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Original Article

A Controlled Trial of Noninvasive Positive Pressure Ventilation (NIPPV) in Patients of COPD with Respiratory Failure

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Abstract :

Objective : *To assess the role of noninvasive positive pressure ventilation (NIPPV) in patients of acute exacerbation of COPD with respiratory failure, also to reduce endotracheal intubation (ETI) and the frequency of complications associated with ETI.*

Materials and Methods : *Prospective, single blind, randomized controlled trial study (RCT) comparing the effect of combined standard medical treatment and noninvasive positive pressure ventilation with standard medical treatment alone in patients admitted to National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Bangladesh over a 12-month period.*

Results : *A total number of 60 patients of acute exacerbation of COPD with type II respiratory failure were enrolled from inpatient department of Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Bangladesh. A total of 30 (thirty) were randomly assigned to standard therapy and 30 (thirty) to noninvasive ventilation. The two groups had similar clinical characteristics on admission to the hospital. The use of noninvasive ventilation significantly reduced the need for endotracheal intubation (which was dictated by objective criteria): 12 of 30 patients (40.0%) in the noninvasive- ventilation group were intubated, as compared with 22 of 30 patients (73.3%) in the standard-treatment group (P=0.01). In addition, the frequency of complications was significantly lower in the noninvasive-ventilation group. The mean (± SD) hospital stay was significantly shorter for patients receiving noninvasive ventilation. 19.2±5.7days vs. 23.5±8.3 days, (P 0.02). The in-hospital mortality rate was also significantly reduced with noninvasive ventilation, 5 of 30 patients (16.7%) in the noninvasive- ventilation group died in the hospital, as compared with13 of 30 (43.3%) in the standard-treatment group(P 0.04)*

Conclusions : *In selected patients with acute exacerbations of chronic obstructive pulmonary disease, noninvasive ventilation can reduce the need for endotracheal intubation, complications, the length of the hospital stay, and the in-hospital mortality rate.*

Key Words: *COPD exacerbation, non-invasive ventilation, randomized controlled trial, ETI*

Introduction:

Chronic obstructive pulmonary disease (COPD) is a major health problem and leading cause of morbidity and mortality worldwide.[1] Moreover the burden of the disease is expected to rise in future. The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD will be the fourth leading cause of death in 2030.[2] Acute xacerbations of COPD are largely responsible for the morbidity and mortality associated with the disease. The frequency of hypercapnic respiratory failure in patients with acute exacerbation of COPD varies from 16-35% with overall mortality of 35-43 %.[3,4] Ventilatory support via endotracheal intubation (ETI) is the standard mode of therapy, for such patients. However, ETI is associated with several complications including nosocomial pneumonia, injury to upper airway causing ulceration, hemorrhage and long term complication like tracheal stenosis. Moreover, patients with COPD are prone to ventilator dependence and may have repeated weaning failures leading to requirement of tracheostomy.[5,6]

Noninvasive ventilation is an alternative approach that was developed to avoid these complications in patients with acute respiratory failure.[7,8] It is often used for acute exacerbations of chronic obstructive pulmonary disease, because such exacerbations may be rapidly reversed and because the hypercapnic ventilatory failure that occurs in patients with this disorder seems to respond well to noninvasive ventilation.[9,10] NIPPV enhances ventilation by unloading fatigued ventilatory muscles and its use has been established in the treatment of patients with AECOPD.[11] NIPPV has the advantage that it can be applied intermittently for short periods, which may be sufficient to reverse the ventilatory failure, sedation is not required allowing the patient to eat, drink and talk also permitting participation in decisions about their own care. In addition,

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the incidence of nosocomial pneumonia with NIPPV use is lower than in intubated patients.[12] Over the last decade NIPPV has been increasingly used as an adjunct therapy in the management of acute exacerbations of COPD. The use of NIPPV in acute exacerbations of COPD has been supported by a number of case series[8] and randomized controlled trials[13,14]. Most recently, meta-analyses reported similar findings regarding the use of NPPV for COPD exacerbations.[15]

With this background, first time in Bangladesh we conducted a randomized controlled trial to compare the noninvasive ventilation delivered through a face mask plus standard medical therapy, with standard medical therapy alone, in patients admitted with acute exacerbation of chronic obstructive pulmonary disease in National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh

Materials And Methods

It was a prospective, single blind randomized controlled trial study (RCT) comparing the effect of combined standard medical treatment and noninvasive pressure-support ventilation with standard medical treatment alone in patients with acute exacerbation of COPD with type II respiratory failure. This study was carried out on patients admitted in the Department of Respiratory Medicine, including intensive care unit (ICU), respiratory care unit (RCU) and indoor in National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh, for one year from January 2012 to December 2012. The ethics committee of NIDCH approved the study protocol and patients or their relatives gave informed written consent.

The study was hospital based clinical trial which comprised of:

- Run-in phase- for confirmation of diagnosis and evaluation of eligibility and equalization of standard treatment in both group
- Clinical and follow-up phase- manage acute exacerbation of COPD either with combined standard medical treatment and noninvasive pressure-support ventilation or standard medical treatment alone to see the effect of NIPPV in respiratory failure.

Initially 64 patients with acute exacerbation of COPD with type II respiratory failure were reviewed and if inclusion and exclusion criteria fulfilled, were properly informed and were registered for the study and data were collected through a standard approved questionnaire. 4 patients dropped out and finally data of 60 patients were analyzed.

During the run-in phase, each subject was evaluated thoroughly. A detailed medical history from patient and his/her attendants was taken regarding the presentation, patient's age, age at onset of symptoms, smoking history, past medical history, current medications etc. Patients were asked also about the cough, sputum production, dyspnoea, wheezing, haemoptysis, and chest pain, associated other lung disease or other systemic disease. Health related quality of life is assessed by using St, George's respiratory questionnaire (SGRQ) on first day only. Each subject was evaluated with history and symptoms and proper clinical examinations were done. Dyspnoea by using mMRC scale was measured before and after treatment. They were examined particularly of level of consciousness/ orientation, cyanosis, edema, respiratory rate, heart rate, temperature, blood pressure, bounding pulse, flapping tremor, papilliedema. Certain baseline investigations were done. Routine investigations included full blood count, liver function test, renal function test, blood sugar, ECG, and chest X-ray, sputum for Gram staining and C/S, arterial blood gas analysis and serum electrolytes done.

After confirming the diagnosis, Patients were subjected to randomize into 'Group A' and 'Group B'. Group A was given standard medical treatment of COPD exacerbation, Group B was given NIPPV along with standard medical treatment of COPD exacerbation. Patients were randomly assigned to receive either standard treatment alone or standard treatment with pressure-support ventilation through a face mask using random number in sealed envelopes.

In Group B NIPPV in BIPAP mode was started immediately in RCU/ICU. Duration of ventilation, IPAP, EPAP were adjusted according to patients clinical status. Standard medical treatment is continued along with NIPPV.

In group A standard medical treatment was continued with good surveillance and follow up and was shifted to ICU for invasive mechanical ventilation whenever indicated at proper time.

Entry Criteria:

We enrolled patients of both sex with acute exacerbation of known chronic obstructive pulmonary disease leading to respiratory acidosis (pH < 7.35 and $PaCO_2$ > 45 mm of Hg).

Exclusion Criteria:

We excluded patients who had-

- respiratory rate below 12 breaths per minute or the need for immediate intubation (as defined below)
- a tracheotomy or endotracheal intubation performed before admission
- the administration of sedative drugs within the previous 12 hours
- a central nervous system disorder unrelated to hypercapnic encephalopathy or hypoxemia;
- cardiac arrest (within the previous five days)
- cardiogenic pulmonary edema
- kyphoscoliosis as the cause of chronic respiratory failure or a neuromuscular disorder; upper airway obstruction or asthma

- a clear cause of decompensation requiring specific treatment (e.g., peritonitis, septic shock, acute myocardial infarction, pneumothorax, hemoptysis, or recent surgery or trauma)
- a facial deformity
- enrollment in other investigative protocols or patients not giving consent to be enrolled in study

Criteria For Intubation

To make the decision whether to perform endotracheal intubation as objective as possible, established criteria based on the clinical experience of the participating physicians and on reported data.

The criteria included-

- respiratory arrest,
- respiratory pauses with loss of consciousness or gasping for air,
- psychomotor agitation making nursing care impossible and requiring sedation,
- a heart rate below 50 beats per minute with loss of alertness,
- hemodynamic instability with systolic arterial blood pressure below 70 mm Hg,
- respiratory rate above 35 breaths per minute and above the value on admission,
- an arterial pH value below 7.25 and below the value on admission,
- a value for the partial pressure of arterial oxygen below 45 mm Hg, despite oxygen therapy;
- mild confusion, or sleepiness during the day;

In both groups, the presence of these criteria was considered to indicate the need for intubation and mechanical ventilation.

Standard Medical Treatment(Smt)

Standard Treatment includes oxygen inhalation limited to a maximal flow rate upto 5 liters per minute, by means of nasal prongs, in order to achieve a level of arterial oxygen saturation above 90 percent. Medications included antibiotic agents, and bronchodilators (short acting beta agonists, short acting anti cholinergic) , corticosteroids and intravenous aminophylline with the correction of electrolyte abnormalities.

NIPPV

A bilevel positive airway pressure (BIPAP) ventilatory system (Nellcor Puritan Bennet, USA) was used for the study. This ventilator is equipped with adjustable pressure limits, and patient is ventilated as per the predefined inspiratory and expiratory airway pressure settings with each inspiration being triggered by patient's spontaneous breath. The interface used during the study was a well fitting facemask. After explaining the details of the process of the NIPPV institution, patient was propped up to a 45° angle. NIPPV was initiated by the investigator in all the cases. Patients were usually initiated on an inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) of 10 cm of H_2O and 6 cm of H_2O respectively. Subsequent adjustments were carried out according to the need of the patient and the results of blood gas analysis. The protocol was to augment IPAP and EPAP by 2 cm H_2O every 5-10 min, patient's comfort and arterial oxygen saturation permitting. All patients were given oxygen at 3-5 l/min during ventilation to maintain oxygen saturation above 90%.

Each patient was encouraged to use the NIPPV up to 16 hrs/day including day and night and duration of ventilation was recorded in each patient accordingly. NIPPV was discontinued for eating and drinking.

After starting treatment each patient was monitored closely for initial one hour. patient's discomfort and intolerance to mask was looked for. Clinical status such as use of accessory muscles of respiration, increase or decrease of dyspnoea, appearance or disappearance of cyanosis, heart rate, respiratory rate and blood pressure were monitored. Level of consciousness was also closely monitored.

Patient assigned to group A received oxygen at a rate of 3-5 L/ min by means of nasal prongs or oronasal mask. Both groups received pharmacologic treatment including bronchodilators (short acting beta agonists, short acting anti cholinergic), corticosteroids and intravenous aminophylline as per the standard guidelines. Intravenous (IV) antibiotics were given to all patients at admission and subsequently the duration of antibiotic was decided on case to case basis by the treating team.

Continuous arterial oxygen saturation was monitored using pulse oxymeter. ABG was done at 1st and 2nd day and any other time if patient's condition required so. Patients who deteriorated in terms of gas exchange parameters (rising $PaCO_2$ and/or worsening pH), level of consciousness (Glasgow coma scale < 8), or haemodynamic stability (mean arterial pressure < 60 mm of Hg) as well as those with copious secretions and inability to tolerate face mask from either group were intubated and initiated on conventional mechanical ventilation.

Presence of sustained clinical improvement with reduction of RR <24/ min, HR <100/ min and presence of normal pH, $PaCO_2$ < 55 mm of Hg and O_2 saturation >90% on ABG were required before patients were considered for weaning from NIPPV in the Group B.Patients who needed endotracheal intubation were mechanically ventilated in the assist-control mode and were weaned with the SIMV & pressure-support mode.

Follow-up

Follow up of the patient was done by the following parameters- level of consciousness/ orientation, Dyspnoea score (modified MRC), Respiratory rate ,Heart rate, Blood pressure, SpO_2, cyanosis, edema, temperature, bounding pulse, flapping tremor, papilliedema, Laboratory- ABG ,Serum electrolytes. These data were obtained once daily. Some investigations were done to diagnose complications as needed- Chest X-ray, Sputum for culture & sensitivity, ECG, Troponin I etc. Then regular follow up done to all patients till discharge for any complications, LOS in hospital, in hospital mortality.

Incidence of need of ETI was the primary outcome variable. Hospital mortality, duration of hospital stay and change in clinical and blood gas parameters were the secondary outcome variables. Various complications including adverse effects related to the procedure of NIPPV such as aspiration, bloating and skin ulcers, development of ventilator-associated pneumonia and hemodynamic instability in the two groups were recorded and compared between the two groups as safety variables.

Statistical Analysis

The primary outcome variable was the need for endotracheal intubation and mechanical ventilation at any time during the study. Secondary end points were the length of the hospital stay, complications not present on admission (such as pneumonia, barotrauma, gastrointestinal hemorrhage, renal insufficiency, neurologic events, and pulmonary embolism) and the mortality rate during hospitalization.

Categorical variable were described in proportions whereas continuous variables were described using mean ± standard deviation. Comparisons were made between the baseline data and post admission data within the two groups as well as between the two groups. Whereas continuous variable were compared between two groups using unpaired t- test, paired t- test was used for intra-group comparisons. Chi square test was used for comparisons between categorical variables. Significance was considered at P<0.05 (two tailed).

Results

The baseline characteristics of the two groups were similar. In this current study, the mean age was 62.9 (±8.8) years in group-A & 59.2(±8.8) years in group-B,P value 0.10 . Male patients were 51(85.0%) among them 26(86.7)were in group A and 25(41.7%) were in group B respectively, P value 0.71. Male were predominant in both groups which indicates that the disease incidence was higher in male patients, maximum of the patients were Ex-smoker in both groups, total 40(66.7%) among them 20(33.3%) in group-A and 20(33.3%) in group-B. Mean pack years were 31.4 (±10.1) in group-A and 26.5(±8.1) pack years in group-B, P value 0.06.

Primary outcome variable

The need of ETI was reduced significantly by use of NIPPV. 22 patients out of thirty 30 (73.3%) in group A required ETI as compared to 12 out of 30(40%) in group B. Here P value (P = 0.01) was statistically significant, Absolute risk reduction 0.33%, Number needed to treat 03. Rise in $PaCO_2$ with or without worsening in the level of sensorium was the indication for ETI in most of the patients.

Need for endo - tracheal intubation	Study population		Total n(%)		P value
	Group A N=30 (%)	Group B N=30(%)			
Intubation needed	22(73.3)	12(40.0)	34(56.7)	ARR-0.33	0.01[s]
Intubation not needed	08(26.7)	18(60.0)	26(43.3)	NNT-03	
Total	30(100)	30(100)	60(100)		

Table I: Comparison of need for endo-tracheal intubation of the study population (n=60)

Timing of intubation is also important. On first day intubation done in 14(23.3%) patients in group A but none in group B. P value (p< 0.05) which is statistically significant. On second day intubation done in 04(6.7%) and 4(6.7%) patients in group A & group B respectively, P value (p> 0.05) which is not statistically significant.

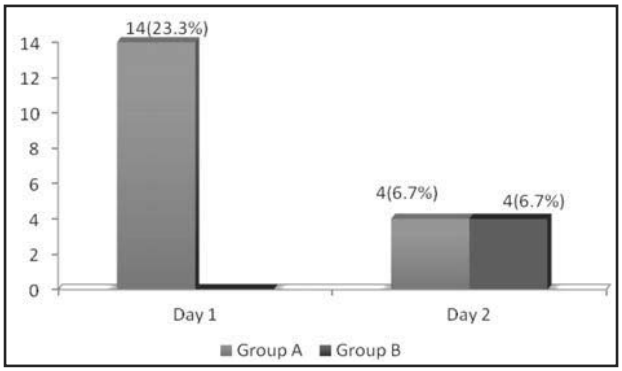

Figure I: Bar diagram showing time of endotracheal intubation among Study population

Secondary outcome variables

The most striking effects of the institution of NIPPV on the blood gas parameters were noticed in second day of initiation itself. In the NIPPV group, a statistically significant change was noted in both pH and $PaCO_2$. Whereas the mean pH rose from a baseline of 7.28(±0.04) to 7.42(±0.09) (P<0.001), mean $PaCO_2$ fell from a baseline value of 80.94(±11.24) mm of Hg to 61.42(±13.75) mm of Hg (P<0.001). In contrast, there was no significant change in the mean pH (7.24(±0.09) to 7.27(±0.13) P=0.27. and

$PaCO_2$ 84.88(±18.42) mm of Hg to 76.45(±24.71)mm of Hg) (P=0.05). levels during this period in the C group. There was no significant difference in the change in the other parameters between the two groups

	Group A			Group B		
	Day 1 Mean ±SD	Day 2 Mean ±SD	P value	Day 1 Mean ±SD	Day 2 Mean ±SD	P value
P^H	7.24(±0.09)	7.27(±0.13)	0.27^{ns}	7.28(±0.04)	7.42(±0.09)	$<0.001^{s}$
PCO_2	84.88(±18.42)	76.45(±24.71)	0.05^{ns}	80.94(±11.24)	61.42(±13.75)	$<0.001^{s}$
PO_2	111.69(±64.25)	116.47(±66.53)	0.79^{ns}	96.53(±48.05)	120.43(±42.50)	0.06^{s}
HCO_3	32.10(±6.30)	37.16(±10.66)	0.03^{s}	35.51(±7.36)	35.29(±4.05)	0.88^{ns}
SaO_2	88.66(±13.7)	92.99(±10.99)	0.21^{ns}	91.13(±10.44)	95.48(±03.42)	0.04^{s}

Table II: Blood gas parameters of the study population on day -1 & Day -2 (n=60)

The mean duration of hospital stay in the group B was 19.2(±5.7) days as compared to 23.5(±8.3) days in the group A(P=0.02).

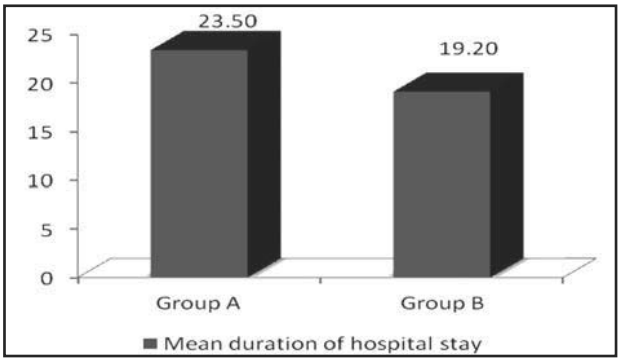

Figure II: Bar diagram showing Duration of hospital stay of the study Population

There was also significant difference in the hospital mortality of the two groups 05 out of 30(8.3%) group B versus 13 out of 30 (21.7%) in the group A,(P= 0.04).

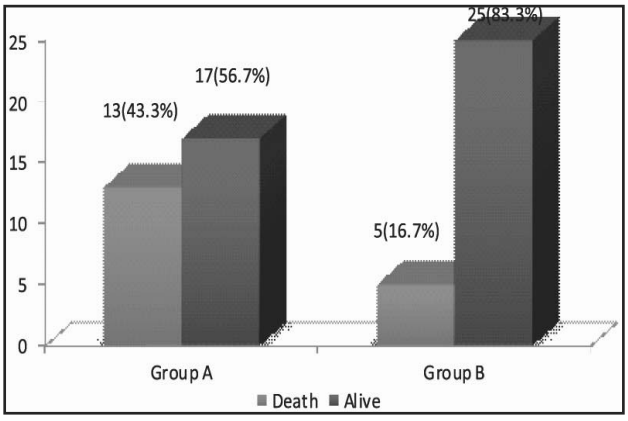

Figure-III: Bar diagram showing in hospital mortality of the study population

Complications are shown in Table III. Ventilator Associated Pneumonia (VAP) was found 10(16.7%) in group A and 03(5.0%) in group B, ($p<0.05$), that was statistically significant. Shock and electrolyte imbalance developed in both groups, p value ($p>0.05$), statistically not significant. Other complications developed in 19(31.7%) in group A and 11(18.3%) in group B, P value ($p<0.05$), that was statistically significant.

Complications	Group A n =30 (50%)	Group B n =30 (50%)	Total N=60 (100%)	P value
Ventilator associated Pneumonia (VAP)				
" Yes	10(16.7)	03(5.0)	13(21.67)	0.02^{S}
" No	20(33.3)	27(45.0)	47(78.33)	
Shock				
" Yes	12(20.0)	06(10.0)	18(30.0)	0.09^{ns}
" No	18(30)	24(40.0)	42(70.0)	
Electrolyte imbalance				
" Yes	13(21.7)	09(15.0)	22(36.7)	0.28^{ns}
" No	17(28.3)	21(35.0)	38(63.3)	
Others				
" Yes	19(31.7)	11(18.3)	30(50.0)	0.03^{s}
" No	11(18.3)	19(31.7)	30(50.0)	

Table III: Distribution of the complications of the study population (n=60)

Discussion

This study shows that the use of noninvasive ventilation in selected patients admitted for acute respiratory failure due to chronic obstructive pulmonary disease can obviate the need for intubation and thus reduce complications and mortality and shorten the hospital stay.

When NIPPV combines applied PEEP (positive end expiratory pressure) to counter balance PEEPi (intrinsic positive end expiratory pressure), and pressure support to assist inspiration it reduces transdiaphragmatic pressure more than either applied PEEP or pressure support alone.[16] The favourable effects of NIPPV are related to a reduction in inspiratory muscle work and avoidance of respiratory muscle fatigue.[17] Till date to our present knowledge, fourteen randomized controlled trial have evaluated the use of NPPV in patients with COPD and acute respiratory failure. Six of the trials were conducted in hospital respiratory/medical wards, five were conducted in ICU.[15]

Bott et al. carried out a prospective randomized controlled trial of conventional treatment versus conventional treatment plus NIPPV, in 60 patients with acute ventilatory failure due to exacerbations of COPD reported significant rise in pH, a reduction in PCO_2 and breathlessness, and reduced mortality. For the NIPPV group there was a rise in pH, compared with a fall in the controls ($p < 0.001$]), and a larger fall in PCO_2 ($p < 0.01$]). Median visual analogue scores over the first 3 days of admission showed less breathlessness in the NIPPV group ($p < 0.025$). Survival rates at 30 days were compared for intention-to-treat and efficacy populations. In the efficacy mortality comparison, mortality in the NIPPV group was reduced: 1/26 vs. 9/30 (relative risk = 0.13, CI = 0.02-0.95, p = 0.014). (4 patients who were randomized to receive NIPPV but did not receive it.) This effect was less in the intention-to-treat analysis: 3/30 vs. 9/30 (relative risk = 0.33, CI = 0.10-1.11, p = 0.106.This study suggests that benefits can be expected from noninvasive ventilation.[10] These results are confirmed and extended in the present study.

Plant et al. did a prospective multicentre randomized controlled study comparing NIPPV with standard treatment in patients with mild to moderate acidosis to find whether early use of NIPPV was effective at reducing the need for intubation and the mortality associated with acute exacerbations of COPD. 236 patients were recruited. Use of NIPPV significantly reduced the need for intubation,32/118 (27%) of the standard group compared to 18/118 (15%) of the NIPPV group (p=0.02).In hospital mortality was also reduced by NIPPV, 24/118 (20%) died in the standard group compared to 12/118 (10%) of the NIPPV group (p=0.05).In both groups, PH, PCO_2, and RR improved at 4 hr ($p<0.01$).However, NIPPV led to a more rapid improvement in pH in the first hour (p=0.02) and a greater fall in RR at 4 hr (p=0.035),the duration of breathlessness was also reduced by NIPPV (P=0.025).[14] Similar results were obtained by Dikensay O, and colleagues, and concluded that NPPV along with standard therapy should be the initial choice in treatment of acute hypercapnic \respiratory failure due to COPD exacerbation[18]

Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2009, Issue 3 on Randomized controlled trials comparing NIPPV plus usual medical care (UMC) versus UMC alone. Trials needed to recruit adult patients admitted to hospital with respiratory failure due to an exacerbation of COPD and with $PaCO_2 > 6$ kPa (45 mm of Hg), to determine the efficacy of NIPPV in the management of patients with respiratory failure due to an acute exacerbation of COPD. An initial search was performed using the Cochrane Airways Group trials register and other relevant electronic databases. Fourteen studies were included in the review. NIPPV resulted in decreased mortality (Relative Risk 0.52; 95%CI 0.35 to 0.76), decreased need for intubation (RR 0.41; 95%CI 0.33 to 0.53), reduction in treatment failure (RR 0.48; 95%CI 0.37 to 0.63), rapid improvement within the first hour in pH (Weight Mean Difference 0.03; 95%CI 0.02 to 0.04), $PaCO_2$ (WMD -0.40 kPa; 95%CI -0.78 to -0.03) and respiratory rate (WMD-3.08 bpm; 95%CI -4.26 to -1.89). In addition, complications associated with treatment (RR 0.38; 95%CI 0.24 to 0.60) and length of hospital stay (WMD -3.24 days; 95%CI -4.42 to -2.06) were also reduced in the NIPPV group.[1]

Present study attempted to deliver NIPPV by a nasal mask using bilevel mode with a low pressure profile based on clinicophysiological monitoring with ABG analysis done at less frequently intervals. The low pressure profile have allowed the patients to accept the NIPPV comfortably with in 1-2 hours. Indeed bedside presence of a clinician well versed with NIPPV application and monitoring is necessary during initial 2-3 hours, which also helps in motivating. Patient to use the non-invasive ventilator appropriately, and to reduce anxiety. By 2nd day significant improvement in respiratory rate, pulse rate, dyspnea score, mean arterial pressure, $PaCO_2$, HCO_3 - and pH in NPPV group as compared to SMT group. These findings correlated well with previous randomized controlled trials. [10,14,18,19,20]

Conclution:

One of the major hindrances to the study analysis was a smaller sample size, owing to stricter criteria of inclusion and exclusion. The study was a single blind one so there remains chances of bias also.

This prospective, randomized controlled study supports recent meta analysis that early application of NIPPV in carefully selected patients with acute on chronic respiratory

failure allows rapid improvement in clinical and gas exchange parameters ,early mobilization and reduction in length of hospital stay with few minor complications ,and allowing its use in less well equipped setup with non-invasive monitoring.

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