 6 and 24 hours after the start of NPPV. The duration of their intensive care unit stay and hospitalization were also recorded. All data required for Acute Physiology Assessment and Chronic Health Evaluation (APACHE) II calculation were collected as per the original publication (23). The lowest values recorded within the first 24 hours were used for the score calculation.

The Application of Non-Invasive Ventilation

Patients in the NPPV group who did not require immediate intubation or those without any contraindications for NPPV outlined below received NPPV through silicone full-face masks.

Contraindications for NPPV include (1,2):

1. The need for urgent intubation,

2. The need for frequent aspiration due to excessive secretions (more frequent than 15 minutes),

3. Inability of the patient to adapt himself/herself to the device or unwillingness to undergo NPPV.

The necessary ventilator settings and FiO_2 levels were determined and recorded in accordance with the needs of the patient by the correspondent physician. A BIPAP vision ventilator device (Respironics, Pennsylvania, USA) was used in BIPAP mode for NPPV. NPPV application time was recorded in hours. A CPAP full-face mask (Respironics, Malaysia) was used during NPPV. PEEP (CPAP, EPAP) was set as PaO_2 > 60 mmHg or SpO_2 of > 90%. Inspiratory pressure support (IPAP) was increased in increments of 2-3 cmH_2O to obtain an exhaled tidal volume (V_T) of > 5 mL/kg and a respiratory rate < 30 breaths/minutes NPPV was deemed successful when respiratory failure of the patient improved and the patient did not feel the need for more than 48 hours of ventilator treat-
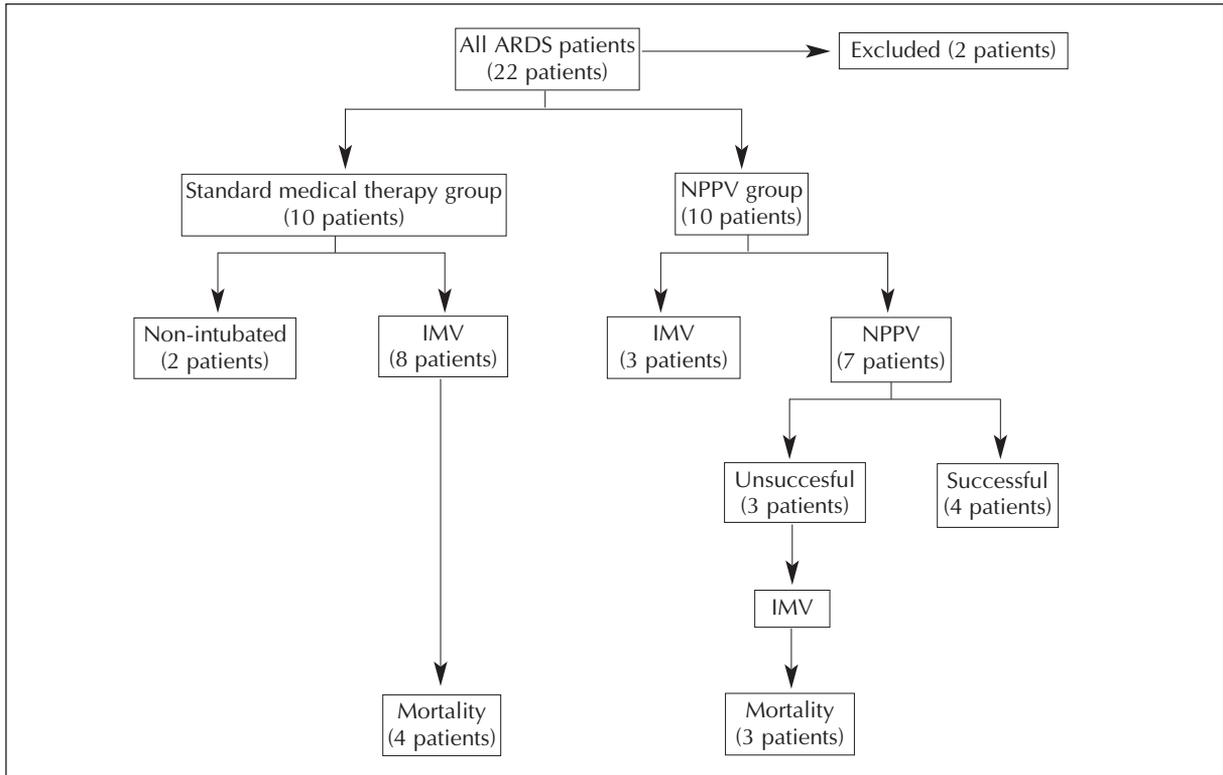
Figure 1. Study flow chart (ARDS: Acute respiratory distress syndrome, NPPV: Non-invasive positive pressure ventilation, IMV: Invasive mechanical ventilation).

ment. When urgent intubation criteria were encountered during any stage of NPPV application, NPPV was considered unsuccessful and the patient was intubated immediately. The degree of dyspnea (Borg scale) and the incidences of adverse effects such as skin erosion, mask leakages, and lower respiratory tract infections were recorded.

Application of Invasive Ventilation

The following criteria indicated immediate intubation was needed (21,22):

1. Apne or respiratory pauses with loss of consciousness or gasping for breath or imminent respiratory arrest,

2. Inability to increase the patient's PaO_2 to more than 40 mmHg and SpO_2 to more than 80% with a $FiO_2 > 0.6$,

3. Inability to increase the patient's pH levels above 7.35, and development of blurred consciousness and confusion (Glasgow Coma Scale < 9) due to respiratory acidosis despite all the support given,

4. Instability of the patient's hemodynamic parameters (such as systolic blood pressure < 80 mmHg or heart rate < 50 beats/minute lasting > 1 hour despite fluid resuscitation).

Amadeus (Hamilton, Via Nova, Switzerland) and Esprit (Respironics, Pennsylvania, USA) ventilators were used for invasive ventilation in assist control ventilation (A/CV) or synchronized intermittent mandatory ventilation modes. The lung protective ventilation strategy was used in ventilation of the ARDS patient (12,24,25). Ventilator settings were adjusted according to low tidal volume (6 mL/kg), low Plato pressure ($P_{Plato} < 35$ cmH_2O) and high PEEP (8-20 cmH_2O). The PEEP needed was determined to be more than 8 cmH_2O, more than 90% oxygen saturation and associated with the fewest hemodynamic adverse effects (undiminished urinary excretion and absence of hypotension). Adequate paralysis and sedation were achieved with atracurium and morphine sulphate. Patients were gradually withdrawn from mechanical ventilation with standard weaning protocol by reducing the pressure support and respiratory rate after regaining conscious-

ness and recovering the ability to breathe on his/her own and provision of adequate oxygenation (PaO_2 > 60 mmHg while FiO_2 < 50%, PEEP < 8 cmH_2O).

Data Collection

Age, gender, risk factors for ARDS, laboratory and radiological findings and APACHE II scores were recorded by an intensive care physician for each patient. Data regarding NPPV such as EPAP, IPAP values, FiO_2, exhaled V_T, respiratory rate, patient's considerations related to mask and pressure, duration of NPPV, adverse effects, arterial blood gases results, duration of hospitalization and patients' outcomes were recorded. A second physician checked the results once again to verify any possible false entry.

The primary outcome variables were determining the efficacy of NPPV, the requirement for intubation, and risk factors associated with failure of NPPV.

Statistical Analysis

For univariate analysis between the "standard therapy" and "NPPV groups", and between patients for whom NPPV was successful or unsuccessful, the chi-square test was used when the variant was categorical and the student t-test was used when it was a continuous variant. "SPSS for Windows 12.0" package software (SPSS, Chicago, IL) was used in the evaluation of statistical procedures and p< 0.05 value was considered statistically significant.

RESULTS

After excluding two patients from 22, the study group remained 20 patients. Six patients could not be clinically or radiological differentiated in terms of cardiogenic pulmonary edema, so PCWP measurements were performed using a pulmonary artery catheter and pressure levels did not exceed 18 mmHg in any of the patients. Three (15%) of the patients were female and the rest (17 pts, 85%) were male. Of the patients, 18 (90%) were treated as primary ARDS. Patients had a mean age of 45.2 ± 19.7 years (range 21-80 years). The general characteristics of all patients are summarized in Table 1.

The patients were successively allocated a standard medical therapy group and a NPPV group (each group contained 10 patients). The initial mean PaO_2/FiO_2 ratio for all ARDS patients was 106.6 mmHg, the mean APACHE II score was 18.7. Eight patients in the standard group who developed indications for immediate intubation received IMV. Immediate intubation criteria were met for three patients in the NPPV group, so these received IMV. The remaining seven patients received NPPV. The mean EPAP value for these seven patients was 9.6 cmH_2O (range 7-12 cmH_2O) and mean IPAP value was 17.4 cmH_2O (range 14-22 cmH_2O).

NPPV was successful in four of the seven patients (57%), and the other three required intubations for need of high O_2 requirement, change in mental status or intolerants of NPPV. For all patients undergoing NPPV, the mean duration of NPPV was 58.3 hours. There was no difference in the duration of NPPV (57.7 and 59 hours, respectively), age (44.7 and 43.7 years, respectively), APACHE II scores (15.5 and 19.7, respectively) and initial PaO_2/FiO_2 values (138.3 and 91.7, respectively) between those responded fa-

Table 1. General characteristics of all patients, and those in the NPPV and standard therapy groups.

Characteristics	All patients (n= 20)	NPPV group (n= 10)	Standard therapy group (n= 10)	p
Age	45.2	43.3	47.1	0.68
Gender (M/F)	17/3	9/1	8/2	> 0.99
APACHE II	18.7	17.4	18.8	0.51
PaO_2/FiO_2	106.6	110.0	103.3	0.71
Duration of ICU stay	11.9	12.7	11.1	0.23

NPPV: Non-invasive positive pressure ventilation, M: Male, F: Female, APACHE II: Acute Physiology Assessment and Chronic Health Evaluation II, ICU: Intensive care unit.

vorably and those who failed to respond to NPPV. There was a statistically significant difference in PaO_2/FiO_2 values after 24 hours between patients for whom NPPV was successful and for whom it was not (193.0 and 93.3, respectively; p= 0.003). The mean initial respiratory rate of NPPV patients was 35.9 breath/minute and the rate measured after six hours was 28.3 breath/minute; however, this result was considered to be of no statistical significance. The distribution of some clinical properties and NPPV parameters are summarized in Table 2.

The mean duration of intensive care unit stay was 11.3 days for patients for whom NPPV was successful, and 11.7 days for those for whom NPPV was unsuccessful (p= 0.81). Of the patients who received NPPV, three developed ulceration on the bridge of the nose and one patient developed atelectasis on the left lower lobe due to the mucus plugs. Invasive ventilation was administered on the three patients for whom NPPV was unsuccessful; however, these patients deceased due to such reasons as no regression in ARDS, sepsis or severe organ failures.

Eight patients from the standard therapy group and six from the NPPV group were intubated. Of the six from the NPPV group, three received urgent intubation, while the other three were intu-

bated after unsuccessful NPPV applications. Three patients in the NPPV group deceased (30% mortality rate) and four of the patients in the standard medical therapy group deceased due to severe sepsis and organ failures (40% mortality rate). The deaths of three patients in the NPPV group, all of whom had been intubated after unsuccessful NPPV applications, led us to assume that NPPV may have delayed intubation.

DISCUSSION

NPPV is often used in cases of acute respiratory failure due to its convenience in relation to preventing intubation (26,27). However, the use of NPPV in cases of ARDS is a new and controversial application, and only a few previous studies have investigated its use in such cases (1,5-10). The role of NPPV in the treatment of ARDS is controversial. ARDS have been much more challenging to NPPV, because their severely deranged pulmonary mechanics and gas exchange necessitate higher levels of PEEP. If NPPV is to be used in an ARDS patient, excessive amounts of alveolar exudation is reduced, gas distribution is ensured, and oxygen consumption of respiratory muscles is reduced (2,28).

We assessed 20 ARDS patients successively and divided them into two groups: a "standard medical therapy group" and a "NPPV group". Of the

Table 2. Distribution of clinical results and characteristics of patients in the NPPV group.

Patient no	Age	Gender	APACHE II	PaO_2/FiO_2 Basic	PaO_2/FiO_2 24th hour	Duration of NPPV (hours)	Success	Duration of IMV (days)	Duration of ICU stay (days)	Survival in hospital
1	26	M	19	63	81	69	N	10	14	H
3	23	M	13	173	194	74	Y	-	10	E
5	67	M	17	88	97	-	-	11	15	E
7	71	M	23	172	218	46	Y	-	14	E
9	39	M	16	118	109	47	N	8	10	H
11	32	M	10	119	208	52	Y	-	9	E
13	20	M	20	69	105	-	-	7	14	E
15	53	M	16	90	152	59	Y	-	12	E
17	66	M	24	95	90	61	N	8	12	H
19	36	F	16	115	125	-	-	13	18	E

APACHE II: Acute Physiology Assessment and Chronic Health Evaluation II, Y: Yes, N: No, NPPV: Non-invasive positive pressure ventilation, IMV: Invasive mechanical ventilation, ICU: Intensive care unit, M: Male, F: Female.

20 patients, the mean APACHE II score was 18.7 and the mean PaO_2/FiO_2 ratio was 106.6 mmHg. Seven ARDS patients deceased (35% mortality), three from the NPPV group and four from the standard therapy group.

NPPV use in ARDS patients, previously presented in the form of several case presentations, was first demonstrated in a university hospital in 1999 on 10 patients (5). In a study involving patients with cases of mild ARDS and acute lung injury, the median APACHE II score was 16, the mortality rate was 30%, the NPPV success rate was 66% and the mean ventilation time was 64 hours. In another study, the effects of NPPV were assessed by dividing ARDS patients into two groups (6). The success rate was 66% for patients with pulmonary ARDS; whereas it was 86% for those with extra pulmonary ARDS. In a more recent study, Antonelli et al. reported the results of a prospective survey of NPPV to treat ARDS performed in three intensive care units (8). Among 479 ARDS patients, 147 (31%) were treated with NPPV, and 46% of these eventually failed. By multivariate analysis, only SAPS II > 34 and $PaO_2/FiO_2 \leq 175$ in one hour independently predicted the need for intubation. In our study, the success rate was shown to be 57% in pulmonary ARDS.

In a study performed by Delclaux et al. in 2000 involving 123 patients with acute lung injury, CPAP was compared with standard therapy (15). Although the PaO_2/FiO_2 ratio increased more rapidly in the CPAP group, the authors failed to demonstrate benefits of NPPV on the prevalence of intubation, duration of hospitalization and mortality. By contrast, in our study, the NPPV mode was BiPAP and patients with ARDS were included.

In a study by Ferrer et al. in 2003 involving patients with severe hypoxemic respiratory failure (of whom 15% were ARDS patients), intubation was required for 52% of patients in the control group but for only 25% of patients in the NPPV group (14). In addition, it was shown that mortality rates of patients in the intensive care unit were significantly lower in the NPPV group than in the standard therapy group (18% versus 39%,

p= 0.028). The multivariate analysis indicated that NPPV significantly reduced the need for intubation and that ARDS is an independent risk factor for intubation. Antonelli et al. studied 64 patients with hypoxemic respiratory failure to compare NPPV with early intubation (7). They concluded that NPPV was as effective as early intubation for improving oxygenation, and of those that received NPPV; only 31% were subsequently intubated. They also reported that patients in the NPPV group had shorter durations of hospitalization, fewer septic complications and reduced mortality rates (7). In our study, patients were also divided into two groups, and it was found that intubation (60% versus 80%, respectively) and mortality rates (30% versus 40%, respectively) were lower in the NPPV group; however, the differences were not significant. ABG values in the NPPV group improved in a short time. This improvement was more evident in patients for whom NPPV was successful, and there was no significant difference in durations of hospitalization and intensive care unit stay.

The most important indicators of the success of NPPV applications are reductions in the respiratory rate and the use of accessory muscles (1-3). In our study, respiratory rates of ARDS patients who received NPPV reduced markedly within the first six hours, and this reduction was less evident in patients for whom NPPV was unsuccessful, thereby indicating that respiratory rate should be considered when determining the level of success.

NPPV can sometimes fail despite a great deal of effort, and intubation of patients may thus become necessary. In a multi-centered study reported that, NPPV was unsuccessful in 30% on patients with hypoxemic respiratory failure, of patients and the highest rate of failure was seen for ARDS (51%) (7). This study also demonstrated that ARDS is an independent risk factor that increases the likelihood of NPPV failure in the multivariate analysis. If NPPV is to be used in an ARDS patient, due to the most failures are in the first 24 hours an early improvement in oxygenation is clearly important to justify continuation. In our study, there was a statistically significant

difference in PaO_2/FiO_2 values after 24 hours between patients for whom NPPV was successful and those for whom it was fail. Similarly, in the study by Antonelli et al. most of the NPPV failures occurred between 12 and 48 hours (8). Antonelli et al. bring us closer to practical guidelines for selection of ARDS patients who might try NPPV (8,29): such as:

1. Be good candidates for NPPV,

2. Not have multiple organ system failure,

3. Not have markedly elevated SAPS II score. The study by Rana et al. identified patients with ALI who have shock, metabolic acidosis or severe hypoxemia as predictors of NPPV failure (10). Great caution should be exercised when choosing candidates for the NPPV application and these patients need very close monitoring; otherwise, they face a high risk of death.

NPPV may be associated with increased incidences of some adverse effects. Most of these are complications caused by the mask used. The most common adverse effects are lesions that occur in positions where the mask exerts pressure on the skin (2,3). In our study, lesions on the bridge of the nose occurred in three patients (43%). When NPPV is interrupted, severe hypoxemia is a significant problem for ARDS. Thus, patients may develop secretion retention if they continually receive NPPV. In our study, one patient also developed left lower lobe atelectasis.

Although our study has such benefits as being a controlled study, there are also some limitations to it. These include the relatively small study sample and the fact that it was not a blind study. Although the need for intubation and the mortality rate were lower in the NPPV group, the differences between the two groups were not statistically significant. However, the present study yielded some very important results that may shed light on the success of NPPV in ARDS, such as the results of the PaO_2/FiO_2 ratio after 24 hours.

The mortality rate was quite low in the NPPV group. All the ARDS patients for whom NPPV was unsuccessful died in the end. The most significant difference between patients for whom NPPV successful and those for whom it failed was in PaO_2/FiO_2 ratios after 24 hours. If improvement is not seen soon after implementation, endotracheal intubation and conventional mechanical ventilation should be implemented immediately.

ACKNOWLEDGEMENT

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