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Comparison of immediate withdrawal and stepwise reduction in duration of non-invasive ventilation in chronic obstructive pulmonary disease patients presenting with acute hypercapnic respiratory failure

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Patient consent: written informed consent has been taken from all patients or legally authorized representatives

Abstract

There is no universally acceptable protocol for the withdrawal of non-invasive ventilation (NIV) in chronic obstructive pulmonary disease (COPD) patients presenting with acute hypercapnic respiratory failure (AHcRF). This study was carried out to evaluate immediate against stepwise reduction in NIV. Sixty COPD patients with AHcRF who were managed with NIV were randomized into two groups - immediate NIV withdrawal (Group A), and stepwise reduction of NIV duration (Group B). The rate of successful NIV withdrawal, time to recurrence of hypercapnic respiratory failure, total duration of NIV use, and hospital length of stay (LOS), were compared among the 2 groups. NIV was successfully withdrawn in 51/60 (85 %) patients. NIV was successfully withdrawn in 24/30 (80%) patients in Group A and 27/30 (90%) patients in Group B ($p=0.472$). The total duration of NIV use was significantly lower in Group A (38.97 ± 17 hours) as compared to Group B (64.3 ± 7.74 hours) ($p<0.0001$). The hospital LOS was significantly lower in group A (5.8 ± 1.6 days) as compared to Group B (7.7 ± 0.61 days) ($p<0.0001$). To conclude, immediate withdrawal of the NIV after recovery of respiratory failure among patients with exacerbation of COPD is feasible and does not increase the risk of weaning failure.

Key words: COPD; NIV; weaning.

Introduction

Non-invasive positive pressure ventilation (NIV) is the preferred initial mode of ventilatory support for Chronic obstructive pulmonary disease (COPD) patients presenting with acute Hypercapnic Respiratory failure (AHcRF). Over the years, multiple studies on patients with invasive mechanical ventilation (IMV) have resulted in definite criteria and protocols for weaning from IMV. Akin to IMV, there are well-defined indications for putting a patient on NIV; however, there are no universally accepted guidelines on how to take the patient off NIV. An early study by Duan *et al.* comparing protocol directed versus physician-directed weaning in NIV patients concluded that protocol-directed weaning decreased the duration of NIV and ICU stay [1]. This small but landmark study brings out a very important issue of protocolized weaning in patients on 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. The 2016 ATS/ERS guidelines state that NIV can be discontinued in COPD patients presenting with AHcRF, by progressively reducing the daytime periods of ventilation in 2 to 3 days, before being discontinued overnight. These guidelines also emphasize the need for more trial data for optimal NIV withdrawal strategy [2].

Hence, this study was planned to compare the rate of successful NIV withdrawal using two NIV weaning strategies i.e., immediate NIV withdrawal and stepwise reduction in duration of NIV. It was also aimed to compare the time to recurrence of hypercapnic respiratory failure from the time of NIV withdrawal in patients who fail to wean from NIV, the total number of hours of NIV use, the total length of hospital stay, and in-hospital mortality among the two groups.

Materials and Methods

Study design, patients and setting

The randomized study was conducted at a tertiary care teaching hospital in India over 18 months. All COPD patients admitted in pulmonary medicine ward or ICU who required only NIV during the hospital stay, were screened for enrolment in the study after clinical stabilization and resolution of underlying cause of AHcRF. Patients not requiring inspiratory positive airway pressure (IPAP) >16 cm H₂O and expiratory positive airway pressure (EPAP) >8 cm H₂O, were then kept on unassisted breathing with Venturi oxygen for 4 hours, at the minimal concentration to achieve the same oxygenation targets of NIV. If after 4 hours of unassisted breathing patients were clinically stable as defined by- arterial pH \geq 7.35, oxygen saturation (SpO₂) >90% on FiO₂ \leq 50%, respiratory rate \leq 25/min, heart rate \leq 120/min, systolic blood pressure \geq 90 mm Hg, and no signs of respiratory distress such as agitation, diaphoresis, or anxiety, were included. Patients who were on home NIV, patients who required NIV for respiratory failure due to diseases other than COPD, and patients with comorbid illnesses like heart failure, chest wall deformity, obstructive sleep apnea, and coronary artery disease were excluded. Written informed consent was taken from the patients or legally authorized representatives. Initial NIV settings, pressure changes as well as other management decisions, before enrolment in the study, were left to the discretion of the treating physicians, and the study investigators were not involved in the same till the patient satisfied inclusion criteria for weaning. All the patients received nursing care and medical management as per the standard departmental protocol throughout the study. Patient data was collected from the time of admission and randomized into the following two groups (1:1) using a variable block randomization method with a block size of 4 using sealed envelopes for group allocation (Figure 1).

- **Immediate withdrawal of NIV – Group A (Gp A):** Patients allocated to this group received the conventional Venturi oxygen mask. The setting of FiO₂ was the same as used before randomization. Oxygen therapy was administered for as long as patients needed; if the

oxygenation target could be achieved without supplemental oxygen, then patients were observed on room air.

- **Stepwise reduction of duration- Group B (Gp B):** the duration of NIV was reduced to 16 hours on the day of randomization (day 0), then reduced to 12 hours on day 1 (including 6–8 hours of overnight use), 6–8 hours of overnight use on day 2, and complete withdrawal on day 3.

Vitals and blood gases were monitored till 48 hours 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 physician. Patients were monitored closely for any signs of weaning failure. The criteria of weaning failure were the appearance of any one of the following features – respiratory rate $>25/\text{min}$ or increase of $>50\%$; heart rate $>110/\text{min}$ or increase $>20\%$; $\text{SpO}_2 <90\%$ on FiO_2 of 50% ; arterial blood pH <7.35 ; or respiratory distress. The appearance of any one of these within 48 hours of withdrawal was considered 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 the institute.

Statistical analysis

The presentation of the categorical variables was done in the form of numbers and percentages (%). The quantitative data were presented as the means \pm SD and as the median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Kolmogorov-Smirnov test. In the cases in which the data was not normal, we used nonparametric tests. The following statistical tests were applied to the results:

1. The comparison of the variables which were quantitative and not normally distributed in nature was analyzed using Mann-Whitney Test and variables that were quantitative and normally distributed in nature were analyzed using the independent *t*-test.
2. The comparison of qualitative variables was analyzed using the Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, a p-value of less than 0.05 was considered significant.

Results

A total of 84 COPD patients presenting with AHcRF were screened for the study. 24 patients were excluded due to various reasons (6 patients were on home NIV, 6 patients had comorbid OSA, 2 patients presented with acute STEMI, and 10 patients required endotracheal intubation and mechanical ventilation). 60 patients fulfilling the inclusion criteria, who were managed with NIV and were clinically stable after 4 hours of unassisted breathing, were randomized into the following two groups: -Immediate withdrawal of NIV (Group A) (n=30), Stepwise reduction of duration (Group B) (n=30). All patients completed the study.

The two groups were comparable in terms of baseline characters (age, gender, BMI, smoking status, and biomass fuel exposure, GCS and APACHE II score at admission, and blood gas parameters) as shown in Table 1. NIV was successfully withdrawn in 24/30 (80%) and 27/30 (90%) patients in groups A and B respectively ($p=0.472$). There was no statistically significant difference in the time to recurrence of hypercapnic respiratory failure from the time of NIV withdrawal in patients who fail to wean from NIV among the two groups (14.5 ± 6.8 hours in Group A vs 20 ± 2 hours in Groups B). The 2 groups were similar in terms of the duration of NIV use before randomization (32.17 ± 8.22 hours in Gp A vs 32.37 ± 7.76 hours in Gp B). However, the total duration of NIV use (in hours) and hospital LOS were significantly less in Group A as compared to Group B (32.17 ± 8.22 hours in GA vs 64.3 ± 7.74 hours in Gp B). There was no in hospital mortality in both groups.

We performed a *post-hoc* analysis of patients who failed and succeeded NIV weaning among both groups. We found that there was a significant difference in NIV duration before randomization (hours), IPAP max (cm H₂O), EPAP max (cm H₂O), GCS score at admission, APACHE II score at admission, pH at admission, pH at randomization, PCO₂(mmHg) at admission, PCO₂ (mmHg) at randomization, between patients who succeeded and failed non-invasive ventilation withdrawal ($p<0.05$) as shown in Table 2.

Based on above findings we further evaluated pH and PCO₂ at admission for predicting successful weaning outcome using Receiver operating characteristic (ROC) curve (Figure 2). Interpretation of the area under the ROC curve showed that the performance of PCO₂ at admission (mmHg) (AUC 0.913; 95% CI: 0.811 to 0.970) was outstanding. Discriminatory power of pH at admission (AUC 0.83; 95% CI: 0.711 to 0.915) was excellent. Among both parameters, PCO₂ at admission (mmHg) was the best predictor of a successful outcome at cutoff point of ≤ 89.4 with an area under curve of 0.913 for correctly predicting successful outcome. The sensitivity, specificity, and positive predictive value of PCO₂ at admission

(mmHg) for predicting successful weaning outcome was 80.39%, 88.89%, and 97.1% respectively. On the other hand, pH at admission (mmHg) had a sensitivity, specificity and PPV of 66.67%, 88.89% and 97.1%, respectively.

When we compared the two high-risk groups as defined by $pH \leq 7.25$ or $pco_2 > 89.4$, we found that 54.54 % in the immediate withdrawal group vs 80% of patients in the stepwise withdrawal group had weaning success according to pH criteria ($p=0.91$), while according to PCO₂ criteria, 37.5% patients achieved success in immediate withdrawal vs 72% of patient in stepwise withdrawal group ($p=0.07$).

Discussion

NIV is an established indication in patients with acute exacerbations of COPD presenting with AHcRF [3]. Although different studies have defined factors predicting the outcome of NIV in terms of intubation and mortality in patients with severe AHcRF [4-6], these studies did not assess the best method to discontinue NIV. There is a paucity of information in defining a strategy to discontinue NIV, and, indeed, the optimal method to discontinue NIV after the recovery of an episode of AHcRF has not been established yet. Damas et al. [7] in 2008 conducted a study to describe the performance of a weaning protocol based on progressive periods of NIV withdrawal in patients with AECOPD and concluded that strategies based on periods with and without NIV are effective and merit further investigation. 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 (Table 3). This study was done to compare two different strategies of weaning from NIV i.e. immediate withdrawal and stepwise reduction in duration of NIV after recovery in COPD patients presenting with AHcRF.

In our study, NIV was successfully withdrawn in 24/30 (80%) and 27/30 (90%) patients in groups A and B respectively. Our study did not demonstrate any significant difference in NIV withdrawal success rate between the immediate and stepwise withdrawal groups as was the case in previous studies. The success rate of NIV weaning of immediate and stepwise withdrawal groups in a similar study by Hadda et al. [8] was 76.6% and 86.6% respectively. Similarly, another study by Lun et al. [4] also did not find any statistically significant difference in NIV withdrawal success rate between the 2 groups. However, both these studies were limited by a small sample size. A recent study by Sellares et al. [9] that recruited 120 COPD patients and compared immediate withdrawal and additional 3 days of nocturnal NIV support after

recovery from respiratory failure, did not find any statistically significant difference in the success rate of NIV withdrawal between these 2 strategies of weaning (83% and 87%: $p=0.56$).

The duration of receiving NIV before randomization was comparable between the 2 groups. However, the total NIV duration was significantly less in the immediate withdrawal group as compared to the stepwise withdrawal group. This may be the result of the study design as the NIV was immediately withdrawn in Gp A whereas it was continued for 3 days after recovery from AHCRF in Gp B. Also, there was no significant difference in NIV parameters at randomization (IPAP, EPAP, IPAP max, EPAP max) between the 2 groups. These findings are consistent with those observed in a similar study by Hadda et al. [8].

Importantly, immediate withdrawal was not associated with any adverse outcome. The Hospital LOS was significantly less in the immediate withdrawal group as compared to the stepwise withdrawal group. The lesser duration of hospital stay may translate into a lesser risk of hospital-acquired infections and NIV-associated complications. There was no significant difference in time to recurrence of hypercapnic respiratory failure after NIV withdrawal between the 2 groups. These results imply that immediate withdrawal is feasible in COPD patients presenting with AHCRF without any additional risk of weaning failure. There was no in-hospital mortality among the 2 study groups. However, since the patients were not followed up after discharge from the hospital, long term inference on late recurrence of AHcRF and mortality cannot be made.

Among the patients who failed NIV weaning ($n=9$), 7 were subsequently withdrawn from NIV and discharged. Two patients continued to require NIV support and were discharged on home NIV. It was observed that patients who failed weaning received a 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. Another probable explanation for this finding may be progressive hyperinflation, resulting from inappropriately higher initial ventilator settings, that led to patient-ventilator asynchrony (PVA) with a high rate of unrewarded inspiratory efforts resulting in deventilation dyspnea [10]. These patients also had a poorer GCS at admission and higher APACHE II score, also pointing towards a more severe disease process. They also had a lower pH and higher PCO₂ levels on admission, randomization, and outcome, a finding consistently noted in both groups. It can be inferred from the above observation that patients with lower pH and higher PCO₂ have a higher likelihood of failing NIV withdrawal and are probably candidates for more stringent monitoring and probably a

more gradual NIV withdrawal. Based on these observations we analyzed pH and PCO₂ at admission using the ROC curve to predict successful weaning outcomes. Although both these parameters performed well to predict successful weaning outcomes. PCO₂ at admission with a cut-off value of ≤ 89.4 mm of Hg had a high AUC of 0.91. The specificity, sensitivity, and PPV of PCO₂ cut off of 89.4 was 80.39%, 88.89%, and 97.6 % respectively. Although there is always a trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity) but overall PCO₂ at admission of ≤ 89.4 mm Hg was the best predictor of successful outcome with maximum AUC. When we compared the two high-risk groups as defined by pH ≤ 7.25 or PCO₂ > 89.4 , we found that 54.54% in the immediate withdrawal group vs 80% of patients in the stepwise withdrawal group had weaning success according to pH criteria (p=0.91), while according PCO₂ criteria, 37.5% patients achieved success in immediate withdrawal vs 72% of patient in stepwise withdrawal group (p=0.07). Although these findings show a favorable trend towards the use of stepwise NIV withdrawal in COPD patients with PCO₂ at the admission of > 89.4 mm Hg, results are not statistically significant. Larger studies with a bigger sample size may be able to confirm these findings.

This study is one of the few studies addressing the important issue of protocolized weaning of NIV in COPD patients presenting with AHCRF. 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.

There are a few limitations of this study that needs to be addressed. First, it was a single-center study with a small sample size, and therefore the results may not be generalizable. Secondly, our enrolment criteria of IPAP < 16 , EPAP < 8 means that a previous reduction of IPAP and EPAP was performed as weaning process in few patients, who required higher pressures in initial period, before randomizing them into two weaning arms. This may have introduced a potential bias in interpretation of results. Thirdly, patients on home/domiciliary NIV and patients using NIV for indications other than COPD were excluded from the study, therefore the results cannot be applied to patients using NIV for indications other than COPD. Fourthly, it was an open-label study where both patients and investigators were aware of the intervention. Last, since patients were not followed up after discharge from the hospital, late recurrence of AHCRF or mortality was not assessed in this study.

Conclusions

Immediate NIV withdrawal is feasible and non-inferior to a stepwise reduction of the duration of NIV as a weaning strategy. Further, the immediate NIV withdrawal strategy results in reduced total duration of NIV and hospital length of stay without any significant increase in the risk of weaning failure. However, patients with high PCO₂ at admission (>89.4 mm Hg) may be candidates for stepwise withdrawal of NIV.

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Table 1. Baseline characteristics of study population.

Characteristic	GROUP A (immediate NIV withdrawal) (n=30)	GROUP B (stepwise NIV withdrawal) (n=30)	p-value
Age in years, (mean±SD)	59.67 ± 8.4	62.03 ± 8.97	0.296
Male gender, n (%)	15 (50%)	19 (63.33%)	0.297
BMI in kg/m ² , (mean±SD)	23.71±2.14	24.44 ± 2.27	0.743
Smoker, n (%)	20 (66.67%)	22 (73.33%)	0.573
Smoking index (mean±SD)	470 ± 232.49	536.36 ± 223.7	0.24
APACHE II score at admission (mean±SD)	17 ± 1.6	16.63 ± 1.92	0.425
GCS score at admission (mean±SD)	14.1 ± 0.84	13.9 ± 0.8	0.395
Blood gases at admission (mean±SD) <ul style="list-style-type: none">• pH• PCO₂ (mm Hg)	7.26 ± 0.03 82.63±10.8	7.27 ± 0.04 82.49±11.1	0.59 0.96
NIV use before randomization in hours (mean±SD)	32.17 ± 8.22	32.37 ± 7.76	0.988

NIV- Non-Invasive Ventilation, SD- standard deviation, GCS- Glasgow Coma Scale, APACHE II-Acute Physiology And chronic Health Evaluation II, PCO₂- Partial Pressure of carbon dioxide in arterial blood

Table 2. Baseline parameters of patients with failed and successful weaning.

Baseline parameters	Success(n=51)	Fail(n=9)	p-value
NIV duration before randomization (hours)	30(25-36)	37(34-41)	0.022
IPAP max before randomization (cm H ₂ O)	16(14-18)	22(20-22)	<0.0001
EPAP max before randomization (cm H ₂ O)	6(6-8)	8(8-8)	0.003
GCS score at admission	14(14-15)	13(13-13)	<0.0001
APACHE II score at admission	16.57 ± 1.75	18.22 ± 1.09	0.008
pH at admission	7.27 ± 0.04	7.24 ± 0.02	<0.0001
pH at randomization	7.41 ± 0.03	7.38 ± 0.01	<0.0001
PCO ₂ (mmHg) at admission	80.25 ± 9.52	95.67 ± 5.68	<0.0001
PCO ₂ (mmHg) at randomization	50.26 ± 5.59	58.89 ± 4.04	<0.0001

NIV- Non-Invasive Ventilation, SD- standard deviation, GCS- Glasgow Coma Scale, APACHE II-Acute Physiology And chronic Health Evaluation II, PCO₂- Partial Pressure of carbon dioxide in arterial blood, IPAP-Inspiratory Positive Airway Pressure, EPAP- Expiratory Positive Airway Pressure

Table 3. Studies of NIV weaning in COPD patients.

Study name	Strategy for NIV withdrawal	Results
Lun et al. [4] (2013) (n=60)	(35 immediate withdrawal v/s 25 stepwise withdrawal) <u>Weaning protocol:</u> NIV duration was reduced to 16 hours on the day of randomization (day 0), then reduced to 12, 8, and 0 hours on days 1–3, respectively.	No statistically significant difference in the success rate NIV successfully stopped in 74.3% and 56% of the stepwise and immediate withdrawal groups, respectively (p=0.139).
Selares et al. [9] (2017) (n=120)	<u>Weaning protocol:</u> 61 patients received three additional nights of NIV v/s direct NIV discontinuation in 59 patients The primary outcome was relapse of AHcRF within 8 days after NIV discontinuation.	No differences in relapse of AHcRF after NIV discontinuation (10 (17%) versus 8 (13%) for the direct discontinuation and nocturnal NIV groups, respectively, p=0.56) No differences in long-term ventilator dependence, hospital stay, and 6-month hospital readmission or survival.
Hadda et al. [3] (2020) (n=90)	Three groups of 30 subjects each– (Group A)-immediate withdrawal (Group B)- stepwise reduction of pressure support PS reduced by 2–4 cm H ₂ O every 4–6 h till IPAP of <8 cm of H ₂ O and EPAP of <4 cm of H ₂ O was attained, f/b complete NIV withdrawal (Group C)- stepwise reduction of duration NIV was reduced to 16 hours on the day of randomization (day 0), then reduced to 12 h on day1 (including 6–8 h of overnight use), 6–8 hours of overnight use on day 2, and complete withdrawal on day 3.	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).

Damas et al. [10] (2008) (n=65)	Weaning strategy: during the first 24 hours in each 3 hours, one hour without NIV (except during the night period), on the second day in every 3 hours, two hours without NIV (except during the night period) and on the third day NIV was used during the night period.	All patients completed the weaning protocol with no re-institution of NIV or invasive ventilation during hospitalization.
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NIV- Non-Invasive Ventilation, PCO₂- Partial Pressure of carbon dioxide in arterial blood, IPAP-Inspiratory Positive Airway Pressure, EPAP- Expiratory Positive Airway Pressure, AHcRF- Acute Hypercapnic Respiratory failure

Figure 1. Recruitment of study subjects.

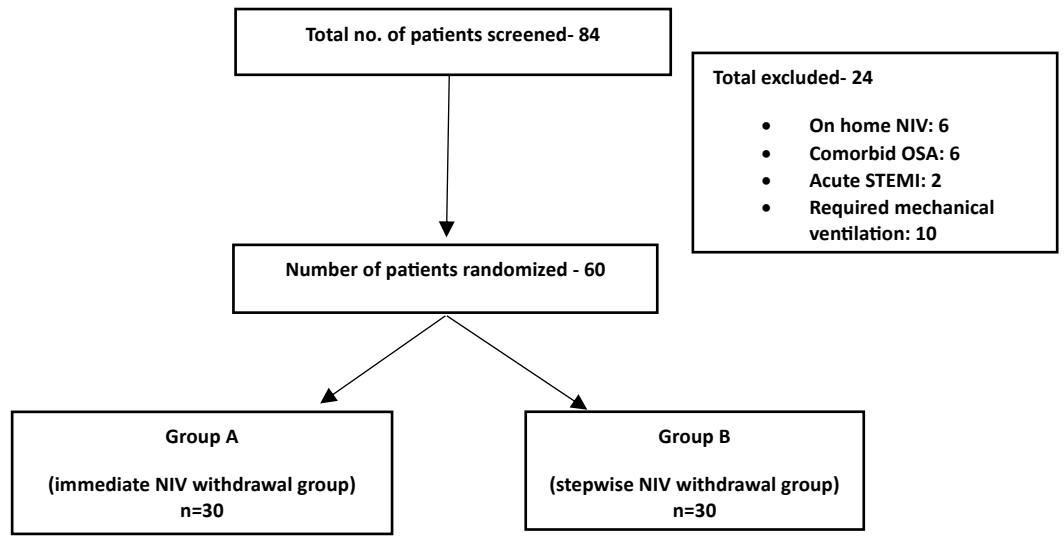


Figure 2. Receiver operating curve (ROC) for pH and PCO₂ (mm of Hg) at admission for predicting successful weaning outcome.

