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EARLY PREDICTORS OF SUCCESS OF NON-INVASIVE POSITIVE PRESSURE VENTILATION IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WITH HYPERCAPNIC RESPIRATORY FAILURE

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KEYWORDS :

Introduction

Chronic obstructive Pulmonary disease (COPD) is a major worldwide health problem that has an increasing prevalence and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the World Health Organization (WHO) defines COPD as follows (www.gold copd.org, 2014).

"Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."

In 2002 COPD was the fifth leading cause of death. Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. Estimates show that COPD becomes in 2030 the third leading cause of death worldwide.

During the last two decades, non-invasive modalities have been developed and have also been popularised to augment alveolar ventilation and oxygenation without the need for an artificial airway. Various recent studies have demonstrated their effectiveness in management of respiratory failure. Non-invasive positive pressure ventilation (NIPPV) using face mask or nasal mask is one such modality. It works by providing pressure support that gives ventilatory assistance during inspiration, allows respiratory muscles to work less, increases the volume inspired per minute and improves arterial blood gas (ABG) levels. Its use has become more common as its benefits are increasingly recognised. In some patients of AECOPD with acute hypercapnic respiratory failure, NIV is inadequate and invasive ventilation is required for management of respiratory failure. The failure rates in such patients range from 24% to 50% in different studies. Failure of initial trial of NIPPV can lead to a delay in endotracheal intubation thus causing an increase in morbidity and mortality. Thus, determination of early predictors of success of NIPPV is important to identify the patients who are likely to benefit from NIPPV. Patients responding to NIPPV will be continued with NIPPV. Rest of the patients will be intubated and put on invasive ventilator early. This will reduce the incidence of higher mortality and morbidity associated with undue delay in putting the patients on invasive Mechanical Ventilation.

Following were the main aims and objective of our study:

- To determine the effectiveness of noninvasive positive pressure ventilation (NIPPV) in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) with Hypercapnic Respiratory Failure.
- To identify factors, based on clinical and laboratory parameters, for predicting the Success of NIPPV in patients with Acute Exacerbation of COPD with Hypercapnic Respiratory failure.
- To validate the finding of previous studies.

Methods:

This prospective study was conducted at Department of Tuberculosis and Respiratory Diseases, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi between July 2014 to July 2015. The hospital serves as a tertiary care center for the patients coming from eastern part of Uttar Pradesh, adjoining area of Bihar, Jharkhand, Madhya Pradesh and Chhattisgarh. A total of 50 patients recruited who received the diagnosis of a/e COPD with hypercapnic respiratory failure.

First of all the Institutional Ethics Committee was asked to approve the protocol. Once protocol was approved, then prior to enrollment in the study the patient was evaluated to determine eligibility and was explained about the study purpose, procedures and patients responsibilities as the potential participant.

When it had been established that the patient was eligible, written informed consent was obtained. Thus enrolled 50 patients receiving the diagnosis of a/e COPD with hypercapnic respiratory failure were subjected to thorough history taking and clinical examination. Clinical evaluation (RR ,HR ,BP ,mMRC score) and presence of pedal edema were recorded and baseline routine investigation were sent including Complete blood count, Liver function test, Renal function test, Serum electrolytes, Blood sugar, ECG and X ray chest PA view(if needed lateral view also). BMI also calculated on admission. Arterial blood gas analysis performed before Applying NIPPV that gave information regarding PaO2, PaCO2, pH, P/F Index and various other parameters. A blood sample was collected on admission to measure baseline serum PCT and CRP before appying NIPPV.

After applying of NIPPV Clinical evaluation (HR ,RR ,BP ,SpO2) arterial blood gas analysis (pH ,PaCo2) will be reevaluated at 1 , 4 and 24 hour.

mMRC dyspnoea grading

Grade 0: Only get breathlessness with sternous exercise.

Grade 1: Shortness of breath when hurrying on the level or walking up a slight hill.

Grade 2: Walk slower then people of same age on the level or have to stop for breath when walking on normal own pace.

Grade 3: Stop for breath after walking about 100 meters or after a few minutes on the level.

Grade 4: Too breathlessness to leave the house or breathlessness when dressing or undressing.

A portable non-invasive ventilator (BiPAP, Respironics) was used in the spontaneous mode, using full face mask (Respironics). The inspiratory pressure support was initially set at 10 cm of water. Expiratory pressure was set at 6 cm of water. The pressure was gradually increased

to reach the optimum level for each patient (max. IPAP of 18 cm H_2O and EPAP of 16 cm H_2O). Oxygen was administered through the full facemask until oxygen saturation (SpO2) was >90%.Standard medical treatment including inhalational bronchodilator intravenous corticosteroids, xanthenes and whenever appropiate, antibiotics, diuretics, or vasopressors were given in addition to NIPPV.

The mask was examined for leak, skin abrasion, and patient satisfaction. Patients were put on invasive MV when there was any deterioration. Treatment with NIPPV was considered successful if there was expression of improvement of breathlessness by the patient, RR improved, there was improvement of signs of increased work of breathing, tachycardia improved (heart rate (HR) < 100/minute), pH became > 7.35 with a fall in PaCO2 from base line, thereby avoiding intubation in these patients.

NIV failure was defined as endotracheal intubation and invasive ventilation after placement on NIV and/or death.

Statistical tools

Statistical analysis was done using SPSS 16. We used statistics to compare proportions. Student's t test and One way analysis of variance was used to compare the significant difference in mean among the group and if this test resulted significant then multiple range test (SNK) was used to find out pair wise difference in means. Pre-NIPPV measurements were compared with the measurements obtained at 1, 4 and 24 hours after NIPPV initiation by generalised linear model (repeated measurement). Data with ***P*** values < 0.05 were considered statistically significant.

Results:

In our study we had 32 (64%) males and 18 (36%) females with male predominance. 38 (76%) are in success group (Improved on NIPPV) and 12 (24%) are in failure group (Not improved on NIPPV and intubated). The mean age in success group was 59.03±5.43 year and mean age in failure group was 62.75±5.77 year. Higher mean age was significantly associated with failure of NIPPV, (P-value 0.047). Most of the patient were in grade 4 mMRC 68% (n=34). Out of total 38 (76%) patients improved on NIPPV and 12 (24%) patients either needed Invasive ventilation or expired during treatment. 23 patients (46%) had history of hospitalization for acute exacerbation for one or more time while 27 patients (54%) had not any history of hospitalization. The mean pack year in success group was 6.05±3.39 whereas mean pack year in failure group was 8.92±6.65.Failure group had more pack year than success group but this analysis is statistically not significant. (p=0.053). The comparison of Mean (SD) heart rate at baseline and during NIPPV is depicted in table 1. Mean heart rate was improved in success group at 1,4 and 24 hour respectively whereas mean heart rate in failure group was not much changed at 1,4 and 24 hour. Success group had significantly lower mean heart rate at 0 hour than failure group and it further improved with NIPPV at 1 hour and this improvement was maintained at 4 and 24 hour. (P-value <0.001).

Mean respiratory rate was improved in success group at 1,4 and 24 hour, 20.63±2.71, 18.37±1.96, 16.00±1.67 breaths/min respectively Whereas mean respiratory rate in failure group was almost unchanged at 1,4 and 24 hour,28.33±3.05, 28.80±3.55 and 28.67±3.31 breaths/min respectively. Success group had significantly lower mean respiratory rate at 0 hour than failure group and it further improved with NIPPV at 1 hour and this improvement was maintained at 4 and 24 hour. (P-value <0.001) (Table 2)

Changes of SBP between both groups were statistically not significant at 1, 4 and 24 hour, (p value-1.604, 0.696 and 0.856 respectively) and Changes of DBP between both groups were statistically not significant at 1,4 and 24 hour, (p value-0.691,0.454 and 0.397 respectively).

Mean SpO_2 was improved in success group at 1,4 and 24 hour,89.66±3.98, 93.95±1.94 and 96.58±1.17 % respectively Whereas mean SpO_2 in failure group was not much changed at 1,4 and 24 hour,72.17±11.41, 77.00 ±9.67 and 76.22±6.20 % respectively. Success group had significantly higher mean SpO_2 at 0 hour than failure group and it further improved with NIPPV at 1 hour and this improvement was maintained at 4 and 24 hour. (P-value <0.001) (Table 3).

Mean $PaCO_2$ was improved in success group at 1,4 and 24 hour, 70.13±9.58, 65.07±9.46 and 54.08±8.79 mm Hg respectively Whereas mean $PaCO_2$ in failure group was not much changed or worsen at 1,4 and 24 hour,93.67±16.51 ,87.55±11.95 and 88.08±12.54 mm Hg respectively. Success group had significantly lower mean $PaCO_2$ at 0 hour than failure group and it further improved with NIPPV at 1 hour and this improvement was maintained at 4 and 24 hour. (P-value <0.001) (Table 4).

Mean pH was improved in success group at 1,4 and 24 hour, 7.30±0.06, 7.34±0.05 and 7.41±0.04 respectively Whereas mean pH in failure group was not much changed or worsen at 1,4 and 24 hour, 7.22±0.09, 7.26±0.06 and 7.25±0.06 respectively. Success group had significantly higher mean pH at 0 hour than failure group and it further improved with NIPPV at 1 hour and this improvement was maintained at 4 and 24 hour. (P-value 0.001, <0.001 and <0.001 respectively) (Table 5). Comparison of laboratory parameters between success and failure is depicted in table 6.

Discussion:

Noninvasive positive pressure ventilation (NIPPV) has been shown to be an effective treatment for respiratory failure, particularly resulting from acute exacerbations of chronic obstructive pulmonary disease (COPD). However, NIPPV is associated with significant failure rates. Hence, there is a need for identifying preadmission predictors for outcome of NIV in patients for acute exacerbation of COPD, thereby sparing the discomfort of a trial of NIV on these patients.

The present study demonstrated that NIPPV is an effective and safe modality for initial management of patients with severe exacerbation of COPD with hypercapnic respiratory failure. Earlier studies from the West have demonstrated the utility of this modality in patients with COPD. Meduri GU et al (1991), Benhamou D et al (1992), Bott J et al(1993), Brochard L et al (1995) and the current work validates the findings in Indian patients. Moreover it also confirms the benefit of NIPPV in patients with much more severe form of exacerbation. Previous studies from India have reported the use of NIPPV in patients with acute respiratory failure (ARF) due to varied etiologies. Singh ***et al***, showed that NIPPV use was associated with significant improvement in clinical and ABG parameters in patients with ARF. Later, George ***et al***., demonstrated benefits of NIPPV in avoiding the need for invasive mechanical ventilation in patients presenting with ARF of diverse etiology. It concluded that NIPPV is more effective in preventing endotracheal intubation in ARF due to COPD than other causes. Notably, these studies have included patient with ARF of varied etiology, therefore, the cohorts are heterogenous as compared to our study which describes the use of NIPPV in COPD patients only.

50 patients of AECOPD with hypercapnic respiratory failure (Diagnosed based on old Spirometry reports) who presented in hospital were enrolled in this study. Out of 50 patients 32 patients (64%) were male and 18 patients (36%) were female. This may be explained by male dominated society, where males seek medical attention early and females are bound to suffer. There is similar finding in national family health survey-3 (NFHS-3) data.

Out of 50 patients 3 patients (6%) were expired during hospital stay. This observation were partially supported by study done by Connors et al who reported an in-hospital mortality of 11% and Fuso et al who reported an in-hospital mortality rate of 14.4%.In the study done by Karin H. Groenwegen et al (2000), mortality rate were 8 % during hospital stay which increases to 16% by 3 months follow up, it was 18% in 6 month follow up and it was 23 % after I year.

In our study Mean age of Success group was 59.03 (SD±5.43) and Mean age of patients of Failure group was 62.75 (SD±5.77). These differences in both groups were significant statistically (p value-0.047). So age has been proven to be an important determinant of predictor of Success of NIPPV in patients of respiratory failure due to AECOPD. This observation is supported by Benhamou et al (1992) who reported a higher rate of treatment failure in elderly patients while Balami et al (2006) reported that NIPPV can be used successfully in elderly patients admitted with hypercapnic respiratory failure secondary to acute exacerbation of COPD. Increase failure rate in elderly patients may be due to associated co-morbidities. This has been supported by Seneff et al (1995) and Morettiet et al (2000). Age also has been associated with an accelerated decline in lung function.

In our study, success group had significantly lower mean HR [(100.61±9.61 vs 130.17±15.66) p=<0.001] and lower mean RR [(24.32±3.64 vs 30.50±3.72) p=<0.001] at the time of admission. this finding was supported by J. Steer et al (2010). Changes in HR and RR after one hour of NIPPV (91.79±8.43 vs 128.50±15.77), (20.63±2.71 vs 28.33±3.05) (p=<0.001) were also found to predict the outcome in our study. We found that patient with improvement in tachycardia and tachypnoea soon after starting of NIPPV (at 1 hour) responded successfully to it .this improvement was maintained and further improved in success group at 4 and 24 hour of applying NIIPV, (85.58±7.02 vs 126.80±15.44) ,(18.37±1.96 vs 28.80±3.55), (p=<0.001) respectively and (79.58±5.75 vs128.60±18.23) , (16.00±1.67 vs 28.67±3.31) (p=0.001) respectively. This finding is supported by Col D Bhattacharyya et al (2011).

In our Study, We found that the success group had significantly higher mean oxygen saturation [(80.84±7.41 vs 68.08±11.48) p=<0.001] at the time of admission. This finding is supported by, PK Plant et al (2001). Changes in SpO_2 after one hour of NIPPV was also found to predict the outcome in our study,(89.66±3.98 vs 72.17±11.41), (p=<0.001) . We found that patient with improvement in SpO_2 soon after starting of NIPPV responded successfully to it and this improvement was maintained at 4 and 24 hour of NIIPV treatment, (93.95±1.94 vs 77.00±9.67) (96.58±1.17 vs 76.22±6.20) (p=<0.001). This finding is correlate with Col D Bhattacharyya et al (2011)

In our study by comparing the ABG values between the successful group and failed group before NIPPV and after 1, 4 and 24 h , it was found that before NIPPV; the successful group showed statistically significantly (p = 0.005) higher mean pH (7.28±0.05 vs 7.21±0.08), statistically significantly (p = <0.001) lower mean $PaCO_2$ than NIPPV failed cases (72.47±9.74 vs 94.28±16.36).Although severe respiratory acidosis <7.21 carry a high failure rate with NIPPV, which may reach more than 50% of cases in some studies N. Ambrosino et al (2008). This finding is supported by Col D Bhattacharyya et al (2011), M.A. Soliman et al (2013),

After 1 h of NIPPV; the successful group cases showed statistically significantly (p=0.001) higher mean pH (7.30±0.06 vs 7.22±0.09) ,lower mean $PaCO_2$ level (70.13±9.58 vs 93.67±16.51) (p=<0.001) than the failed group. This means that the severity of acidemia and the degree of hypercapnea may be predictive factors for the success of NIPPV in COPD cases especially in the 1st hour after NIPPV and this is in agreement with findings of PK Plant et al (2001), A. Anton et al (2000), Agarawal et al.(2008),G.C. Khilnani et al (2010) and in disagreement with the findings of Poponick et al (1999).

This improvement in pH,$PaCO_2$ were maintained and continued to improve in success group at 4 hour (7.34±0.05 vs7.26±0.06), (65.07±9.46 vs 87.55±11.95) (p=<0.001) and at 24 hour (7.41±0.04 vs 7.25±0.06), (54.08±8.79 vs 88.08±12.54) ,(p=<0.001).This finding is supported by PK Plant et al (2001), Col D Bhattacharyya et al (2011).

Success group had significantly lower median PCT levels on admission compared to failure group [0.08, IQR (0.06-0.26)] versus [0.29, IQR (0.08-0.49)] , p = 0.014].This finding is supported by J. Steer et al (2010). In our study success group also had significantly lower median CRP levels on admission as compared to failure group [4.80 (3.80-7.60)] versus [21.29, IQR (5.79-33.24), p=0.01] .

In our study significantly lower serum creatinine level (1.29±0.62 vs 2.35±1.43) (p=0.001) at the time of admission was found to be a predictor of NIPPV success. This observation is supported by Singh et al (2006) who reported that in patients with acute respiratory failure, presence of one or more organ dysfunction was associated with failure of NIPPV.

In our study Mean Bircarbonate (HCO_3) level of patients of success group was 29.78 (SD±6.79) mEq/dl and mean HCO_3 of patients of failure group was (39.58 SD±7.36) mEq/dl. This difference between these two groups was not statistically significant (0.664). This observation is supported by studies done by GC Khilani et al (2004), Divay Chandra et al (2007). They mentioned that increase in serum bicarbonate level shows there is compensation in respiratory acidosis. Acute respiratory acidosis which is not compensated is risk factor for mortality in patients of acute exacerbation of COPD.

In the present study, We found that there was a high incidence of NIPPV Failure in those patients with a longer duration of illness than those with a short duration of illness. The mean total duration of COPD in the patients of success group was 7.05 (SD±2.13) years and in the expired group was 9.92 (SD±4.16) years. Difference identified between these two groups was statistically significant (p value-0.003). Long duration of illness leads to gradual decline in lung functions like FEV_1, FVC etc so decline in lung functions lead to disturbances in arterial blood gases which leads to respiratory failure. So duration of illness is one of the important predictor of success in patients of AE-COPD with hypercapnic respiratory failure. This finding is supported by J. Steer et al (2000).

In our study Total leucocyte count was raised in both groups (15852.2±62767.12 vs 17600.00±6023.35).This difference between these two groups was not statistically significant (P value-0.601).This observation shows that infection is the most common cause of COPD exacerbation.

In Our study shows that mean total protein at the time of admission in success group was 6.43 (SD±0.51) gm/dl and mean total protein in group of NIPPV failed patients was 6.34 (SD±0.54) gm/dl. This difference between these two groups was not significant statistically (P value-0.601).

In our study Mean serum albumin at the time of admission of Success group was 3.32 (SD±0.70) gm/dl and Mean serum albumin of patients of Failure group was 2.86 (SD±0.34) gm/dl. This differences in both groups was statistically significant (p value-0.036). So serum albumin has been proven to be an important determinant of predictor of Success of NIPPV in patients of respiratory failure due to AECOPD. This observation is supported by Connors AF Jr et al (1996);who reported worse outcomes in COPD patients with low serum albumin levels. This observation was also supported by GC Khilani et al (2004) who conclude serum albumin in the first 24 hour of admission is independent predictor of mortality in patients of acute exacerbation of COPD. On the other hand Albumin is known to reflect the underlying nutritional status and to be affected by the severity of chronic illness. These factors are of obvious significance in deciding the outcome of these patients.

Further research will be required to identify factors that predict success of NIPPV more accurately, and it is essential that conventional mechanical ventilation by endotracheal intubation be available promptly.

Table 1: Comparison of Mean (SD) heart rate at baseline and during NIPPV

Time interval	Success group Mean±SD	Failure group Mean±SD	t-value	P-value
heart_rate_0	100.61±9.61	130.17±15.66	-7.904	<0.001
heart_rate_1	91.79±8.43	128.50±15.77	-10.484	<0.001
heart_rate_4	85.58±7.02	126.80±15.44	-12.483	<0.001
heart_rate_24	79.58±5.75	128.60±18.23	-14.404	<0.001

Table 2: Comparison of Mean (SD) Respiratory rate at baseline and during NIPPV

Time interval	Success group Mean±SD	Failure group Mean±SD	t-value	P-value
respiratory_rate_0	24.32±3.64	30.50±3.72	-5.094	<0.001
respiratory_rate _1	20.63±2.71	28.33±3.05	-8.316	<0.001
respiratory_rate _4	18.37±1.96	28.80±3.55	-12.431	<0.001
respiratory_rate _24	16.00±1.67	28.67±3.31	-16.542	<0.001

Table 3: Comparison of Mean (SD) SpO2 (oxygen saturation) at baseline and during NIPPV

Time interval	Success group Mean±SD	Failure group Mean±SD	t-value	P-value
SpO_2_0	80.84±7.41	68.08±11.48	4.523	<0.001
SpO_2_1	89.66±3.98	72.17±11.41	8.142	<0.001

SpO_2_4	93.95±1.94	77.00±9.67	10.321	<0.001
SpO_2_24	96.58±1.17	76.22±6.20	19.446	<0.001

Table 4: Comparison of Mean (SD) PaCO2 (partial pressure of CO_2) at baseline and during NIPPV

Time interval	Success group Mean±SD	Failure group Mean±SD	t-value	P-value
$PaCO_2$ _0	72.47±9.74	94.28±16.36	-5.679	<0.001
$PaCO_2$ _1	70.13±9.58	93.67±16.51	-6.155	<0.001
$PaCO_2$ _4	65.07±9.46	87.55±11.95	-6.326	<0.001
$PaCO_2$ _24	54.08±8.79	88.08±12.54	-9.584	<0.001

Table 5: Comparison of Mean (SD) pH at baseline and during NIPPV

Time interval	Success group Mean±SD	Failure group Mean±SD	t-value	P-value
pH _0	7.28±0.05	7.21±0.08	2.916	0.005
pH _1	7.30±0.06	7.22±0.09	3.705	0.001
pH _4	7.34±0.05	7.26±0.06	4.147	<0.001
pH_24	7.41±0.04	7.25±0.06	8.008	<0.001

Table 6: Comparison of Mean (SD) Variables

Variables	Success group Mean±SD	Failure group Mean±SD	P-value
Hb	12.38±1.15	12.17±2.08	0.663
TLC	15852.26±2767.12	17600.00±6023.35	0.168
TP	6.43±0.51	6.34±0.54	0.601
Alb	3.32±0.70	2.86±0.34	0.036
TB	1.07±0.46	1.41±0.76	0.070
Creat	1.29±0.62	2.35±1.43	0.001
Sodium	129.71±8.46	128.08±4.03	0.524
pottasium	4.02±0.75	4.46±0.68	0.081
HCO_3	29.78±6.79	39.58±7.36	0.664
TDI	7.05±2.13	9.92±4.16	0.003
RBS	147.52±38.77	135.96±63.22	0.447
BMI	25.53±2.15	24.28±3.16	0.125
CRP	4.80 (3.80-7.60)	21.29 (5.79-33.24)	0.003
PCT	0.08 (0.06-0.26)	0.29 (0.08-0.49)	0.014
SGOT	66.00 (51.75-86.25)	68.00 (50.35-88.25)	0.254
SGPT	64.00 (44.75-86.25)	93.50 44.00-384.75)	0.251
Urea	43.00 (25.25-54.50)	83.00 (32.75-161.75)	0.109

Hb-Hemoglobin,TLC-Total Leucocyte count,TP-Total protein, Alb-Albumin, TB-Total Bilirubin, Creat-Creatinine, HCO_3-Bicarbonate,TDI-Total duration of illness, RBS-Random Blood Sugar, BMI-Body Mass Index.

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