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EVALUATION OF HIGH FLOW NASAL CANNULA AND NON INVASIVE VENTILATION AS FIRST LINE THERAPY IN ACUTE HYPOXEMIC RESPIRATORY FAILURE.

Anaesthesiology

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ABSTRACT

Background: Acute hypoxemic respiratory failure (AHRF) is one of the serious complication and most frequent reason for admission to the intensive care unit (ICU). **Aim:** To evaluate the outcomes of high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) as first line therapy in acute hypoxemic respiratory failure (AHRF). **Methods:** We undertook a prospective observational study of patients with an estimated PaO2/FIO2 ratio of <300 who received HFNC and NIV as first line respiratory support for AHRF between July 2021 and December 2022. In all subjects for study, detailed clinical history was taken with relevant clinical examination and baseline investigations. The baseline ABG including pH, PCO2, PaO2, HCO3 and SPO2, PaO2/FiO2 ratio and respiratory rate were also taken. These parameters were repeated on follow-ups continuously before any outcome was concluded and entered on proforma. The primary outcome was either recovery of patient or failure of treatment. Failure of treatment was defined by intubation for invasive ventilation or death of patient. Results: A total of 86 patients were included in the study. Among patients who received HFNC, 59.5% (22/37) improved, 18.9% (7/37) were intubated and 21.6% (8/37) died. Among patients who received NIV, 63.3% (31/49) improved, 18.4% (9/49) were intubated and 18.4% (9/49) died. **Conclusion:** High flow nasal cannula and non-invasive ventilation both were associated with the reduction of the number of deaths and significantly improving PaO2/FiO2 ratio. There was no favorable option in the comparison between the two groups in the need for invasive mechanical ventilation and mortality of patients. Well designed studies are required to assess the utility of HFNC and NIV in moderate to severe AHRF.

KEYWORDS

Acute Hypoxemic Respiratory Failure (AHRF), Non Invasive Ventilation (NIV), High Flow Nasal Cannula (HFNC), Invasive Mechanical Ventilation (IMV).

INTRODUCTION:

Acute hypoxemic respiratory failure (AHRF) is one of the serious complication and most frequent reason for admission to the intensive care unit (ICU)[1]among hospitalized patients and carries an in-hospital mortality rate of 20.6%. Among those patients with AHRF, 42.1% of patients require invasive mechanical ventilation (IMV), which is associated with a significant increase in duration of the hospital stay as well as medical expenses.

The main stay of therapy for AHRF is supplemental oxygen and treatment of the underlying cause. Options for oxygen therapy include conventional oxygen therapy delivered via nasal cannula or face masks initially, followed by non-invasive ventilation (NIV) and finally intubation or IMV. Traditional nasal cannula and face mask can achieve flow rates of up to 15L/min. However, these flow rates may be lower than patient's inspiratory flow rates needed and the oxygen is also diluted as it gets mixed with room air. Consequently, the fraction of inspired oxygen (FiO2) delivered is variable and this is thought to explain why so many patients require an escalation of oxygen therapy to NIV or IMV. Non-invasive respiratory support includes high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) delivered via facemask. These devices are applied externally with pressure and flow delivered to upper airways with minimal invasiveness. Use of non-invasive oxygenation strategies preserves physiological pathways of airway protection (e.g., cough and clearance of secretions) and may directly reduce the complications related to IMV (e.g., laryngeal and tracheal trauma). The other complications include ventilator induced lung injury, ventilator associated pneumonia, sedation and neuromuscular paralysis[2]. Use of non-invasive support reduces the risk of discomfort and delirium by preserving patient's alertness and interaction with the environment. Maintenance of spontaneous breathing has further benefits related to lung, heart and diaphragm physiology. Spontaneous breathing specifically prevents diaphragm dysfunction and atrophy, allows maintenance of cardiac preloading and cardiac output and yields increased aeration of the dependent lung, which minimizes V/Q mismatch[3]. As such, non-invasive respiratory support is the less invasive strategy to improve hypoxemia in case of failure of conventional oxygen therapy. NIV has been used to manage acute respiratory failure of many etiologies and as a first line mode of ventilatory support in cardiogenic pulmonary edema and hypercapnia secondary to COPD exacerbation[4].

The role of NIV in patients with de novo acute respiratory failure caused by various diseases without pre-existing cardiac or lung diseases is controversial. Multiple studies have shown that NIV reduces the rate of endotracheal intubation, ICU admission and mortality. The main hallmark of NIV is its assistance of the spontaneous activity of the respiratory system by administration of positive pressure into the lungs through a mask

Technical characteristics of NIV:

NIV refers to use of ventilatory methods without the use of an endotracheal tube or a tracheostomy tube which are artificial invasive methods. NIV provides ventilatory support through the patient's upper airway using a noninvasive interface.

Interface:

The interface is crucial for the success of NIV and minimising leakage is the first major challenge. Leaks result from a poor fit between the mask and the face. Excessive leaks may reduce alveolar ventilation and synchrony between the patient and the machine. For these reasons, different mask sizes, shapes and models should be available to provide the best fit in each case. The most common interfaces used for NIV are oro-nasal and full-face masks fixed by straps.

Modalities of non-invasive ventilation:

There are two main modalities of NIV: continuous positive airway pressure (CPAP) and non-invasive pressure support ventilation (NIPSV).

CPAP:
This technique is simple and may be performed with an oxygen source connected to a tight fitting mask, provided with an expiratory valve (PEEP valve). CPAP is used to deliver a pressure which is constantly set during inspiration as well as expiration which leads to an increase in the functional residual capacity. The level of CPAP used in patients range between 5 and 15 cmH2O, although the most frequent pressure used in clinical practice is 10 cmH2O[5].

NIPSV / BiPAP:
This technique is more complex and constitutes a true ventilation mode because it always requires a ventilator. This modality is also called bi-level positive airway pressure (BiPAP) because it is generally applied using two levels of pressure: one is the pressure support on inspiration, inspiratory positive airway pressure (IPAP) and other is a positive pressure on expiration, expiratory positive airway pressure (EPAP). EPAP provides a dual benefit by ensuring proper flow in order to flush carbon dioxide to avoid rebreathing along with increasing functional residual capacity and opening up the upper airway to prevent apnea as well as hypopnea**.** NIPSV is usually started with inspiratory pressures of 8-12 cmH_2O and expiratory of 3-5cmH_2O. As the patient adapts to the system, pressure support should be increased to obtain adequate tidal volumes. Patient confidence with the technique is crucial, which includes clear explanations from the attending team and the appropriate use of sedation. In clinical practice, the most frequently used pressures are IPAP of 15–20 cmH2O and EPAP of 5 cmH_2O[5].

Both CPAP and BiPAP increase airway pressure, ameliorate arterial oxygenation, increase end expiratory lung volume and improve cardiac function by reducing left ventricular afterload and right ventricular preload[6].

Drawbacks in the use of positive pressure ventilation are difficulties arising from the discomfort of the mask, headgear or straps and air leaks. Patients also complain of nasal pain, erythema or breakdown of skin due to use of mask. Nasal congestion or dryness as well as ulceration of the nasal bridge are also concerns related to long duration of mask usage.

HFNC is a recently introduced mode of oxygen therapy and more patient comfortable mode. This mode of therapy allows the delivery of heated and humidified oxygen up to 60L/min via wide bore nasal cannula, providing expiratory positive airway pressure (EPAP) by physiological effects[7] and a washout effect of CO2 in the upper airway[8] with unloading of respiratory muscles. HFNC for AHRF in small observational trials has shown improvement in dyspnoea, frequency of breathing and oxygenation. In healthy volunteers treated with HFNC with a closed mouth and a flow rate of 60L/min, the measured PEEP was as high as 7cmH2O[9]. However, this level of PEEP can decrease easily, as soon as the mouth is opened. Each 10L/min increase in flow rate increases the mean airway pressure by 0.69cmH2O when subjects breathe with their mouths closed, and by 0.35cmH2O when they breathe with their mouths open[10]. Furthermore, HFNC delivers a heated and humidified flow, providing more comfort than dry air. HFNC also increases the water content of mucus, which facilitates secretion removal and avoids desiccation and epithelial injury. Finally, compared to NIV, the tolerance of HFNC is higher due to its interface, as simple nasal prongs enable patients to speak, eat and drink.

Mechanism of action:
While the clinical use of HFNC therapy is rapidly growing, the exact mechanism through which it works remains unclear. There is increasing physiological evidence that supports the postulation by Dysart K *et al*[11] that there are a number of factors that influence the mechanism of action of HFNC therapy.

Washout of nasopharyngeal dead space:
The first postulated mechanism of action is that HFNC therapy washes out anatomical nasopharyngeal dead space. This reduces the dead space overall and provides a physiological explanation for improved alveolar ventilation and respiratory effort.

Reduction in work of breathing:
A second postulated mechanism is that HFNC therapy reduces the overall work of breathing. This may be through either stenting of the airways or through higher flow rates that exceed a patient's peak inspiratory flow and hence minimise the inspiratory resistance associated with the nasopharynx.

Delivery of warmed and humidified gas:
Another important mechanism is HFNC's effect on respiratory mechanics from the delivery of warmed and humidified gas. A recent study focusing on epithelial cells demonstrated that and dry gas with low humidity resulted in increased inflammation and reduced cell function[12]. Humidification from HFNC therapy ameliorates this effect and demonstrates that adequate warming and humidifying of the airways has a beneficial physiological effect.

Positive distending pressure:
Finally, HFNC therapy is postulated to provide positive airway pressure (PAP)[13]. PAP can help to recruit alveoli and maintain alveolar patency, subsequently reducing V/Q mismatch. PAP usually generates pressure ranging from 2–8 cmH2O.

Clinicians should be aware of the potential harmful effects of HFNC. First, HFNC can mask patient worsening and subsequently delay intubation, which may be harmful. As recently reported by an observational study in acute respiratory failure patients treated by HFNC, patients intubated after more than 48 hours of treatment had a higher mortality than those intubated within 48 hours[14]. In hypoxemic acute respiratory failure, HFNC preserves spontaneous breathing and permits highly negative intrathoracic pressure. Therefore, HFNC can contribute to lung injury in patients breathing with high drive and large tidal volume. As opposed to NIV, no monitoring of pressures or volume is available for patients breathing with HFNC.

METHODS:
A prospective observational study was conducted on patients of AHRF receiving respiratory support in the form of HFNC and NIV in department of Anaesthesiology and Critical Care Medicine of Government Medical College, Srinagar after approval from institutional ethical committee.

Adult patients (≥18 years old) with an estimated PaO2/FIO2 (P/F) ratio of <300 were included in the study. Patients below 18 years of age, with type 2 respiratory failure (PaCO2 >50 mmHg), chronic respiratory failure without acute exacerbation, patients who needed urgent airway intervention (respiratory arrest, asphyxia, massive hemoptysis etc), comatose patients and patients with pulmonary embolism or massive pleural effusion in which prognosis was independent of respiratory support were excluded from the study. In all subjects for study, detailed clinical history was taken with relevant clinical examination and baseline investigations. The baseline ABG includung pH, PCO2, PaO2, HCO3 and SPO2, PaO2/FiO2 ratio and respiratory rate were also taken. These parameters were repeated on follow-ups continuously before any outcome was concluded and entered on proforma. Clinical cause of hypoxemia was noted.

NIV was managed according to current guidelines. Face mask was the first choice of delivery of NIV to the patients. The initial PEEP was set to 5 cm H2O. If the patient tolerated this pressure, it was gradually increased to improve the oxygenation. The initial inspiratory pressure was set to 8–10 cm H2O. If the patient tolerated this pressure, it was gradually increased to relieve dyspnoea. The FiO2 was titrated to maintain the peripheral oxygen saturation (SpO2) of more than 90%.

HFNC was managed based on current consensus. The temperature was set between 31 and 37°C, the flow between 30 and 60 L/min, and the FiO2 was set to maintain the SpO2 more than 90%. When the respiratory distress was relieved and the oxygenation was improved, we gradually shortened the duration of HFNC or NIV until it was totally weaned. If the respiratory distress and oxygenation progressively deteriorated, intubation for IMV was performed. However, all the decisions were taken at the discretion of the attending physician.

The data was compiled on Microsoft Excel spread sheet and then exported to data editor of SPSS Version 23.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean and SD while as categorical variables were summarized as frequencies and percentages. Paired t-test was used to analyze the difference between the continuous variables at two occasions. Repeated measures ANOVA was used to analyze the differences in continuous variables over multiple followups between two groups. A p-value of less than 0.05 was considered statistically significant. The primary outcome was either recovery of patient or failure of treatment. Failure of treatment was defined by intubation for invasive ventilation or death of patient.

Conflict of interest: Nil
Funding: Nil

RESULTS:
A total of 86 patients meeting the inclusion criteria were studied from July 2021 to December 2022. 43% (37/86) of patients received HFNC and 57% (49/86) of patients received NIV (Table 1). All analysis was done on an intention to treat bias.

The baseline characteristics of both the groups were comparable in terms of age, baseline ABG parameters, PaO2 /FiO2 ratio, respiratory rate and mean duration of oxygen therapy (Table2). We observed that main cause of AHRF was pneumonia 80.23% followed by pulmonary edema 6.98% and others including interstitial lung disease, carcinoma lung, endobronchial tuberculosis, pleural effusion, hemoptysis, post tubercular fibrotic lung disease and ARDS (Table 3). Among patients who received HFNC, 59.5% improved, 18.9% were intubated and 21.6% died. Among patients who received HFNC, 59.5% (22/37) improved, 18.9% (7/37) were intubated and 21.6% (8/37) died. Among patients who received NIV, 63.3% (31/49) improved, 18.4% (9/49) were intubated and 18.4% (9/49) died (Fig 1). The relationship between NIV and HFNC with the outcome of patients was not significant (p-value=0.95). The mean duration of treatment was 9.72 days for HFNC and 7.06 days for NIV (p-value 0.07) (Fig 2).

Table 1: Distribution of patients according to mode of therapy provided

Mode of therapy	Frequency	%
HFNC	37	43.0
NIV	49	57.0
Total	86	100.0

Table 2: Comparison between baseline criteria and characteristics of the patients.

Characteristic	Mode	N	Mean ±SD	Mean Difference	p value
Age (years)	HFNC	37	57.35± 13.26	-3.18	0.26
	NIV	49	60.53± 12.42		
pH	HFNC	37	7.35± 0.09	0.00	0.83
	NIV	49	7.35± 0.11		
PCO2	HFNC	37	34.48± 6.48	-1.17	0.42
	NIV	49	35.65± 6.85		
PaO2	HFNC	37	47.97±9.36	-2.28	0.25
	NIV	48	50.25±8.64		
HCO3	HFNC	37	23.55±5.49	-1.96	0.12
	NIV	49	25.51±5.89		
SPO2	HFNC	37	78.30±7.57	-1.34	0.36
	NIV	49	79.63±5.03		
PaO2:FiO2 RATIO	HFNC	37	228.43±44.58	-10.85	0.25
	NIV	48	239.28±41.15		
RESP. RATE	HFNC	37	21.73±5.35	1.44	0.17

Table 3: Distribution of patients according to diagnosis

Diagnosis	Frequency	%
Pneumonia	69	80.23
Pulmonary Edema	6	6.98
ILD	4	4.65
CA Lung	2	2.33
Pleural Effusion	1	1.16
Endobronchial TB	1	1.16
Hemoptysis U/E	1	1.16
Post TB Fibrotic LD	1	1.16
ARDS	1	1.16

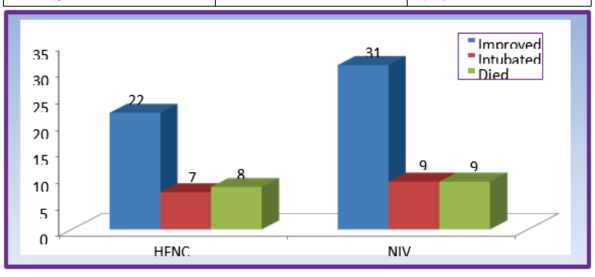

Fig 1.

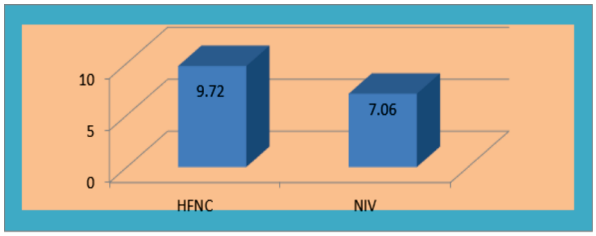

Fig 2

DISCUSSION:
In the present study, we compared the the effectiveness and impact of HFNC as compared to NIV in patients with AHRF. How to improve patient's survival rate, reduce the occurrence of IMV and improve the prognosis of patients are the questions that always have been discussed. Therefore, the use of various non invasive mechanical ventilation methods to maintain the patient's PaO2 at a high level has become the global consensus. NIV is an oxygen therapy modality that emerged in the 1990s of the last world. **Esteban A et al., (2008)**[15]conducted a nested comparative study in 349 ICUs in 23 countries, and found out that NIV usage rate increased from 4% in 1998 to 11% in 2004. NIV has long been in widespread use and has become the favorable option for ventilation support in patients with respiratory failure.However, the shortcomings of NIV were also quickly exposed. An RCT carried out by **Lemiale V et al., (2015)**[16] found out that early use of NIV did not reduce 28-day mortality in immunocompromised patients with acute respiratory failure. Oxygen flow in NIV is often limited to <15 l/min and FiO2 is unstable as well which makes it less effective than expected[17]. This is what made HFNC therapy receive considerable attention when it was introduced in the 2000s as an alternative respiratory support for patients with respiratory failure. By providing a constant gas flow rate of up to 60 l/min, HFNC can improve the ability to flush the dead space of the upper airway better than NIV and reduce the patient's work of breathing. In a prospective study,**Parke R et al., (2009)**[18] found that HFNC therapy could produce low levels of positive airway pressure, approximating the effect of PEEP. Advantages of HFNC are that patients can tolerate oral feeding, hold verbal communication, or even ambulate while receiving oxygen therapy. Despite the many advantages of HFNC as outlined above, too much reliance on HFNC therapy can lead to delayed intubation and increase mortality[19]. There are limited randomised controlled trials comparing HFNC and NIV in AHRF. One meta-analysis by **Stéphan F et al., (2015)**[20] compared the use of HFNC and bilevel positive airway pressure (BiPAP) in acute respiratory failure in patients who had undergone cardiothoracic surgery. They found that HFNC was not worse than NIV for the primary outcome of reintubation or premature discontinuation of therapy. Another study by **Doshi P et al., (2018)**[21] comparing NIV and HFNC for the treatment of respiratory failure in the emergency department, found that HFNC was noninferior to NIV for the treatment of respiratory failure in adult patients and is consistent with our results. **Frat JP et al., (2015)**[22]demonstrated no difference in the time interval between randomization to intubation among patients receiving different oxygen therapy. While use of NIV may delay intubation and increase mortality, this was not true for HFNC in this study. However our study demonstrated that mortality rate was not significant between HFNC and NIV groups. These results must be interpreted in the context of a recent retrospective observation study which reported that late intubation with HFNC was also associated with an increase in ICU mortality[19]. The "FLORALI" trial[23] conducted in 23 ICUs across France and Belgium, included 310 patients and compared high-flow nasal oxygen (HFNO) therapy and NIV.

The study included AHRF patients with PaO2/FiO2 ratio of <300 mmHg. In FLORALI study, the overall need for intubation was higher 45% (139/310) than in our study 18.6% (16/86). In the NIV group, the need for intubation was 50% (55/110) which was higher than our study which is 18.4% (9/49), and in the HFNO group, the need for intubation was 38% (40/106) which was also higher than our study that is 18.9% (7/37). The mean PaO2 /FiO2 ratio in FLORALI study varied from 149 to 161 mmHg. Our study looked at cases with a mean PaO2 /FiO2 ratio of 228 to 239 mmHg at the time of inclusion in the study. Our study showed non significant increase in the need for intubation for patients in the HFNC group as compared to the NIV group. **Shoukri AM (2021)**[24]in a retrospective analysis of patients with AHRF admitted to the ICU found that HFNC is effective in the management of AHRF. Its

efficacy is similar to NIV, with no difference in the duration of treatment, endotracheal intubation rate or mortality rate. **Frat JP et al., (2015)**[22] found that HFNC seems to be a good alternative to NIV as treatment for patients with hypoxemic respiratory failure. Its good tolerance, physiological effects including high FiO2, PEEP effect and dead space washout lead to decreased work of breathing and probably avoid lung strain.

The present study was a prospective, observational study looking at patients with AHRF who failed conventional oxygen therapy and required either HFNC or NIV. There are no large-scale data comparing NIV and HFNC, even though the use of HFNC is routine in patients with mild respiratory failure. Our study could look at all common etiologies of AHRF because we are a tertiary level hospital.

The present study has a number of limitations. First, we note the relative dearth of patients receiving HFNC and NIV as first line of oxygen therapy. This severely limits our ability to draw conclusions about the generalizability of our study. Second, in our study, the characteristics of both groups were not controlled. Lastly our study was an observational study rather than randomized trial. The ability to conduct blinded randomized trials is a persistent problem involving oxygen delivery systems, as the systems make blinding virtually impossible. These limitations support the need for further larger studies to provide credible results.

CONCLUSION:

HFNC and NIV both were associated with the reduction of the number of deaths and significantly improving PaO2/FiO2 ratio. There was no favourable option in the comparison between the HFNC and NIV groups in the occurrence of IMV. HFNC offers advantages over NIV in patients with AHRF as it is safe and well tolerated means of oxygen delivery and provides equivalent oxygenation. Patients can tolerate oral feeding, hold verbal communication, or even ambulate while receiving HFNC. Well-designed studies are required to assess the utility of HFNC and NIV in moderate to severe AHRF.

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