Original Article

Effectiveness of high flow nasal cannula (HFNC) versus bilevel positive airway pressure (BiPAP) in preventing tracheal reintubation in patients with high risk of extubation failure in intensive care unit – A randomised comparative trial

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ABSTRACT

Background and Aims: The incidence of tracheal extubation failure in high-risk patients is higher, and non-invasive ventilation is suggested to avoid tracheal reintubation. This study compares the effectiveness of bilevel positive airway pressure (BiPAP) and high flow nasal cannula (HFNC) to reduce the rate of reintubation in intensive care unit (ICU) patients with increased risk of extubation failure. **Methods:** This randomised comparative trial was conducted on 60 high-risk patients on mechanical ventilators admitted to the ICU, ready for weaning after a spontaneous breathing trial. They were randomised to Group H for HFNC and Group B for BiPAP therapy. Designated therapy was administered in these high-risk patients for up to 48 hours after tracheal extubation. Haemodynamic parameters [mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), a saturation of peripheral oxygen (SpO_2), electrocardiogram (ECG)], arterial blood gas analysis (ABG) parameter [potential of hydrogen (pH), partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen/fraction of inspired oxygen (paO_2/FiO_2) ratio], the effectiveness of cough, comfort level was recorded and continuous monitoring for signs of respiratory distress and failure was done. **Results:** Most of the patients were obese and had more than two risk factors for extubation failure. Several patients in Group B have significantly higher successful extubation than in Group H ($P = 0.044$). Most of the reintubation took place within 24 hours. The HFNC therapy was more comfortable and acceptable to patients. **Conclusion:** BiPAP therapy was more efficient than HFNC in preventing tracheal reintubation among patients with a high risk of extubation failure.

Keywords: Bilevel positive airway pressure, extubation failure, high flow nasal cannula, intensive care unit, non-invasive ventilation, reintubation, tracheal extubation

INTRODUCTION

Extubation and weaning from ventilatory support are critical aspects of patient care in the intensive care unit (ICU). In critically ill patients, tracheal reintubation following extubation occurs in about 10% -15% of cases, and it can rise to 20% in instances where patients have significant risk factors.[1] Reintubation has been shown to increase morbidity and mortality by 40%.[2] The most common associated risk factors are age, prolonged mechanical ventilation,

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higher acute physiology and chronic health evaluation (APACHE) II score, difficult weaning, obesity, presence of co-morbidities, etc.[3-7]

Recent international clinical practice guidelines recommend using non-invasive ventilation, based on moderate-grade evidence, to prevent tracheal reintubation in patients at high risk of extubation failure.[8,9] Bilevel positive airway pressure (BiPAP) and high flow nasal cannula (HFNC) are the two most commonly used modes of non-invasive ventilation. HFNC can deliver heated and humidified gas at extremely high flow rates. This is advantageous because patients with acute respiratory failure can become very tachypnoeic, and their peak inspiratory flows (PIF) can increase to above 120 L/min. For every 10 L/min of flow provided with closed mouth breathing, 1 cm H_20 of positive end-expiratory pressure (PEEP) is generated, by which HFNC therapy can increase the patient's functional residual capacity (FRC) at the end of expiration. It also increases positive pharyngeal pressure and carbon dioxide (CO_2) clearance to support alveolar ventilation and improve oxygenation, thus helping reduce breathing.[10] BiPAP uses positive pressure to assist the patient's spontaneous respiration by delivering airflow at two different pressures during inspiration and expiration. The primary objective of this study was to compare the effectiveness of BiPAP with HFNC therapy in preventing reintubation in high-risk cases. The secondary objective was to assess the comfort level and acceptability of treatment. We hypothesised that BiPAP is superior to HFNC in decreasing the extubation failure rate in high-risk patients.

METHODS

This randomised comparative trial was conducted after obtaining clearance from the institutional ethics committee (vide approval no. 2022/IEC/IGIMS/2020 dated 11-01-2021) and trial registration at Clinical Trials Registry- India (vide registration number CTRI/2021/07/035131, www.ctri.nic.in). Prior informed written consent was obtained from patients' attendants for participation in the study and use of the patient data for research and educational purposes. We excluded the patients who declined the therapy even if their attendants had consented. The study procedures follow the guidelines of the World Medical Association, and the study was carried out by the principles of the Declaration of Helsinki, 2013 and good clinical practice.

Patients admitted to ICU, aged more than 18 years of either gender, tracheally intubated for more than 24 hours, and having associated cardiac or pulmonary disease, liver disease, renal disease, diabetes mellitus, or cancer, etc., as a risk factor for difficult extubation were included in this study. The Charlson Comorbidity Index was used to classify the co-morbidities. Diseases were broadly divided into ten components – 1) arterial hypertension, 2) heart diseases, 3) peripheral vascular diseases, 4) neurological diseases, 5) respiratory diseases, 6) diabetes mellitus, 7) renal diseases, 8) liver diseases, 9) cancer and 10) others (diseases not in above components). Two co-morbidities in the same component were considered one high-risk factor, whereas having more than two co-morbidities in the same component was counted individually. Co-morbidity in separate components was counted as an individual high-risk factor [Appendix 1]. Patients with Glasgow Coma Score (GCS) <12, traumatic brain injury, paralysed, non-cooperative, any other contraindications to either of the therapies and patients who self-extubated were excluded from the study.

Sixty patients who fulfilled the inclusion and extubation criteria after a spontaneous breathing trial (according to weaning guidelines[11]) were randomly selected. Randomisation was done as per the computer-generated random number table, and allocation concealment was done using the sequentially numbered sealed opaque envelope technique. This was an open-label or unblinded trial. Investigators involved in the weaning process, providing respiratory support after extubation, and collecting data were not blinded to the group allocation. Only the statistician involved in processing and analysing the recorded data was blinded.

For the weaning process, an initial trial of a T-tube or pressure support of 5–7 cm H_2O for 120 min was given. Weaning was considered successful when patients were able to breathe for at least 30 minutes with respiratory rate (RR) <35 breath/min, no significant fall or elevation in mean arterial pressure (MAP), saturation of peripheral oxygen (SpO_2) >90%, and no signs of distress. Positive cuff leak test and strong cough were ensured. The effectiveness of the cough and the minimal or abundant amount of secretions following extubation were assessed and noted. This was a subjective assessment by the investigator. Successful weaning was followed by tracheal extubation, and just

after extubation, patients were randomised into two groups- Group H and Group B.

In Group H, patients were given respiratory support by HFNC for at least 48 hours with an initial flow of 50 L/min and a fraction of inspired oxygen (FiO_2) was titrated to achieve SpO_2 >92%. The temperature of the heated humidifier was set at 37°C. In Group B, patients were given supportive therapy with BiPAP via full facemask for at least 4 hours in the first session and a minimum of 12 hours during an observation period of 48 hours with an initial pressure support level of 5 cm H_2O to achieve a tidal volume around 6–8mL/kg, PEEP of 5–10 cmH_2O and FiO_2 such that SpO_2 is more than 92%.

Demographic profiles of all the patients, such as age, gender, body mass index (BMI), and number of associated risk factors for failed extubation, were documented. The heart rate (HR), non-invasive blood pressure (NIBP), RR, SpO_2, arterial blood gas (ABG) parameters, and quick sequential organ failure assessment (qSOFA) score before tracheal extubation were also recorded. Oxygen therapy was provided with HFNC and BiPAP masks in respective groups for at least 48 hours after extubation. Haemodynamic parameters like NIBP, SpO_2, HR, RR, and electrocardiogram (ECG) were continually monitored in the ICU. ABG analysis was done 1 hour after initiating the therapy, then at an interval of 12 hours to 48 hours, and the potential of hydrogen (pH), partial pressure of carbon dioxide (pCO_2), and partial pressure of oxygen/fraction of inspired oxygen (PF ratio) were recorded. All patients were continuously monitored for signs of respiratory distress and failure. If no signs of respiratory failure were present after 48 hours of extubation, assigned therapy was stopped and switched to standard oxygen supplementation if needed. Reintubation criteria after extubation were tachypnoea (RR >35/min), dyspnoea, signs of respiratory muscle fatigue, respiratory acidosis (pH <7.30 and $PaCO_2$ >60 mmHg), hypoxaemia (FiO_2 ≥80% to maintain SpO_2 of 92%), ABG showing PaO_2:FiO_2 ≤100 mmHg, copious secretions, hypotension systolic blood pressure (SBP) <90 mmHg) for more than 30 minutes despite adequate volume resuscitation, use of vasopressor, or both, neurological depression (GCS <12) or cardiac-pulmonary arrest.

The primary outcome was to assess the number of successful tracheal extubation in the patients, that is, having less incidence of tracheal reintubation in assigned therapy. The questionnaire recorded the subjective comfort level to therapy as a numerical score (3-comfortable, 2-less comfortable, 1-uncomfortable). In case of extubation failure within 48 hours of assigned therapy, the time and day of reintubation were recorded.

Based on the previous study by Jean-Pierre Frat *et al*.,[12] which revealed that patients treated with HFNC alone had a lower intubation rate than the others 31% with HFNC versus 43% with standard oxygen and 65% with non-invasive ventilation (NIV), $P = 0.04$, the sample size was determined using the expectation that there would be a 30% difference between the two groups (HFNC and BiPAP group) in terms of reintubation prevention. Calculated sample sizes for each group came out to be 30 at a minimum of 80% study power. The data were recorded, and analysis was done using Statistical Package for the Social Sciences (SPSS) statistics software version 27.0 (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5 (Informer Technologies Inc). The qualitative data like distribution of patients according to gender, BMI, American Society of Anesthesiologists physical status, cause of intubation, co-morbidity index, incidence of successful extubation, reintubation, effectiveness of cough, amount of secretion after extubation, and comfort score were shown in terms of percentages. The quantitative data, such as age, SBP, diastolic blood pressure, HR, RR, SpO_2, pH, PF ratio, and qSOFA score, were expressed in percentages or mean and standard deviation (SD). The Chi-square or Fisher exact test was used to analyse the differences between the two proportions. Students' t-tests were used to determine the difference between the two means. The appropriate degree of freedom was given in each case. All analysis were two-tailed, and the threshold chosen for statistical significance was $P < 0.05$.

RESULTS

During the study period, out of 354 patients assessed for eligibility, 60 patients on mechanical ventilation admitted in the ICU, ready to be weaned, were screened for risk factors associated with extubation failure and were randomised into two groups [Figure 1].

The demographic profiles recorded were comparable in both groups [Table 1]. Most of the patients were more than 50 years old, overweight and had more than two risk factors for extubation failure.

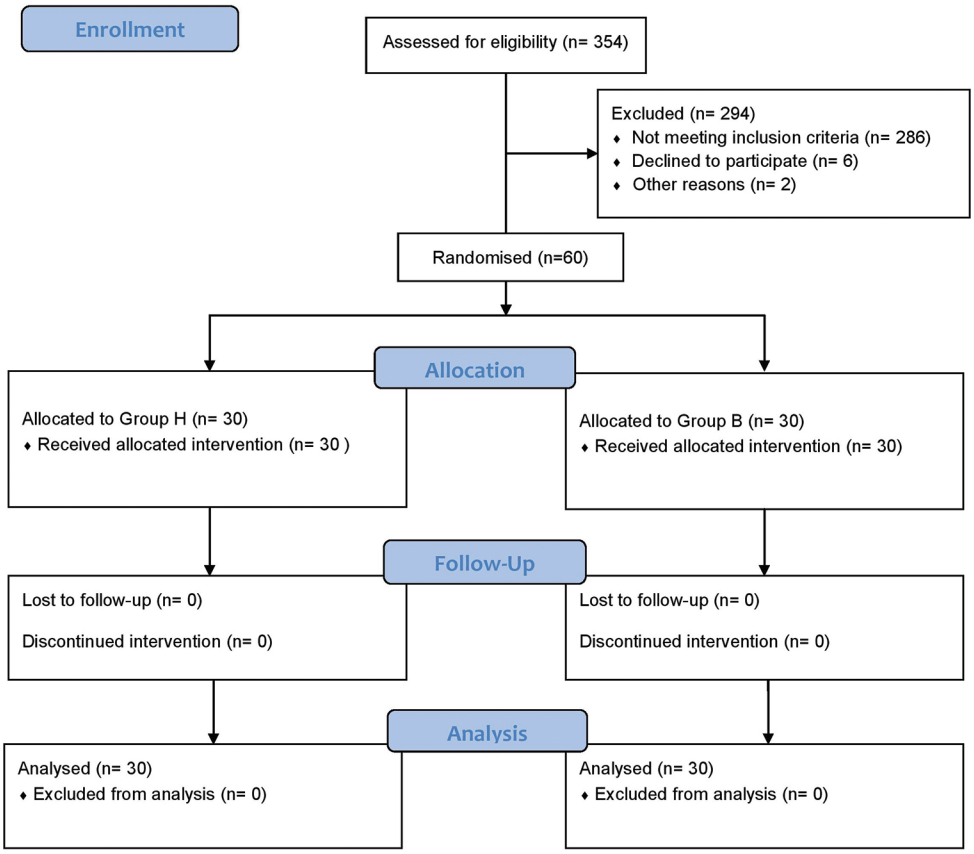

Figure 1: Consolidated standards of reporting trials (CONSORT) flow diagram

Table 1: Demographic profile

Parameters	Group H (*n*=30)	Group B (*n*=30)	*P*
Age (years)	53 (16.72)	53.57 (18.72)	0.902
Gender: male/female	21/9	20/10	0.781
Body mass index (kg/m^2)	27.16 (2.67)	28.09 (3.12)	0.220
Number of Risk Factors (Charlson Comorbidity Index): 1/2/3/4	0/7/19/4	0/5/14/11	0.241

Data is expressed as mean (standard deviation) or numbers. *n*=number of patients

Parameters recorded before extubation were also comparable. Cough and secretions after extubation were assessed for effectiveness and amount and were comparable ($P > 0.05$) [Table 2].

We observed that 16 patients in Group H and 24 patients in Group B had successful extubation ($P = 0.044$) [Table 3]. While analysing the time of reintubation, we noticed that 9 out of 14 in Group H and 2 out of 6 reintubated patients in Group B were reintubated within 24 hours of extubation [Table 3].

It was observed that under Group H, 6.7% of the patients were uncomfortable, 40% of patients were less comfortable, and 53.3% of patients were comfortable, while under Group B, 36.7% of the patients were uncomfortable, 46.7% of patients were less comfortable, and only 16.7% of patients were comfortable to the assigned therapy. Patients in Group H reported the assigned therapy was more comfortable than Group B patients [Table 3].

The HR and SpO_2 were comparable in both groups. However, RR and MAP were significantly higher in Group B during the first 24 hours ($P = 0.026$ and $P < 0.001$ respectively). Episodes of tachypnoea were more frequent in Group H than in Group B. Within 24 hours of therapy, ABG analysis showed significantly more CO_2 retention and acidosis in Group H than Group B. Higher PF ratio was found in Group B than in Group H. We found that the amount of secretions, effectiveness of cough, and SpO_2 after extubation in both groups were comparable [Table 3].

Table 2: Extubation parameters

	Group H (*n*=30)	Group B (*n*=30)	Mean difference (95%CI)	*P*
Before Extubation Parameters				
SBP (mmHg)	140.2 (18.86)	138.8 (14.7)	1.4 (-9.9, 7.1)	0.750
DBP (mmHg)	80.3 (8.68)	81.4 (9.327)	-1.1 (-3.5, 5.6)	0.648
HR (beats/min)	94.9 (16.59)	94.4 (14.15)	0.6 (-8.3, 7.2)	0.446
RR (breaths/min)	22.3 (4.07)	22.4 (3.53)	-0.1 (-1.8, 2.0)	0.929
SpO_2 (%)	98.3 (2.06)	98 (2.30)	0.3 (-1.4, 0.8)	0.557
pH	7.4 (0.06)	7.4 (0.07)	-0.0 (-0.0, 0.1)	0.090
pCO_2 (mmHg)	41.7 (6.55)	42.5 (6.59)	-0.7 (-2.6, 4.1)	0.667
PF ratio (mmHg)	252.5 (70.29)	268.0 (71.24)	-15.5 (-20.1, 51.3)	0.352
qSOFA	0.8 (0.63)	0.5 (0.51)	0.3 (-0.5, 0.0)	0.102
After Extubation Parameters				
Cough (effective/non-effective)	16/14	2/8		0.180
Secretions (minimal/abundant)	25/5	19/11		0.080

Data expressed as mean (standard deviation) or numbers. *n*=number of patients, CI=confidence interval, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate, RR=Respiratory rate, SpO_2=Saturation of peripheral oxygen, pH=Potential of hydrogen, pCO_2=Partial pressure of carbon dioxide, PF ratio=PaO_2/FiO_2 ratio, qSOFA=Quick Sequential Organ Failure Assessment

DISCUSSION

We observed that BiPAP therapy was more effective in preventing reintubation when compared to HFNC therapy. More reintubation occurred in the HFNC group (46.6%) than in the BiPAP group (20%). Most reintubation in the HFNC group (30%) occurred within the first 24 hours, while most reintubation in the BiPAP group (13.3%) occurred between 24 and 48 hours after extubation.

Subjective comfort level to therapy recorded by questionnaire in the form of numerical score suggested HFNC had better tolerability and was more comfortable. We used a full-face BiPAP mask. We could have improved the comfort level by interface optimisation and actively humidified the inspired gas.[13]

We also observed a higher RR in the HFNC group in the first 24 hours of therapy, which might have led to a higher rate of respiratory failure, leading to higher reintubation in the HFNC group. However, our study did not observe the association between a PF ratio of less than 200 mmHg with reintubation. During an observation period of the first 24 hours, the PF ratio was always more than 200 in both groups, except at 12 hours in the HFNC group, which was recorded to be 192.8 mmHg. We found a statistically higher PF ratio in the BiPAP group. For the therapy, we adjusted FiO_2 and flow rate of HFNC to maintain SpO_2 of more than 92%. As HFNC is known to improve alveolar recruitment by applying some amount of PEEP, which improves gaseous exchange and oxygenation, it could have resulted in a mean PF ratio of more than 200 mmHg. Still, a higher PF ratio did not predict reintubation. Thus, the prediction of extubation failure by PF ratio alone was equivocal.

Weak cough was associated with more risk of extubation failure.[14] However, we observed that effective cough and the amount of secretions after extubation were comparable in both groups. We could not establish any association between effective cough, secretion amount and higher reintubation incidence.

On comparing pH and pCO_2, it was seen that retention of CO_2 and respiratory acidosis was statistically significant in the HFNC group, which might explain the greater number of respiratory failures and, thus, higher incidence of reintubation in that group.

Response to preventive HFNC or BiPAP therapy after extubation differs in patients with different risk factors.[15] Clinical trials conducted to test the effect of the application of HFNC and BiPAP after extubation on post-extubation respiratory failure in high-risk patients have shown varied results. Some concluded that HFNC was not inferior to BiPAP, whereas some found NIV with active humidification was superior to HFNC for preventing reintubation in very high-risk patients.[13,16] Some studies have shown that patients with a high risk of extubation failure can benefit more regarding decreased incidence of post-extubation respiratory failure and reintubation with combined or alternative NIV and HFNC therapy.[3] Multiple and dynamic factors put critically ill patients at high risk for extubation. Various authors highlighted the inadequacies of the conventional definition of a high-risk category. Apart from associated cardiac and pulmonary

Table 3: Primary and secondary outcomes parameters

	Group H (*n*=30)	Group B (*n*=30)	Mean difference (95%CI)	*P*
Successful Extubation (no reintubation required)	16	24	-	0.044
Incidence of Reintubation	14	6	-	0.305
Time of Reintubation				
Within 24 hours	9	2	-	0.336
24 – 48 hours	5	4		0.336
Heart Rate (beats/min)				
1 hour	95 (14.75)	105.8 (12.80)	-10.8 (3.8, 17.8)	0.0036
12 hours	92.5 (15.28)	101.6 (16.61)	-9.1 (1.0, 17.2)	0.0305
24 hours	90.9 (15.92)	90.3 (12.781)	-10.6(-8, 6.7)	0.0264
36 hours	82.5 (10.09)	89.9 (15.76)	0.6 (0.6, 14.3)	0.086
48 hours	81.7 (6.16)	83.4 (9.25)	-1.8(-2.2, 5.7)	0.519
Respiratory Rate (breaths/min)				
1 hour	27.6 (4.31)	21.4 (3)	6.2(-8.2, -4.2)	<0.001
12 hours	29.2 (4.5)	21.6 (4.90)	7.6(-10.0, -5.2)	<0.001
24 hours	25.1 (4.98)	22 (4.02)	3.1(-5.4, -0.8)	0.022
36 hours	19 (3.25)	19.4 (3.56)	-0.4(-1.4, -2.1)	0.736
48 hours	17.7 (2.60)	19.3 (3.66)	-1.6(-0.0, 3.2)	0.159
Oxygen Saturation (SpO_2) (%)				
1 hour	99. (1.43)	99.0 (2.02)	-0.1(-0.8, 0.9)	0.883
12 hours	97.8 (2.245)	97.8 (2.46)	-0.0(-1.1, 1.2)	0.968
24 hours	98.2 (1.85)	97.8 (2.05)	0.4 (4.6, 6.6)	0.506
36 hours	98.1 (1.39)	97.9 (2.52)	0.2(-1.2, 0.8)	0.791
48 hours	98.7 (0.96)	98.3 (2.18)	-0.4(-1.3, 0.4)	0.479
Mean Arterial Pressure (mmHg)				
1 hour	82.1 (5.90)	92.1 (8.96)	-10 (6.3, 13.7)	<0.001
12 hours	82.3 (7.53)	90.5 (7.84)	-8.2 (4.1, 11.9)	<0.001
24 hours	80.6 (10.64)	92.8 (9.68)	-12.2 (7.1, 17.4)	<0.001
36 hours	79.4 (6.90)	81.3 (9.74)	-1.8(-2.4, 6.1)	0.498
48 hours	79.2 (5.35)	79.0 (6.21)	0.2(-3.2, 2.7)	0.435
pH				
1hour	7.4 (0.08)	7.3 (0.52)	0.1(-0.1, -0.0)	0.443
12 hours	7.2 (0.08)	7.4 (0.52)	-0.2(-0.0, 0.4)	<0.01
24 hours	7.3 (0.07)	7.4 (0.532)	-0.1(-0.1, 0.3)	0.014
36 hours	7.3 (0.06)	7.3 (0.071)	-0.0 (0.0, 0.1)	0.942
48 hours	7.4 (0.04)	7.2 (0.63)	0.1(-0.3, 0.1)	0.426
pCO_2 (mmHg)				
1 hour	42.3 (7.67)	42.1 (11.7)	0.2(-5.2, 2.8)	0.928
12 hours	52.1 (10.04)	38 (9.87)	14.1(-19.2, -9.1)	<0.001
24 hours	53.5 (5.97)	40.1 (8.03)	13.4(-17.0, -9.8)	<0.001
36 hours	38.4 (4.35)	41.2 (15.45)	-2.8(-2., 8.6)	0.452
48 hours	38.3 (4.73)	39.2 (4.85)	-0.9(-1.5, 3.3)	0.583
PF ratio (mmHg)				
1 hour	248.3 (91.94)	260.5 (78.26)	-12.2(-31.0, 55.4)	0.174
12 hours	192.4 (107.18)	223.1 (97.67)	-30.7(-21.2, 82.6)	0.014
24 hours	223.5 (111.69)	278 (93.29)	-54.4 (2.4, 106.5)	<0.001
36 hours	258.1 (82.15)	274.2 (76.36)	-16.2(-23.9, 56.3)	0.703
48 hours	284.8 (75.17)	274.4 (66.53)	10.4(-46.3, 25.5)	0.550
Comfort score				
1	2	11		0/005
2	12	14		0.602
3	16	5		0.003

Data expressed as mean (standard deviation) or numbers. *n*-number of patients. CI=confidence interval, pH=potential of hydrogen, pCO_2=partial pressure of carbon dioxide, PF=partial pressure of oxygen/fraction of inspired oxygen

diseases, other factors which can influence the rate of post-extubation respiratory failure and incidence of reintubation are obesity, APACHE II scores, number of associated co-morbidities, airway patency problem and hypercarbia at the end of spontaneous breathing trial, etc. There is a linear increase in the

reintubation rate with the increasing number of risk factors.[17] A meta-analysis and systemic review reported that 10%–20% of patients will still have extubation failure even if they pass through SBTs for weaning before extubation.[18] Grade 2B evidence supports the recommendation of using preventive therapies for successful extubation in high-risk patients by clinical practice guidelines[19]; clinical trials have also shown that these preventive therapies might increase morbidity and mortality by delaying reintubation.[20,21] Thus, the benefits of intermediate therapies must be counterbalanced against safety by intensive monitoring to detect early warning signs of respiratory failure.

However, there were certain limitations in our study. It was conducted on a small sample, and investigators were not blinded to study groups. Our methodology's only limited patient inclusion criteria might not be adequate to define high-risk patients, as risk factors for extubation failure are diverse and complex. We did not correlate the type of high-risk factors with the outcome. This might have influenced our result. As per the study protocol, the duration of therapy and monitoring was only 48 hours, and there was no scope to switch the treatments in a single patient. However, some patients might have benefitted from switching the HFNC therapy to BiPAP or vice versa. We could have focused on active humidification and used another comfortable interface for BiPAP for better patient tolerability.

CONCLUSION

Among patients with a high risk of extubation failure, post-extubation BiPAP therapy is found to be more efficient than HFNC therapy in preventing reintubation. However, the comfort level was higher with HFNC therapy.

Study data availability

We declare that de-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX 1

Charlson Comorbidity index

The Charlson Co-morbidity Index was used to classify the co-morbidities. In longitudinal studies, this co-morbidity index offers an easy, broadly applicable, and reliable method of assessing the probability of death from co-morbid disease.[1,2] Diseases were broadly divided into the following 10 components.

1] Arterial hypertension: Systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg in patients

2] Heart disease

I. Myocardial infarction: ≥1 definite or probable myocardial infarction (hospitalisation for chest pain or an equivalent clinical event with electrocardiographic and/or enzyme changes
II. Congestive heart failure: hospitalised or treated for heart failure.
III. Angina: includes patients with chronic exertional angina, those who have coronary artery bypass grafts, and those initially admitted with unstable angina.
IV. Arrhythmia: includes patients with chronic atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring chronic treatment.
V. Valve disease: includes patients with haemodynamically significant aortic stenosis and/or insufficiency, with significant mitral stenosis and/or insufficiency, with prosthetic aortic or mitral valves, with asymmetric septal hypertrophy requiring treatment, or with tricuspid insufficiency.
VI. Cardiogenic shock or cardiopulmonary resuscitation: includes patients with these events before admission to the intensive care unit (ICU) or during ICU stay.

3] Peripheral vascular disease

This category encompasses patients with intermittent claudication, those with a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with a treated or untreated thoracic or abdominal aneurysm measuring ≥6 cm.

4] Neurologic disease

I. Cerebrovascular accident or transient ischaemic disease: including patients with minor or no residual symptoms.
II. Hemiplegia: hemiplegia or paraplegia resulting from a cerebrovascular accident or other conditions.
III. Alzheimer's disease, dementia of any cause, or serious cognitive impairment: moderate-to-severe chronic cognitive deficit resulting in impaired function, regardless of the cause.
IV. Other neurologic conditions: Parkinson's disease, uncontrolled seizures, or syncope without an identified cause.

5] Respiratory disease

I. Chronic obstructive pulmonary disease (COPD): includes patients diagnosed with COPD who have ongoing symptoms such as dyspnea or cough on light or moderate activity.
II. Asthma: includes patients diagnosed with asthma who have ongoing symptoms such as dyspnea or cough on light or moderate activity.
III. Other respiratory conditions: include patients with interstitial lung disease, chronic restrictive lung disease, pulmonary embolism disease, vascular disease or severe pulmonary hypertension (>40 mmHg) of any cause resulting in severe exercise restriction (e.g., unable to climb stairs or perform household duties).
IV. Smoking habit: includes active smokers consuming >10 cigarettes/day with >10 pack years.

6] Diabetes mellitus

This category includes all patients with diabetes treated with insulin or oral hypoglycaemic agents, but not those treated with diet alone.

7] Renal disease

I. Moderate renal insufficiency: serum creatinine >2 mg/dl.
II. Severe renal disease: patients on dialysis, those who have undergone transplantation, and those with uraemia.

8] Liver disease includes patients with mild liver disease (chronic hepatitis (B or C) or cirrhosis without portal hypertension), those with moderate liver disease (cirrhosis with portal hypertension, but without bleeding), and those with severe liver disease (ascites, chronic jaundice, portal hypertension or a history of variceal bleeding, or liver transplant).

9] Cancer

I. Lymphoma: patients with Hodgkin's disease, lymphosarcoma, Waldenstrom's macroglobulinaemia, myeloma, or other lymphomas.
II. Leukemia: includes acute or chronic myelogenous leukaemia, acute or chronic lymphocytic leukaemia, or polycythemia vera.
III. Solid organ tumor: solid tumors without documented metastases, including breast, colon, lung, prostate, melanoma, and a variety of other tumours.
IV. Metastatic cancer: includes patients with metastatic solid tumours, including the same locations as detailed above.

10] Other diseases

a. Peptic ulcer disease: includes patients who have required treatment for gastric or peptic ulcers
b. Rheumatic or connective tissue disease: includes systemic lupus erythematous, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyalgia rheumatica, vasculitis, sarcoidosis, Sjogren's syndrome, or any systemic vasculitis.
c. HIV or AIDS: includes patients with definite or probable AIDS, i.e., AIDS-related complex, as well as asymptomatic HIV-positive patients.
d. Decubitus ulcers, peripheral skin ulcers, or repeated episodes of cellulitis: include partial thickness loss of skin over legs or back with open ulcers or two or more episodes of cellulitis requiring treatment with antibiotics, regardless of etiology.
e. Depression: includes patients receiving treatment for depression, whether pharmacologic or psychotherapy, and those with signs indicating probable or definite depression.
f. Coagulopathy: includes patients with coagulation disorders and those with circulating anticoagulants for any medical condition.
g. Other endocrine diseases: hypopituitarism, adrenal insufficiency, or recurrent acidosis.
h. Inflammatory bowel disease: ulcerative colitis, Crohn's disease, or regional enteritis.
i. Gastrointestinal bleeding: bleeding requiring transfusions from causes other than ulcer.
j. Alcoholism: regular intake of >80 g alcohol per day.
k. Other causes of reduced resistance to infection: having undergone treatments that suppress resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids) or having a condition considered a cause of suppressed resistance to infection.

Two co-morbidities in the same component were considered as one high-risk factor, whereas having more than two co-morbidities in the same component was counted individually. Co-morbidity in separate components was counted as an individual high-risk factor.

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