Comparison of the different oxygen delivery and ventilatory support methods for treating patients with COVID-19 induced type 1 hypoxemic respiratory failure

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ABSTRACT

Having claimed the lives of over five million people in the span of two years, SARS-COV-2 caused a global health crisis and a debate between clinicians on the best respiratory interventions to use in fighting this disease. This paper aims to evaluate the different methods of respiratory support at a clinician's disposal when treating COVID-19 induced type 1 hypoxemic respiratory failure. Data was acquired by running a literature search on MEDLINE and Web of Science using terms such as "COVID-19", "Mortality", "CPAP", "Outcomes". From 355 papers found, 11 are included in this paper. Studies have shown both CPAP and HFNO are effective when treating mild hypoxemia in COVID-19 patients, however if they fail, then chances of patient survival are slim, even if a patient's treatment is escalated. The literature has shown that mechanical ventilation has a slightly higher survival rate than both CPAP and HFNO when used as a primary treatment and patients who are escalated to mechanical ventilation have a slim chance of survival. Considering the findings, it is crucial that clinicians consider factors such as a patient's initial PaO_2/FiO_2 as well as age when deciding on whether a patient should be ventilated or treated with CPAP or HFNO.

INTRODUCTION

SARS-COV-2 is the virus that causes Coronavirus Disease 2019 (COVID-19), a disease of zoonotic origin, first identified in the Chinese city of Wuhan, where several clusters of a severe pneumonia began to emerge in early December 2019.[1-4] Symptoms include: a dry, non-productive cough; anosmia; a fever and in some cases severe viral pneumonia.[1, 2, 4] The virus spread globally, causing economic collapse and the world as we knew it to change for most of 2020 and 2021 due to the global lockdowns.[2, 5] However, the most daunting issue the virus presented was to healthcare. Resources were directed at treating severely ill COVID-19 patients, to prevent unnecessary deaths, as well as ensuring ICUs did not become overwhelmed, which could have caused healthcare systems to collapse. Since the beginning of the pandemic, COVID-19 has infected 262,995,279 people and sadly claimed the lives of 5,219,398 people (as of 1st December 2021), however, these stark figures are expected to be much higher as many cases go undetected and there is underreporting of mortality.[6]

The virus spreads through aerosolised droplets which bind to receptors on epithelial cells in the respiratory tract if inhaled, causing a person to become infected.[2, 3, 5] If an infected person does not generate a strong immune response early on, the virus may infect type 2 pneumocytes in the lungs.[2] Viral replication leads to excessive inflammation in the lungs, caused by a dysregulated immune response, which then leads to alveolar damage, and in severe cases of COVID-19, Type 1 respiratory failure because of ARDS (acute respiratory distress syndrome).[2, 3, 5] Type 1 respiratory failure is where hypoxemia occurs as the lungs are unable to perform adequate gas exchange to keep blood oxygenation levels at/above a safe threshold, and the PaO_2/FiO_2 ratio falls between 200-300 mmHg in mild cases; 100-200 mmHg in moderate cases and below 100 in severe cases.[2, 4, 7, 8]

In moderate to severe cases of COVID-19, there are several different oxygen delivery methods, however the ones that will be focused on are: conventional oxygen therapy (COT); non-invasive ventilation by continuous positive airway pressure (CPAP); high-flow nasal oxygen (HFNO) and invasive mechanical ventilation (IMV). In the administration of COT, the patient is fitted with a simple face mask, and oxygen is delivered.[2, 4] With HFNO, patients are fitted with a nasal cannula and oxygen is delivered to the patient at a rate of 30-40L/min.[2] In CPAP, patients are fitted with either a helmet or oro-nasal mask and oxygen is delivered at 8-10cm H_2O with a FiO_2 of around 60%.[2, 9, 10] In IMV, patients are sedated, intubated and placed on a mechanical ventilator which then pushes a mixture of air and oxygen into the lungs.[2, 11]

From the 2002 SARS-COV pandemic, it was recommended that oxygen delivery methods such as CPAP and HFNO should not be used as these are aerosol-generating procedures that can cause nosocomial transmission, and that early intubation is preferred for patients with impending respiratory failure.[12] However, as the early reports from China demonstrated, mortality seemed to be high even in patients who were subject to IMV, so patients were also treated with CPAP and HFNO as clinicians thought it may be better practice to avoid the risks associated with ventilation such as lung injury.[2, 4, 12, 13] This essay aims to critically appraise the use of different oxygen delivery methods for moderate to critically ill COVID-19 patients.

METHODS

Articles were predominantly selected from MEDLINE; however, Web of Science was also searched to detect any additional literature. Search terms included "COVID-19", "Outcomes", "Mortality". In total 355 articles were found, of these 122 were duplicates, leaving 233 and of these only 19 were deemed to be relevant and finally 11 were used in this study. ICNARC data was also included in the study.

RESULTS

In a retrospective case-series conducted in Liverpool, UK, that observed the outcomes of CPAP in 24 patients with Type 1 respiratory failure who were eligible for IMV, 14 (58%) patients successfully recovered and were discharged without requiring escalation of treatment to IMV and one died whilst on CPAP. However, of the nine patients who failed CPAP and required escalation to IMV, four died taking the mortality rate (MR) in this study to 20.8%. All the patients who failed CPAP, deteriorated within a matter of hours.[14]

In a retrospective, multi-centre cohort study, across the Northwest of England, the outcomes of COT vs. CPAP were compared in 479 patients who were deemed unsuitable for IMV, however out of the seven centres included in this study, only five offered CPAP as a form of treatment. Of the 246 patients who were placed on COT, 186 (75.6%) died and of the remaining 233 patients who were placed on CPAP, 181 (77.6%) died. 117/233 (50.2%) of CPAP patients decided to discontinue their treatment which could be indicative of the discomfort of CPAP. Given the data, there was no statistically significant benefit in terms of mortality comparing CPAP to COT, however there was no evidence of harm raising the possibility that CPAP remains beneficial to patients who tolerate it well.[15]

Treatment type	Number of patients	Number of patients who were intubated/died	% of patients
COT	468	158	44.4
CPAP	377	137	36.3
HFNO	414	184	44.4
Total:	**1272**	**479**	**41.7**

Table 1: Recovery RS trial data.[16]

Results from the Recovery RS trial, which followed 1272 patients in the height of the pandemic and functioned as an unblinded, multi centre randomized-control trial demonstrate that CPAP reduces the risk of IMV or mortality when compared to COT due to lower mortality rates and an odds ratio (OR) = 0.72. Comparing escalation to IMV or mortality in HFNO and COT the OR=0.97, showing no difference in outcome. However, when comparing CPAP and HFNO, no significant difference in mortality had been documented.[16]

A retrospective study in China examined the oxygen delivery methods and outcomes in 27 patients experiencing hypoxemic respiratory failure. One patient was intubated straight away, nine were non-invasively ventilated and 17 were treated with HFNO. Of the nine that went under NIV, one was intubated and from the 17 treated with HFNO, seven needed escalations to NIV, and two from the seven required intubation. In this small cohort, HFNO had a success rate of 58.8%, whilst NIV had a success rate of 88.9%.[17]

In a retrospective study of 41 patients in Sweden, HFNO was used in 20 patients who were treated with HFNO as a primary, step-up treatment. Of these 20 patients, ten died and ten survived, placing the MR at 50%.[18] A South African study, which was prospective, found that in 293 patients where HFNO was used as a primary treatment, the failure rate of HFNO was 53% as 156 patients either required to be intubated and mechanically ventilated (111) or died (45 (29%)). Of the 111 patients that were intubated and ventilated, 84 died. This takes the total death count from using HFNO as a primary treatment strategy to 129, meaning the MR lies at 44%, similar to the results found in Sweden.[19]

In a study of 102 patients treated with HFNO undertaken in Croatia, 42 patients died either on HFNO or after their treatment was escalated to IMV. The mortality rate of using HFNO as a primary treatment in this study was therefore 41.2%.[20]

A retrospective study of 61 patients across two hospitals in Moscow who underwent NIV in the form of CPAP as first line treatment found that this form of oxygen delivery was successful in 44 patients (72.1%) and failed in 17 patients (27.9%) so they were subsequently intubated and placed on IMV. Of the 17 patients placed on IMV, 15 of these died, bringing the MR of NIV via CPAP as a primary treatment to 24.6%.[21]

From a study that examined the treatment of 5,700 patients in the New York City region, 1,147 patients above the age of 18 were placed on IMV. Of the 589 18–65-year-old patients placed under IMV, 107 died (MR of 18.2%) 33 were discharged and 449 remained in hospital under IMV. Of the 558 patients above the age of 65 that were ventilated, 175 died (MR of 31.4%), only five were discharged and 378 remained in hospital under IMV at the time of the study. The overall MR for both groups was 24.6%.[22]

A retrospective study from Seattle which looked at 24 patients across three different sites, found that of the 18 patients who required IMV, nine had died (MR=50%), three remained ventilated, and six had been extubated.[23]

From the ICNARC data (which encompasses all critical care admissions in England, Wales, and Northern Ireland) it is evident that patients who received any form of advanced respiratory support (ARS) (MR=55.6%) had slightly higher mortality rates than those who went under IMV (MR+49.3%) within 24 hours of an ICU admission. Interestingly, a higher proportion of patients who underwent ARS (58.6%) had severe respiratory failure in the first 24 hours of admission when compared to IMV patients (53.3%).[24]

The data from this retrospective, multi-centre cohort study shows that IMV had the highest mortality rate at 70.8%, then NIV at 63%, followed by COT at 52.2% and then HFNO at 36.7%. However, this data only includes patients with a definitive outcome (discharged or died) and does not include patients still hospitalised who may be still receiving treatment.[25]

	Number of patients	Number of deaths	MR (%)	PaO_2/FiO_2 mmHg (percentage of patients) *		
				<100	100-200	200<
Invasively ventilated in first 24 hours	7,864	3,879	49.3	53.3	35.5	11.2
Received any form of advanced respiratory support	14,265	7,937	55.6	58.6	33.3	8.2
Total number for ICU	**25,839**	**9,883**	**38.2**	**51.8**	**38.4**	**9.8**

Table 2: ICNARC data from 1st September 2020 – 30th April 2021. Shows mortality in patients who were either IMV within 24 hours of admission or received any form of advanced respiratory support during their admission.[24]
Derived from lowest arterial PaO_2 within first 24 hours of critical care admission.

Respiratory support ever received	All patients	Discharged alive	Died	MR (%):
IMV	161	47	114	70.8
NIV	27	10	17	63
HFNO	90	57	33	36.7
COT	159	76	83	52.2

Table 3: data from a study in Michigan, US. Data shows the highest level of respiratory support a patient ever received.[25]

DISCUSSION

The Liverpool data evidences that CPAP has a role to play in treating patients with COVID-19 type 1 respiratory failure as over half were successfully treated with CPAP without requiring escalation to IMV.[14] However, for the ten patients where CPAP was unsuccessful, their MR was 50% suggesting that CPAP should only be used in patients who have milder type 1 respiratory failure. In this study the median PaO_2/FiO_2 was 122 mmHg (ranging from 97-175), perhaps the patients with lower PaO_2/FiO_2 would have benefited more from IMV as their primary treatment. The multi-centre UK cohort study demonstrated that between using COT and CPAP, there was no significant difference in mortality rates (75.6% vs. 77.6%) and patient outcomes, however they also had no better chance of recovery.[15] This study included centres where CPAP was not offered which effectively acted as a control group and eliminated bias from a specific site.

In contrast, the results of the recovery RS trial, set up as a three-arm RCT and had a large cohort (n=1272) showed that CPAP did reduce the risk of escalation to IMV, although there was no significant difference between the use of CPAP and HFNO.[16] This study is an RCT and was done prospectively so the results which show CPAP reduces the chances a patient will be escalated to IMV should be considered when making clinical decisions in a moderately ill COVID-19 patient, but as it is unblinded it is possible that an element of bias may be present in this study, as well as the way in which treatments were assigned to patients that may have introduced selection bias.

From the Chinese study which compared NIV and HFNO outcomes, it is evident that NIV has a higher success rate than HFNO when used as a primary treatment.[17] However, all of the patients who failed HFNO treatment had a baseline PaO_2/FiO_2 less than or equal to 200 mmHg, indicating moderate-severe hypoxaemia, so the patients may have responded more positively if they were given NIV as their primary treatment.

Considering the Swedish study, it is evident that HFNO can be used as an effective means to treat patients with COVID-19 induced respiratory failure, without the need to ventilate them.[18] The study shows that those who didn't survive treatment were significantly older than survivors (median age of 78 vs. median age of 64).

Data from the studies in South Africa and Croatia shows that patients who failed HFNO as their primary treatment have extremely high mortality rates when they are ventilated (75.7% and 76.2% respectively).[19, 20] The Croatian study also highlights that in non-survivors, their age is significantly older (on average eight years).[20] The South African study also demonstrates that those who failed HFNO had statistically significant lower baseline PaO_2/FiO_2 when compared to their successful counterparts (median of 63mmHg vs. 76mmHg).[19] These studies have demonstrated that when HFNO is successful, it has proven to be an effective treatment method for the moderate to severe hypoxemic COVID-19 patient, however when it fails the chances of being discharged are slim (7% in South African study), which raises the question as to whether patients with increasing age and lower initial PaO_2/FiO_2 should be intubated and placed under IMV as their primary treatment. However, due to the nature of these studies, it is impossible to state whether the patients who were intubated as a secondary treatment had a higher mortality rate because they weren't intubated earlier, or if they had a more severe form of the disease.[19, 20]

The study in Moscow echoes similar results but with CPAP, instead of HFNO, as they found it to be an effective treatment method when successful, but as the mortality rate was at 88% when CPAP failed, it raises questions as to who should be treated with CPAP, however, interestingly this study found no significant differences in the PaO_2/FiO_2 values between patients who failed or succeeded NIV.[21]

Drawing on the data for patients who were mechanically ventilated across nine sites in Seattle the mortality rate for IMV lies at 50%, however at least four of the patients who died in this study had DNACPRs in place, so this could explain the higher mortality rate.[23] The data from the New York study presented a lower mortality rate (18.2% in 18-65 year olds and 31.4% in over 65s), however the majority of these patients (827/1,147) remained in hospital, and their outcomes were not reported.[22] Both studies show that even in IMV, age plays a role in the success of treatment.[22, 23] Considering the ICNARC data, patients who received advanced respiratory support had on average lower PaO_2/FiO_2 values when compared with patients who were IMV within 24 hours of admission. This could be suggestive of worsening disease in those who aren't ventilated as soon as possible, or alternatively, it could be due to patients with critical disease, who are too frail for immediate ventilation.[24]

When looking at the data from Michigan, IMV patients had the highest mortality rate, however this data is the maximum level of respiratory support that was given to these patients so this number will also include patients who were placed on other treatments first which could have led to their death. Furthermore, this data does not include patients still hospitalised but only patients with a definitive outcome, i.e., discharged alive or died.[25]

Due to the nature of the pandemic, most of the studies included in this paper were either retrospective case-series or cohort, and whilst these don't provide the highest quality of evidence and may be more prone to include elements of bias in their findings, the data gathered is crucial in determining the best way to treat a hypoxemic COVID-19 patient. Many of the studies included patients who were still admitted into intensive care units and hospitals at the time they were published meaning that mortality rates will unfortunately be much worse than the findings of this paper. Furthermore, in most of the studies in this paper, treatment escalation and termination were generally decided by the clinical team, and not by a set of standardised guidelines, which may have influenced the outcomes.

CONCLUSION

Based on the current literature published around the outcomes of different methods of oxygen delivery and ventilatory support in a hypoxemic COVID-19 patient, it is evident that HFNO and CPAP are an effective means of treating these patients, however patients with increasing age and lower baseline PaO_2/FiO_2 should be strongly considered for immediate IMV to attempt to stabilise the patient and prevent unnecessary death by treating them with the most appropriate treatment. However, it is worth noting that the data included in this essay is from the pre-vaccination era, so with the immunity provided by vaccines, it is hoped that it will become easier to treat patients and mortality rates of COVID-19 in general will fall. Further studies should be conducted to follow-up on patients who were still admitted in hospitals at the time previous studies were conducted, to gain a more precise mortality rate of the different respiratory support methods, as well as studies which that investigate the effect of vaccination on respiratory support outcomes.

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