Original Article

A comparison of three strategies for withdrawal of noninvasive ventilation in chronic obstructive pulmonary disease with acute respiratory failure: Randomized trial

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ABSTRACT

Background: The optimal strategy for the withdrawal of noninvasive ventilation (NIV) remains unknown. This study was planned to compare three different strategies for the withdrawal of NIV among patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with hypercapnic respiratory failure (HcRF). **Materials and Methods:** Patients with AECOPD with HcRF who improved on NIV were randomized into three groups – immediate withdrawal (Group A), stepwise reduction of pressure support (Group B), and stepwise reduction of duration (Group C) of NIV. The probability of successful withdrawal was compared among the groups. **Results:** This study included 90 patients (males – 86.6%) with a mean (±standard deviation [SD]) age of 59.9 ± 8.3 years. The mean (±SD) pH and $PaCO_2$ at admission were 7.23 ± 0.04 and 84.4 ± 12.0 mm Hg, respectively. The duration of NIV received before randomization was 31.6 ± 9.2 h with maximum inspiratory positive airway pressure and expiratory positive airway pressure of 17.6 ± 2.7 cm H_2O and 7.4 ± 1.4 cm H_2O, respectively. NIV was successfully withdrawn in 23/30 (76.6%) in Group A, 27/30 (90%) in Group B, and 26/30 (86.6%) in Group C ($P = 0.31$). The total duration of NIV use and length of hospital stay was lower in Group A and B as compared to Group C ($P = 0.001$). **Conclusions:** Immediate withdrawal of the NIV after recovery of respiratory failure among patients with exacerbation of COPD is feasible. Immediate withdrawal did not increase the risk of weaning failure from the NIV.

KEY WORDS: Chronic obstructive pulmonary disease, exacerbation, noninvasive ventilation, weaning

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INTRODUCTION

Noninvasive ventilation (NIV) has revolutionized the management of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with hypercapnic respiratory failure (HcRF). NIV use has been shown to reduce the need for endotracheal intubation, hospital and intensive care unit (ICU) length of stay, and mortality.[1,2] Akin to invasive mechanical ventilation, it is desirable to minimize the duration of NIV as well, to reduce the complications of the NIV itself and other complications acquired due to prolonged hospital stay.[3,4] Multiple studies have been conducted on weaning strategies among patients

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requiring invasive mechanical ventilation.[5,6] As a result of these studies, definite criteria and protocols have been laid down for weaning from invasive mechanical ventilation. However, no such data are available for the withdrawal of NIV.

There has been a marked heterogeneity in the weaning strategies used among previous studies that aimed at studying the utility of NIV in acute respiratory failure.[7-9] Guidelines have suggested a 4-day weaning plan comprising a stepwise reduction of duration of NIV.[10] These guidelines were based on a multicenter randomized study that was designed to compare the effect of NIV and standard medical treatment among patients with AECOPD, rather than comparing different methods of NIV withdrawal.[11] Therefore, the application of those study results to decide about weaning protocol may not be appropriate. Recently, the importance of protocolized weaning from NIV has been highlighted.[12] Conceptually, there may be three possible weaning strategies that can potentially be used – stepwise reduction of duration of NIV use, stepwise reduction in pressure support of NIV, and immediate withdrawal of NIV. Stepwise reduction of either duration of use or pressure support is time-consuming as compared to immediate withdrawal of NIV. Immediate withdrawal strategy will potentially reduce the time spent on NIV and hence shorten the hospital stay and health-care cost. However, there has been no study that has compared these three strategies of weaning from NIV. A single study comparing gradual reduction of duration with immediate withdrawal and reported no difference between the two strategies.[13]

A study comparing three potential strategies of weaning from NIV-stepwise reduction of duration of NIV use, stepwise reduction in pressure support of NIV, and immediate withdrawal of NIV is required. Therefore, we conceived this study to compare three different strategies of withdrawal from NIV among patients with HcRF due to acute exacerbation of COPD.

MATERIALS AND METHODS

Study design, patients, and settings

The randomized study was conducted at tertiary care teaching hospital in India from August 2014 to May 2015. All COPD patients admitted in the pulmonary medicine ward or ICU with acute HcRF who were managed with NIV without the need for invasive mechanical ventilation were eligible for inclusion in the study. Patients on home NIV and those who required NIV for respiratory failure due to diseases other than COPD were not considered for the study.

Patients were enrolled in the study once they have recovered from acute respiratory failure and satisfied weaning criteria as evidenced by all of the following on NIV with inspiratory positive airway pressure (IPAP) ≤16 cm H_2O and expiratory positive airway pressure (EPAP) ≤8 cm H_2O. The weaning criteria adopted from the earlier study[13] were – arterial pH ≥7.35, oxygen saturation (SpO_2) >90% on FiO_2 ≤ 50%, respiratory rate ≤25/min, heart rate ≤120/min, systolic blood pressure ≥90 mm Hg, and no signs of respiratory distress such as agitation, diaphoresis, or anxiety.

Initial NIV settings, pressure changes as well as other management decisions, prior to enrolment in the study, were left to the discretion of the treating physicians, and the study group was not involved in the same till the patients satisfied inclusion criteria for weaning. All the patients received nursing care and medical management as per the standard departmental protocol by the same team of doctors throughout the study. Patients' data were collected from the time of admission; however, the study investigator was not involved in patient management until they satisfied the inclusion criteria.

Noninvasive ventilation withdrawal protocol

Patients satisfying the inclusion criteria were randomized into the following three groups (1:1:1) using variable block randomization method with a block size of 3 or 6 using sealed envelopes for group allocation.

- Immediate withdrawal of NIV (Group A): patients were immediately withdrawn from NIV and monitored on spontaneous breathing
- Stepwise reduction of pressure support (Group B): pressure support was reduced by 2–4 cm H_2O every 4–6 h with vitals and blood gas monitoring till IPAP of <8 cm of H_2O and EPAP of <4 cm of H_2O was attained, after which NIV was completely withdrawn
- Stepwise reduction of duration (Group C): the duration of NIV was reduced to 16 h on the day of randomization (day 0), then reduced to 12 h on day 1 (including 6–8 h of overnight use), 6–8 h of overnight use on day 2, and complete withdrawal on day 3.

Vitals and blood gases were monitored till 48 h after the complete withdrawal of NIV in all the groups. All patients received standard medical treatment with inhaled bronchodilators, systemic steroids, and antibiotics as deemed appropriate by the treating team.

All patients were monitored closely for any signs of weaning failure. The criteria of weaning failure included the appearance any one of the following features – respiratory rate >25/min or increase of >50%; heart rate >140/min or increase >20%; SpO_2 <90% on FiO_2 of 50%; arterial blood pH <7.35; or respiratory distress. Appearance of any one of these within 48 h of withdrawal was considered as a weaning failure. Such patients were restarted on NIV with pressures increased to previously tolerated levels.

The study protocol was approved by the Ethics Committee of Institute. Written informed consent was obtained from the patients or legally authorized representatives.

Primary objective

The primary objective of the study was to compare the rate of successful withdrawal of NIV, defined as no requirement of reinstitution of NIV within 48 h of withdrawal, among the three groups.

Secondary objectives

Secondary objectives included the comparison of time to recurrence of HcRF (from the time of randomization), total number of hours of NIV use, length of hospital stay, and in-hospital mortality among the three groups.

Statistical analysis

In the absence of any study comparing three strategies of withdrawal of NIV, we computed sample size to detect a minimum absolute difference of 40% (30% vs. 70%) between any two groups, with a confidence level of 95% and power of 80%. With this assumption, a sample size of 29 evaluable patients in each of the three groups was calculated and decided to enroll 30 patients in each group.

Variables following approximately normal distribution were summarized by mean ± standard deviation, and one-way analysis of variance was used to compare the three groups. For the analysis of primary and secondary objectives, the effect size (difference in percentage of patients not requiring reinstitution of NIV) and its 95% confidence interval were computed. The total duration of NIV use and hospital stay was calculated from the 1st day of NIV initiation and admission in the emergency, ward, or ICU, respectively. For the secondary objective (time to recurrence of HcRF), the analysis was done using the Kaplan–Meier survival analysis. All analysis was performed as per the principles of intention to treat analysis. STATA 11.0 statistical software (StataCorp. LP, Texas, USA) was used for the analysis. All statistical tests were two-tailed and $P \leq 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

One hundred and nine patients with exacerbation of COPD and HcRF were screened for the study. Nineteen patients were excluded due to various reasons [Figure 1]. Remaining 90 patients fulfilling the inclusion criteria were randomized to Groups A, B, or C (30 in each group). All patients completed the study.

The baseline characteristics of all three groups were comparable in terms of age, gender, smoking status, APACHE II scores, and arterial blood gas parameters. Other baseline characteristics are shown in Table 1.

Primary objectives

NIV was successfully withdrawn in 23/30 (76.6%), 27/30 (90%), and 26/30 (86.6%) patients in Groups A, B, and C, respectively. This difference was not statistically significant, as shown in Table 2 and Figure 2. Among the

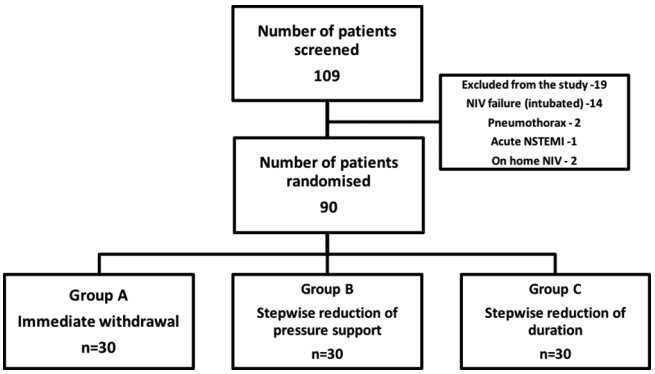

Figure 1: Recruitment of study subjects

patients who failed NIV weaning (n = 14), eight patients were subsequently withdrawn from NIV and discharged. Six patients continued to require NIV support and were discharged on home NIV.

Secondary objectives

The total duration of NIV use was longer in both stepwise withdrawal groups (Groups B and C) compared to immediate withdrawal (Group A). Between Groups B and C, the duration of NIV use was longer in Group C.

Length of hospital stay was longer in both the stepwise withdrawal groups (Groups B and C) as compared to immediate withdrawal (Group A). Comparison of Groups B and C showed longer hospital stay among patients assigned to stepwise reduction in duration (Group C) as compared to pressure support reduction arm (Group B). The comparison of various primary and secondary outcomes is shown in Table 2.

There was a single mortality during the study period (Group A). However, the mortality occurred after 48 h of withdrawal of NIV due to hospital-acquired pneumonia and septic shock. All other patients were successfully discharged from the hospital.

Post hoc analysis

We performed an analysis comparing the characteristics of patients who were successfully withdrawn from NIV and those who failed withdrawal combining all the three groups [Table 3]. Patients who failed NIV withdrawal had a lower pH, higher $PaCO_2$ at admission, and at withdrawal, they also required longer duration of NIV before randomization and higher IPAP, and they had poorer Glasgow Coma Scale (GCS) at admission [Table 3].

DISCUSSION

This randomized trial comparing three strategies of weaning from NIV among patients with acute exacerbation of COPD has shown that immediate withdrawal, stepwise reduction of pressure support, and stepwise reduction of duration of NIV have similar success rates. Immediate withdrawal had the lowest duration of NIV use and hospital stay. The

Table 1: Baseline characteristics of patients enrolled in the study (*n*=30)

Characteristics	Group A	Group B	Group C	*P*
Age (years), mean±SD	61.7±9.07	59.8±8.33	58.3±7.4	0.29
Male gender, *n* (%)	25 (83.3)	27 (90)	26 (86.6)	0.92
Smoker, *n* (%)	25 (83.3)	27 (90)	26 (86.6)	0.92
Smoking index, median (IQR)	450 (120-1200)	400 (200-1000)	550 (200-1200)	0.25
History of exacerbation during the last 1 year, *n* (%)	15 (50)	13 (43.3)	11 (36.6)	0.58
Long-term oxygen therapy, *n* (%)	3 (10)	4 (13.3)	4 (13.3)	0.90
APACHE II score at admission (mean±SD)	15.4±3.91	14.5±3.45	14.3±3.19	0.42
Comorbidities, *n* (%)	10 (33.3)	11 (36.6)	10 (33.3)	0.87
Cor-pulmonale, *n* (%)	12 (40)	11 (36.6)	12 (40)	0.95
Blood gases at admission (mean±SD)				
pH	7.22±0.05	7.24±0.03	7.24±0.04	0.13
$PaCO_2$ (mmHg)	84.2±13.3	84.0±11.9	85.9±11.2	0.80
Blood gases at randomization (mean±SD)				
pH	7.37±0.01	7.37±0.01	7.37±0.01	1.0
$PaCO_2$ (mmHg)	56.3±7.26	57.5±8.47	60.1±8.9	0.19
NIV parameters at randomization (mean±SD)				
Duration of use (h)	32.8±10.6	31.8±9.87	30.4±7.05	0.60
IPAP (cmH_2O)	15.4±1.19	15.7±1.02	15.3±1.37	0.37
EPAP (cmH_2O)	7.06±1.14	7.33±1.09	7.06±1.11	0.45
IPAP maximum (cmH_2O)	17.8±2.31	18.0±2.73	17.1±3.18	0.45
EPAP maximum (cmH_2O)	7.46±1.47	7.66±1.29	7.26±1.50	0.55

SD: Standard deviation, IQR: Interquartile range, NIV: Noninvasive ventilation, IPAP: Inspiratory positive airway pressure, EPAP: Expiratory positive airway pressure

Table 2: Comparison of primary and secondary end points in the three study groups

Outcome	Study Groups (*n*=30)			Pairwise effect size (95% CI), *P*		
	Group A, *n* (%)	Group B, *n* (%)	Group C, *n* (%)	A versus B	A versus C	B versus C
Successful withdrawal	23 (76.6)	27 (90.0)	26 (86.6)	−13.4 (−31.9-5.2), 0.16	−10.0 (−29.4-9.4), 0.31	−3.4 (−19.6-12.8), 0.68
Total duration of NIV (h), mean±SD	32.8±10.6	51.6±12.0	64.0±8.1	−18.8 (−24.6-−12.9), <0.001	−31.2 (−36.1-−26.3), <0.001	−12.4 (−17.7-−7.1), <0.001
Length of stay in hospital (days), mean±SD	5.8±1.5	6.5±1.4	7.6±1.2	−0.7 (−1.4-0.05), 0.06	−1.8 (−2.5-−1.1), <0.001	−1.1 (−1.8-−0.4), <0.001

CI: Confidence interval, NIV: Noninvasive ventilation, SD: Standard deviation

Table 3: Comparison of baseline parameters between patients who succeeded and failed noninvasive ventilation withdrawal

Parameters (mean±SD)	Successful withdrawal (*n*=76)	Failed withdrawal (*n*=14)	*P*
NIV duration before randomization (h)	30.8±8.7	36.4±10.7	0.03
IPAP maximum (cm H_2O)	17.3±2.6	19.7±2.7	0.002
EPAP maximum (cm H_2O)	7.37±1.3	8.0±1.7	0.13
Glasgow Coma Score at admission	13.6±1.3	12.5±0.9	0.005
pH at admission	7.24±0.04	7.23±0.01	0.22
$PaCO_2$ at admission (mmHg)	82.7±11.2	95.6±11.3	0.001
pH at randomization	7.38±0.02	7.37±0.01	0.20
$PaCO_2$ at randomization (mmHg)	56.3±7.7	67.4±7.7	0.001
pH at withdrawal	7.42±0.02	7.38±0.01	0.001
$PaCO_2$ at withdrawal (mmHg)	51.1±8.0	64.9±5.3	0.001
pH at outcome	7.39±0.01	7.32±0.01	0.001
$PaCO_2$ at outcome (mmHg)	53.9±6.7	74.8±4.4	0.001

SD: Standard deviation, NIV: Noninvasive ventilation, IPAP: Inspiratory positive airway pressure, EPAP: Expiratory positive airway pressure

duration of NIV use and hospital stay was shorter among patients weaned by stepwise reduction in pressure support as compared to stepwise reduction in duration of NIV use.

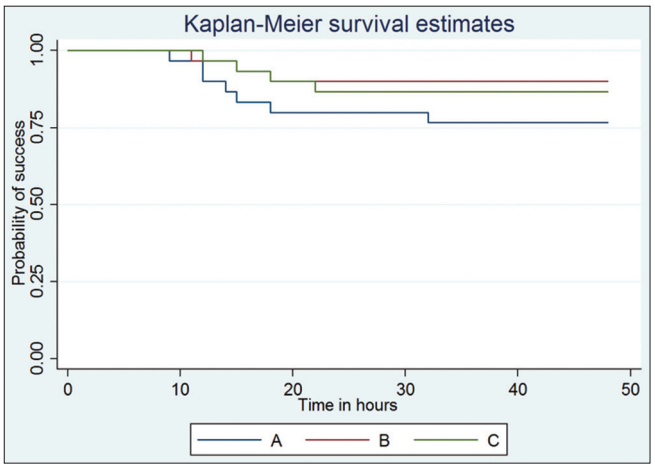

Figure 2: Kaplan–Meier curve for time to successful withdrawal

Among the various indications of NIV, data regarding its utility for patients with exacerbation of COPD and HcRF are most robust. One question remains unanswered till now as to what is the best protocol for withdrawal of the NIV once patients recover from the respiratory failure. There are three possible methods of doing it. First, withdraw NIV immediately once the patient's respiratory

failure has recovered and monitor closely for failure. Second, gradually reduce the IPAP and EPAP at a defined interval and once patient requires minimum pressure support (IPAP of <8 cm of H_2O and EPAP <4 cm of H_2O) then remove the NIV. Third, the duration of NIV use may be reduced gradually and then withdrawn completely. Our study results suggest that there is no difference in rate of successful withdrawal of NIV among the above-mentioned three strategies. Lun *et al*. compared stepwise reduction in the duration of use with immediate withdrawal of NIV and reported a success rate of 74.3% and 56%, respectively.[13] Another randomized trial, published after the completion of our study, by Sellares *et al*. also compared immediate withdrawal and additional 3 days of nocturnal NIV support after recovery from the respiratory failure.[14] They also reported that the success of withdrawal was comparable between the groups (83% and 87%; $P = 0.56$).[14] However, the immediate withdrawal group spent the lowest time on NIV and in the hospital. Importantly, immediate withdrawal was not associated with any adverse outcome. These results imply that immediate withdrawal of NIV is feasible in AECOPD patients without any additional risk of weaning failure. The lesser duration of hospital stay may translate into lesser risk of hospital-acquired infections and NIV-associated complications.

Patients who failed withdrawal received the longer duration of NIV with higher IPAP and EPAP before randomization probably pointing towards a more severe disease exacerbation which took a longer time to recover. These patients also had a poorer GCS at admission, also pointing towards a more severe disease process. They also had higher $PaCO_2$ levels at admission, randomization, and withdrawal, a finding consistently noticed in all the three groups. It can be inferred from the above observations that patients with a higher $PaCO_2$ have a higher likelihood of failing NIV withdrawal and are probably candidates for more stringent monitoring and probably a more gradual withdrawal. However, due to the small sample size, the above inferences need to be confirmed in trials that are adequately powered and have a larger sample size.

Our study is the first randomized trial to compare three different strategies to withdraw NIV in patients with AECOPD with HcRF who improved with NIV. It is also one among the few studies which have addressed the issue of protocols to withdraw NIV in these patients. There was no protocol violation or dropouts during the study.

There are a few limitations of this study. The most important being the small sample size which was calculated based on the difference in the two study arms, instead of three. However, we think that this study is important as results of this may be useful for the calculation of sample size for future trials. Furthermore, it was an open-label study where both patients and the investigators were aware about the intervention. It was a single-center study, and the results may not be generalizable. The study was conducted following good clinical practices for biomedical research involving human subjects, including prior approval of study protocol by the Institutional Ethics Committee.

CONCLUSIONS

Immediate withdrawal of NIV after recovery of HcRF among patients with AECOPD is feasible. Immediate withdrawal did not increase the risk of weaning failure. Adequately powered, multicenter studies are required to assess the impact of immediate withdrawal strategy of NIV on various outcomes such as the time spent on NIV, duration of stay in ICU and hospital, and cost of care.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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