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Anaesthesia Section

Sequential Oxygen Therapy in COVID-19 Diabetic Patients: A Retrospective Cohort Study

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ABSTRACT

Introduction: Acute respiratory failure is the most common clinical feature in patients with severe Coronavirus Disease -2019 (COVID-19) who are admitted to an Intensive Care Unit (ICU) and may require invasive mechanical ventilation, which is generally linked with a high fatality rate. Patients with established co-morbidities, such as diabetes, invariably fall into the category of patients with severe disease presentation and rapid disease progression.

Aim: To study the clinical outcomes of COVID-19 diabetic patients after sequential oxygen therapy using a reservoir bag mask, High Frequency Nasal Oxygen (HFNO), and Non-invasive Ventilation (NIV).

Materials and Methods: In this retrospective cohort study, adhering to the STROBE statement criteria, the authors included 150 patients suffering from COVID-19 acute respiratory failure, who were known diabetics, divided into three groups based on admission oxygen saturation and Respiratory Rate (RR) for Non-Rebreather Bag-Mask (NRBM) therapy, HFNO, and NIV. For two weeks, all patients were monitored, and measures such as Saturation of peripheral Oxygen (SpO_2), Respiratory Rate (RR) escalation of oxygen requirement, glycaemic management, compliance and problems with continued oxygen therapy, the need for invasive mechanical ventilation, and mortality were recorded. The recorded parameters among the three groups were compared using Analysis of Variance (ANOVA) test.

Results: Among the demographic parameters recorded, the authors noted that individuals older than 50-55 years of either sex were admitted for HFNO (56.02±11.71 years) and NIV (54.28±14.67 years) therapy, whereas no such preponderance was noted among the two genders. Significant results were noted in all three groups in terms of the escalation of oxygen fraction (FiO2) requirements on the 10^{th} day of observation (NRBM 12.63±2.48%, HFNO 37.74±13.56%, NIV 82.44±11.11%). The need for tracheal intubation was higher in patients in the NIV group (10) compared to the HFNO (9) and NRBM (1) groups. Patients whose blood sugar levels remained uncontrolled throughout the course of observation in the study were disparagingly seen to have been a part of the HFNO and NIV groups, and hence the subsequent mortality.

Conclusion: There was a steady escalation of mean oxygen requirements in all three groups of oxygen therapy over the course of two weeks, coinciding with the ensuing ‘cytokine storm’ associated with Severe Acute Respiratory Syndrome-Coronavirus- 2 (SARS-CoV-2) infection. This trend of escalation of oxygen requirement also in turn coincided with the raised glycaemic charting trends of the patients over the same course of two weeks, delineating those individuals with diabetes mellitus, in view of their compromised immunity and innate pro -inflammatory state, are more prone to develop severe form of the disease with more serious complications, which may even lead to mortality. With regards to the compliance, NRBM & HFNO provided best results in comparison to NIV. The rates of complications were also noted to be higher with the use of NIV in this instance.

Keywords: Coronavirus Disease-2019, Diabetes mellitus, Hypoxemia, Intubation

INTRODUCTION

In late 2019, a new coronavirus was identified as the source of a cluster of pneumonia cases in Wuhan, China. It had subsequesntly spread fast, culminating in a pandemic, with the World Health Organisation identifying the disease as COVID-19 [1].

The COVID-19, induced by SARS-CoV-2, causes moderate acute respiratory infection to severe pneumonia with respiratory failure, acute distress syndrome, and septic shock. Severe illness typically affects the elderly and people with underlying medical disorders such as diabetes, hypertension, cardiovascular disease, chronic lung disease, cancer, and chronic renal disease [2,3]. Several retrospective studies have been conducted to determine the association between pre-existing patient co-morbidities and clinical outcomes and death in COVID-19 patients. Diabetic individuals were shown to have a more severe illness progression and death among SARS-CoV-2 patients, necessitating more watchful treatment [4-8]. Diabetes patients are more vulnerable to infection by bacteria, viruses, and fungi than non-diabetics due to their decreased immune function [3,4]. As a result, these individuals may be at a higher risk of SARS-CoV-2 infection, especially in terms of severity of features as well as the associated complications.

Supplemental oxygen treatment should be administered quickly to patients with severe acute respiratory infection, respiratory distress, hypoxaemia, or shock, as per recommendation. However, when conventional oxygen therapy via face mask with a reservoir bag fails to relieve the patient’s respiratory distress and/or hypoxaemia as a result of an intra-pulmonary ventilation-perfusion mismatch or shunt, mechanical ventilation or tracheal intubation is usually considered as the next step in management [9,10]. However, to limit the danger of aerosol formation associated with laryngoscopy and tracheal intubation, there has been an increase in the use of HFNO or NIV to relieve the patient’s respiratory distress and/or hypoxaemia.

As most COVID-19 positive patients who suffer from Acute Respiratory Distress Syndrome (ARDS) require mechanical ventilation, especially patients with pre-existing co-morbidities such as diabetes tend to deteriorate faster. So, the authors summarised that the use of advanced equipment like HFNO or NIV could serve as a helpful alternative in order to decrease the work of breathing of COVID-19 diabetic patients without directly turning to invasive mechanical ventilation, given the strain on available resources and the number of highly skilled medical professionals for active airway instrumentation and management during the peak of the COVID-19 pandemic. In comparison to standard oxygen treatment, the present study comprises the afore-mentioned two alternative ways in oxygen therapy (HFNO and NIV) for the management of COVID-19 diabetic patients, to observe the progress of the disease in adherence to suitability and compliance to the selected oxygen therapy.

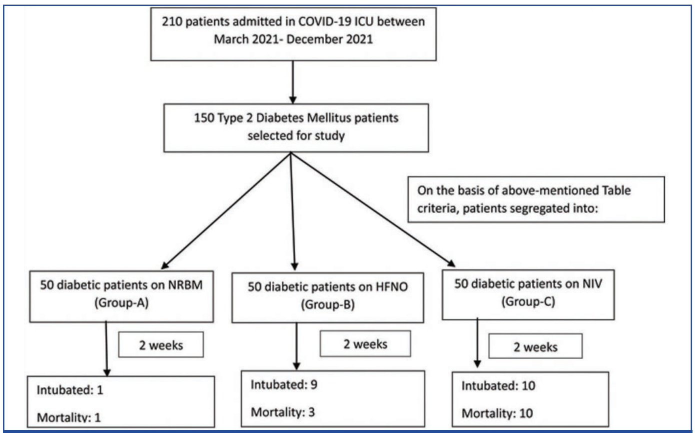
MATERIALS AND METHODS

This retrospective cohort research, following the STROBE statement criteria [11], was undertaken at Dr DY Patil Medical College, Hospital, and Research Centre, Pimpri, Pune, Maharashtra, India. The data was collected between March 2021 and December 2021 to coincide with present findings of the second wave of the COVID-19 outbreak in India. The study was planned and designed between August 2020 and September 2020, and Institutional Ethics Committee was obtained on 27th October 2020. Data analysis and interpretation took an additional three months from July 2022 to September 2022.

Sample size calculations: The percentage of diabetic COVID-19 patients requiring mechanical ventilation was found to be 9.8%, as per a retrospective cohort study conducted by Shang J et al., examining the relationship between diabetes mellitus and COVID-19 prognosis, published in The American Journal of Medicine [4]. Entering this data in WINPEPI software and taking an allowable error of 5% at a 95% confidence interval, the calculated sample size comes out to be 136. Which was rounded off to include 150 patients. All the selected participants were divided into Group A, Group B and Group C according to the criteria depicted in [Table/Fig-1,2].

Group A	Cases with baseline SpO_2 ≥91% and RR <30/min were started on oxygen therapy using reservoir bag mask (Flow rate was decided as per peripheral SpO_2 reading and the RR from the time of admission)
Group B	Cases with baseline SpO_2 of 81%-90% and RR of 30-40 min were started on High Flow Nasal Oxygenation (HFNO)
Group C	Cases with baseline SpO_2≤80% and RR > 40 min were started on Non-Invasive Mechanical Ventilation (NIV)

[Table/Fig-1]: Depicted the selection criteria and group divisions of all patients and participants.



[Table/Fig-2]: Flowchart depicting the selection and segregation of patients into the three groups, followed by the sequelae in each group.

Inclusion criteria: All adult patients diagnosed with COVID-19 pneumonia of either gender, including those with Type II Diabetes mellitus, aged 30-70 years, and willing to sign consent forms, were included.

Exclusion criteria: Pregnant women, patients with cognitive and behavioural disorders, patients with any known lung pathology such as active Tuberculosis (TB), bronchial asthma, bronchiectasis, pulmonary embolism, chronic respiratory failure, and other significant respiratory disorders, cigarette smokers, and obese individuals were also excluded. Patients with cardiovascular, cerebrovascular, and hepato-renal illness, as well as those who were immuno-compromised or had cancer, were excluded from the trial.

Procedure

Confirmed RT-PCR positive cases of COVID-19 were segregated into three groups at the time of admission, as per the following criteria [12,13].

Each group's oxygen levels were gradually increased to a maximum FiO_2 of 100% as needed. The primary outcome was to note if there was an increase in oxygen demand in each group on day 5, day 10, and day 15 after admission. Secondary clinical outcomes such as SpO_2 (peripheral oxygen saturation), RR, and Arterial Blood Gas (ABG) were measured in each group on days 5, 10, and 15 after admission. Compliance with each form of oxygen therapy, the length of Intensive Care Unit (ICU) stays, and any death during hospitalisation were also recorded. Complications such as pressure sores, asphyxia, aspiration, and hypercapnia, if any, were also observed. Throughout the trial, the decision to intubate was based on clinical (RR, deterioration of respiratory status, high respiratory-muscle exertion) and physiological (arterial partial pressure of oxygen) factors.

Diabetic patients were identified by fasting plasma glucose levels greater than 120 mg/dL or random plasma glucose levels greater than 200 mg/dL, as well as glycated haemoglobin (HbA1c) values greater than 5.8% at the time of admission. All COVID-19 diabetic patients who were hospitalised were kept on insulin therapy on a sliding scale, with a target fasting and post-prandial glucose range of 100-120 mg/dL and 140-180 mg/dL, respectively.

Patients were kept on a regular medication regimen with maintainence i.v. fluid set by the institution during their in-hospital stay. Biomarkers and radiographic imaging of patients were performed in accordance with institutional procedure. Each sort of oxygen treatment technique was explained to the patient, and signed informed consent was obtained.

STATISTICAL ANALYSIS

The tabulated data of all the groups were used to compare between the three groups using an ANOVA Test. The mean and standard deviation were compared between the groups using ANOVA Test, with a p-value <0.05 considered statistically significant.

RESULTS

Amongst the vitals recorded over the period of two weeks and compared using ANOVA test, the respiratory rate (RR) and partial pressure of oxygen in the arterial blood sample denote the significant underlying event of COVID-19-induced hypoxaemia and ventilation-perfusion mismatch. The escalation of oxygen requirement shows a steady trend in the first two weeks of infection in all three forms of oxygen therapy. The rise in oxygen requirement is mostly seen on the 10th day of infection, denoting the peak of infection and the ensuing cytokine storm in the first two weeks of infection.

The fasting blood sugar level shows a similar pattern as seen in the oxygen requirement escalation. The authors see that the escalation of oxygen requirement coincides with the raised fasting blood glucose levels over the course of 15 days of observation of the illness. Thus allowing clinicians to de-lineate that the raised blood glucose levels correspond with lower immunity and a more severe state of infection. A similar picture is elucidated in the case of post-prandial sugar monitoring, where average blood sugar levels were persistently above 220 mg/dL in patients receiving a higher form of oxygenation therapy with HFNO and NIV [Table/Fig-3].

Demographic and clinical data of all participants		NRBM (M+SD)	HFNO (M+SD)	NIV (M+SD)	p-value
Age (years)		44.04±10.59	56.02±11.71	54.28±14.67	**0.0001**
Gender	Male	29	39	34	0.1005
	Female	21	11	16	

SpO_2 (%)	5th day	93.9±1.37	91.92±4.02	90.8±2.51	**0.0001**
	10th day	93.8±1.72	93.90±1.55	91.78±3.16	**0.0001**
	15th day	92.36±13.60	94.52±1.58	93.09±2.69	0.3968
Respiratory Rate (breaths per minute)	5th day	26.87±2.28	35.64±2.15	46.4±4.9	**<0.00001**
	10th day	27.14±3.05	35.92±1.67	42.02±4.98	**<0.00001**
	15th day	26.47±5.27	36.18±2.31	38.74±5.43	**<0.00001**
$PaCO_2$ (mmHg)	5th day	35.94±5.50	35.84±4.09	37±4.05	0.378
	10th day	37.54±4.43	35.66±3.14	37.17±4.2	**0.045**
	15th day	35.90±5.92	35.28±2.85	38.11±3.49	**0.003**
$PaCO_2$ (mmHg)	5th day	84.24±3.00	78.38±10.59	68.58±4.15	**<0.00001**
	10th day	89.00±7.86	87.54±13.37	72.36±9.93	**<0.00001**
	15th day	92.94±9.13	90.38±15.86	78.86±6.11	**<0.00001**
Fasting blood sugars (mg/dL)	5th day	198.7±33.2	230.22±58.97	229.77±66.75	**0.007**
	10th day	182.83±35.33	217.76±61.9	222.54±66.95	**0.0008**
	15th day	168.72±37.65	204.58±71.65	194.06±56.97	**0.0281**
Postprandial sugars post lunch (PP1) (mg/dL)	5th day	204.68±31.06	236.62±63.30	230.77±77.75	**0.023**
	10th day	182.8±35.32	226.12±57.22	220.4±59.29	**<0.00001**
	15th day	203.84±30.66	227.36±59.98	214.83±53.57	0.052
Postprandial sugars post dinner (PP2) (mg/dL)	5th day	195.56±44.88	233.82±67.87	223.89±71.98	**0.007**
	10th day	182.8±35.32	223.48±64.33	208.15±56.59	**0.0008**
	15th day	199.04±37.05	227.82±71.53	205.30±53.85	**0.0281**
O_2 fraction (%) escalation	5th day	12.22±2.47	37.70±13.56	91.2±9.39	**<0.00001**
	10th day	12.63±2.48	37.74±13.56	82.44±11.11	**<0.00001**
	15th day	12.27±2.30	35.78±13.58	73.02±13.18	**<0.00001**

[Table/Fig-3]: Data collected on 5th, 10th and 15th day of ICU stay with regards to mean peripheral saturation, Respiratory Rate (RR), ABG ($PaCO_2$ and $PaCO_2$), Fasting blood sugars, postprandial sugars and Escalation in oxygen requirement. (data between the three groups compared using ANOVA test).
(NRBM: Non-rebreather reservoir bag mask; HFNO: High flow nasal oxygen device; NIV: Non-invasive ventilation mask; SpO_2: peripheral oxygen saturation; $PaCO_2$: partial pressure of carbon dioxide in arterial blood sample; PaO_2: partial pressure of oxygen in arterial blood sample; BSL: blood sugar levels [mg/dl]; PP1: post prandial blood sugars post lunch [mg/dl]; PP2: post prandial blood sugars post dinner [mg/dL]).

In the present study, patients' compliance with the reservoir bag mask and HFNO was very satisfactory, whereas only nine out of 40 patients receiving NIV support found the use of NIV to be satisfactory. Fourteen patients on NIV therapy had either developed mild to moderate pressure ulcers over the bridge of the nose, pain over the neck and jaw due to the NIV mask tightening bands, drying of the mouth, or had difficulty in tandem breathing with the NIV machine [Table/Fig-4].

Comparative clinical data		NRBM	HFNO	NIV	p-value
Compliance to O_2 therapy	Yes	50	50	9	**<0.00001**
	No	0	0	41	
Complications	Yes	0	0	14	**<0.00001**
	No	50	50	36	
Tracheal intubation	Yes	1	9	10	**0.014**
	No	49	41	40	
Mortality	Yes	1	3	10	**0.0051**
	No	49	47	40	
Length of ICU stay (Days)		8.33±2.88	24.22±7.59	19.56±5.55	**0.0001**

[Table/Fig-4]: Data collected over the course of two weeks of hospital stay with regards to compliance to and complications with each type of oxygen therapy need for tracheal intubation and mortality. (data between the three groups compared using ANOVA test).
NRBM: Non-rebreather reservoir bag mask; HFNO: High flow nasal oxygen device; NIV: Non-invasive ventilation mask

The need for subsequent tracheal intubation is mostly comparable in both the HFNO and NIV group, which also coincides with finding of present study of patients with raised blood sugar levels leading to a pro-inflammatory homeostatic immune response, leading to the aggravation of infection ensuing higher forms of oxygenation therapy (HFNO or NIV). Though the mortality rate is considerably higher in the NIV group, the length of ICU stay was comparably similar in both the HFNO and NIV group, 24 days and 19 days, respectively [Table/Fig-4].

DISCUSSION

The present research was conducted during the second wave of the COVID-19 epidemic in our nation. This study was a simple attempt to study the severity of the infection in patients with pre-existing medical illnesses such as type 2 diabetes mellitus. The authors here attempted to investigate the relationship between the mean escalation of oxygen requirement and active glycaemic control, compliance and complications to each type of oxygen therapy, and subsequent disease progression, the need for tracheal intubation, and mortality, as well as any association between poor glycaemic control and disease severity in this retrospective cohort study.

As per the results illustrated by this study, patients presenting with the milder form of the disease and good glycaemic control tend to require minimal oxygen support (non-rebreather bag mask), with rapid recovery and fewer complications. However, moderate to severe cases most definitely require ICU support, with patients either on HFNO and/or NIV, and are hence also more prone to complications due to both manifested diseases as well as treatment-associated complications.

The mean escalation of oxygen requirement showed a steady trend in the first two weeks of infection in all three forms of oxygen therapy. The rise in oxygen requirement is mostly seen on the 10th day of infection, denoting the peak of infection and the ensuing cytokine storm in the first two weeks of infection. In a study conducted by Gautret P et al., on the natural history of COVID-19 and therapeutic options, they explained in their findings that on approximately the tenth day of infection, COVID-19 associated pneumonia may evolve toward acute respiratory failure due to ARDS requiring ICU admission and high-flow oxygen or mechanical ventilation, with a severe prognosis [13]. This is caused by underlying immunological factors, such as elevated circulating inflammatory cytokine levels, described as a 'cytokine storm', rather than due to the virus itself [13,14].

The authors observed that raised fasting and post-prandial blood sugar levels coincide with the trend of escalated oxygen requirements. With either parameter, the authors see the escalation of oxygen requirement and persistently raised blood glucose levels, even on the 10th day of the illness (refer to [Table/Fig-2]). As evident from the pathophysiology of diabetes mellitus, especially in those patients with uncontrolled blood sugar levels, their innate immune system and humoral immunity are often compromised, making their first line of defense against any infection, including SARS-CoV-2, incompetent. Diabetes mellitus is also known to cause a pro-inflammatory state, which is associated with an exaggerated cytokine response. As elicited by various studies to date, individuals with diabetes infected by COVID-19 have significantly higher levels of interleukin-6 (IL-6) and C-Reactive Protein (CRP) compared to those without diabetes [15,16]. Thereby making diabetic individuals afflicted with COVID-19 pneumonia more susceptible to a cytokine storm with potential organ damage.

A study conducted by Cuschieri S et al., on COVID-19 and Diabetes: The Why, the What and the How also expounded on the association between poor glycaemic control and increased severity and progression of COVID-19 disease. They surmised that diabetic patients were at a higher risk of infection that required hospitalisation, particularly for those with uncontrolled glycaemic indices. This corresponds to the underlying pathological mechanism in diabetes, where hyperglycaemia increases pathogen virulence, lowers both interleukins production in response to infection and their phagocytic activity, also in turn making them at a higher risk of developing Diabetic Ketoacidosis (DKA), which causes additional metabolic complications in these individuals [17].

In the present study, individuals with uncontrolled blood sugar levels over two weeks of observation ended up requiring higher forms of oxygen therapy than they were initially started on, or even mechanical ventilation. Twenty individuals in the present study eventually required mechanical ventilation, and fourteen individuals succumbed to the disease within seven days following ICU admission.

In terms of compliance and complications, no complaints were reported from the patients in the NRBM and HFNO groups, though this does not in any way provide definitive evidence to support the superiority of HFNO over NIV, owing to a lack of data and the lesser number of available HFNO devices in many Indian healthcare centers during the surge of COVID-19 cases. The use of HFNO comes with its own set of risks, such as the increased spread of infection due to aerosolisation and hence the need for individual isolation chambers [18]. Thus, the authors too strongly recommended wearing face masks to our patients on HFNO therapy. In the NIV group, there were complaints of discomfort, (probably due to it being a closed space), as well as the development of mild to moderate pressure ulcers over the bridge of the nose, pain over the neck and jaw due to the NIV mask tightening bands, drying of the mouth, and difficulty in tandem breathing with the NIV machine, as well as hamper in performing daily activities such as feeding and drinking water, due to the risk of aspiration on the application of the mask immediately post-feeding [19].

Although at the time of completing the present study, there were many COVID-19-positive cases, as well as post-COVID-19 cases of Mucormycosis that had begun infecting diabetic individuals all across India, however, discussions related to various oxygen therapies and associated Mucormycosis were not a part of this study. With the advent of mass vaccination across the globe and as more studies gradually shed light on this COVID-19-induced global pandemic and its associated complications in patients with diabetes and other co-morbidities, despite not having specific ammunition toward this virus, the clinicians are hopeful that the cumulative effort of all these studies being conducted regarding SARS-CoV-2 will trigger further research and will hopefully yield a solution soon.

Limitation(s)

As one of the few studies on COVID-19 associated with diabetes, the compact size of the present study population renders us short of delineate effective guidelines regarding the same. Also, the multi-system affliction of the infection makes it difficult to arrive at a more holistic treatment protocol for all COVID-19-infected patients.

CONCLUSION(S)

The COVID-19 pandemic proved to be devastating for the medical fraternity as well as for many nations throughout the world. Patients, especially those living with known co-morbidities like diabetes, were considered to be at a higher risk of complications and fatality. A flurry of incentivised research was hence undertaken to find out the effects of the virus not only on systemic-specific ailments but also on generalised multi-systemic disorders. From this work, the present clinicians could surmise that there was a steady escalation of mean oxygen requirements in all three groups of oxygen therapy over the course of two weeks, coinciding with the ensuing 'cytokine storm' associated with SARS-CoV-2 infection. This trend of escalation of oxygen requirement also coincided with the raised glycaemic charting trends of the patients over the same course of two weeks, de-lineating that individuals with diabetes mellitus, in view of their compromised immunity and innate pro-inflammatory state, are more prone to develop a severe form of the disease with even more serious complications, which may even lead to mortality. Regarding compliance, NRBM and HFNO provided the best results in comparison to NIV. The rates of complications were also noted to be higher with the use of NIV in this instance.

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