INTRODUCTION

Coronavirus disease 2019 (COVID19) is a new coronavirus infection that spread from Wuhan, China to the whole world since December 2019, forming a pandemic. It is also named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its potential to cause serious acute respiratory illness and similarity to SARS-CoV-1.

COVID19 primarily causes damage to the capillary endothelium and thus it leads to ventilation-perfusion mismatch. The patients with COVID19 require admission to intensive care units (ICUs) are usually male gender, over the age of 60 and have comorbidities such as hypertension, diabetes, chronic respiratory disease, heart disease, malignancy, immunodeficiency and obesity. Recent consensus statements have focused some topics including infection control, laboratory tests, hemodynamic and ventilator support for treatment management of COVID19 in the ICUs. Part of discussion in the treatment modalities of the COVID19 has focused on invasive and noninvasive ventilation strategies of severely ill patients. In critically ill COVID19 patients, hypoxia plays a
decisive role for predicting prognosis, so correction of hypoxia is the main goal of the treatment.

Among the patients with COVID19 admitted to the ICUs, although different rates of intubation are specified in published reports, the true incidence of intubation is not clear. When hypoxemic respiratory failure develops, many methods can be applied according to the patient’s clinic, from low flow oxygen support with nasal cannula to invasive mechanical ventilation. According to our current knowledge, there is insufficient evidence about the superiority of invasive and noninvasive mechanical ventilation in the patients with COVID19 pneumonia.

Gattinoni et al described COVID19 patients as two phenotypes, H and L. The treatment modalities recommended for Type L (low elastance) and Type H (high elastance) patients are different. In the patients with Type L, respiratory system compliance upper than 50 mL/cmH2O and the patients have low elastance, low ventilation perfusion ratio, low lung weight, low lung recruitment. The first option to reverse hypoxemia is to increase inspired oxygen fraction (FiO2) in this phenotype. Conversely, H phenotype is similar to ARDS, the patients have high elastance, high right to left shunt, high lung weight, high requirability in addition to low respiratory system compliance (<50 mL/cmH2O). In the H phenotype, treatment may need to be more invasive, for example intubation, recruitment maneuver, prone position, positive end expiratory pressure (PEEP), sedation with paralysis or inotropic support. During the illness, transition from phenotype L to phenotype H may be observed.

Many center avoid the use of non-invasive modalities in the patients with COVID19, but with non-invasive mechanical ventilation (NIV) strategies, the risks of ventilator-induced lung injury (VILI) can be prevented. If the patient has dyspnea, non-invasive strategies can be applied via continuous positive airway pressure (CPAP or BPAP) or high-flow nasal cannula (HFNC). More satisfactory results can be obtained with non-invasive strategies, especially in Type L patients. However, one of the most important concerns regarding the use of non-invasive ventilation techniques is the increased airborne transmission. In the recent guideline of Surviving Sepsis Campaign, supplemental oxygen therapy is recommended as the first choice for adult COVID19 patients with acute hypoxemic respiratory failure. If conventional oxygen therapy fails to correct hypoxia (persistent SpO2<90%), using HFNC instead of non-invasive positive pressure ventilation (NIPPV) is suggested. In this guideline, NIPPV is only suggested if HFNC is absent and the patient does not require urgent endotracheal intubation.
If possible, inspiratory esophageal pressure measurement with esophageal manometry is recommended before non-invasive administrations. Increase in esophageal pressure between 5 and 10 cmH2O is generally well tolerated. However, the risk of lung injury increases as esophageal pressure rises above 15 cmH2O, in this situation endotracheal intubation should be considered. In the absence of the esophageal manometry, central venous pressure swings or clinical observation of excessive inspiratory effort should be used. Observation and palpation of increased contractions accessory respiratory muscles (such as sternocleidomastoid muscle) may be a more convenient, simple and easier method for clinicians.

The failure indicators of non-invasive strategies include increased tachypnea and tachycardia, impaired oxygenation despite a high flow rate or FiO2, development of dyssynchronous or abdominal breathing, alteration in mental status, hemodynamic instability, increase in PaCO2.

**HIGH FLOW NASAL CANNULA OXYGEN THERAPY (HFNC)**

High flow nasal cannula oxygen therapy (HFNC) refers to the delivery of high flow oxygen through nasal cannula, which is heated (37° C) and humidified (100% relative humidity) at maximum flows ranging from 40 to 80 liters per minute with 21% to 100% fraction. Flow rate and FiO2 can be titrated according to the patients’ requirements, comfort and clinical condition.

Although HFNC has not been used as long as other NIV methods, it has become more preferred in recent years. HFNC treatment is simple, safe and easily tolerated in suitable patients. It is more comfortable than standart oxygen therapy with non-breathing mask and NIPPV. The nasal cannula has a soft and loose structure, thus it does not prevent the patients from talking and eating during HFNC therapy. A dry and cold gas at such high flow rates causes rapid drying of the nasal mucosa and an uncomfortable burning sensation. Heating and humidification contributes to the elimination of these side effects. Another benefits of heat and humidification are the hydration of secretions and protection of the mucosilier activity.

The working principle of HFNC is to aid oxygenation by washing the nasopharynx during exhalation. The washing the nasopharynx also clears anatomical dead space, increases ventilation efficiency, decreases airway inflammation and reduces the work of breathing. External PEEP of approximately 4-6 cmH2O is provided during HFNC. Other advantages of HFNC include avoiding unnecessary intubation and protect much-needed ICU ventilators.
for the patients really needs it in resource-limited settings. However, NIPPV
provides better oxygenation than HFNC due to its ability to provide higher
positive pressure. There are numerous studies in the literature comparing
standard oxygen therapy, NIV and HFNC, and 90-day mortality were signifi-
cantly less in the ICUs patients undergoing HFNC therapy. However, we do
not have sufficient evidence to show the effectiveness of HFNC compared to
standard oxygen therapy and CPAP in the patients with COVID19.

Due to its many advantages, HFNC should be considered the first-line
strategy in the patients with mild to moderate hypoxemic COVID19 pneu-
monia. However, it should be kept in mind that HFNC is an aerosol-generat-
ing procedure and the risk of COVID19 transmission is increased. Therefore
the use of negative pressure rooms, high energy particulate collector (HEPA)
filters and personal protective equipment are extremely important. In addi-
tion, the use of surgical masks over the nasal cannula during HFNC therapy
may greatly reduce aerosol distribution.

When using HFNC, especially unstable or severely hypoxemic COVID19
patients should be closely monitored due to possible respiratory arrest.
Otherwise, the deepening of hypoxia and the urgent intubation may result in
catastrophic consequences. In recent years, ROX index \[(SaO2/FIO2)/respira-
tory rate\] is suggested for estimate the failure of HFNC and thus low or high
risk for intubation. The ROX score> 4.88 at 12 h predicts HFNC success but
\( \leq 3.85 \) indicates HFNC failure. A reasonable target peripheral oxygen satura-
tion (SpO2) range is between 92% and 96% for COVID19 patients receiving
oxygen therapy. It is not recommended to maintain SpO2 higher than 96%.

**NON-INVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)**

Non-invasive positive pressure ventilation (NIPPV) has been used successfully
in the treatment of chronic obstructive pulmonary disease (COPD) exacerba-
tion, hypercapnic respiratory failure and acute cardiogenic pulmonary edema.
The use of non-invasive positive pressure ventilation may also beneficial in the
early post-operative period. It is less invasive than endotracheal intubation
and does not include risks associated with intubation. Randomized controlled
trials and meta-analyses showed that non-invasive positive pressure ventila-
tion decreased intubation rate and mortality in these patient groups. Non-
invasive positive pressure ventilation with helmet, oronasal or full face mask
is suitable for the patients with mild to moderate respiratory failure. Generally,
the initial FiO2 is set to 100% and is titrated to SpO2 between 92 to 96. However, it has low success rate in the patients with acute hypoxemic respiratory failure without cardiogenic pulmonary edema.

Although there are various studies on the successful use of NPPV in previous pandemics (Middle East Respiratory Syndrome; MERS, H1N1, SARS, etc), data on use of NIPPV in the COVID19 pandemic is still not clear.

Non-invasive positive pressure ventilation types

Non-invasive positive pressure ventilation can be applied in two ways; continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BIPAP). While CPAP is preferred in acute hypoxemic respiratory failure (AHRF), BIPAP is generally useful in hypercapnic respiratory failure. Since the patients with COVID19 pneumonia have severe hypoxemia, CPAP may be more beneficial than BIPAP. However, BIPAP may be considered in obese patients (or other obstructive airway disease) with COVID19 pneumonia because of hypercapnia.

Using non-invasive positive pressure ventilation in COVID19 patients

Although some association do not recommend and there is insufficient data on this issue, NIPPV is still widely used in many centers in COVID19 patients, especially with L phenotype. In a small number of observational studies, the use of NIPPV have been shown to reduce the need for intubation in COVID19 patients. Non-invasive positive pressure ventilation can be also used after unsuccessful HFNC therapy or in addition to HFNC due to providing more positive inspiratory pressure.

Like many health organizations, World Health Organization (WHO) guideline also recommended the use of NIPPV in the selected patients with COVID19. However, American Thoracic Society does not include NIPPV in the treatment of COVID19 patients and NIPPV has not any role in their COVID19 guideline. They recommend prone ventilation as first opinion for progressive COVID pneumonia, if it fails they suggest that extracorporeal membrane oxygenation (ECMO). Similarly, Infection Diseases Society has not comments any breathing strategies including NIPPV in their COVID19 guidelines. In Australian and New Zealand Intensive Care Society Guideline routine use of NIPPV is not recommended.
The effects of non-invasive positive pressure ventilation on lung mechanics

NIPPV can be administered with most intensive care ventilators. It is often used with spontaneous modes to increase patients’ synchronization and comfort. Therefore, deep sedation is not preferred during NIPPV. The use of NIPPV is limited to mild to moderate hypoxaemic patients only, because it is pressure-supported ventilation rather than volume-targeted. The purpose of using NIPPV is to contribute to the improvement of oxygenation by providing external pressure support. NIPPV increases tidal volume, improves alveolar ventilation, lowers PaCO2, increases end-expiratory volume, opens atelectatic and collapsed lung areas and alveoli, provides higher mean airway pressures, reduces work of breathing and thus improves PaO2 levels and oxygenation. However, it provides high tidal volumes and thus may increase the risk of ventilator-induced lung injury. In addition, it does not provide mucociliary clearance as much as HFNC. Moreover, NIPPV is not suitable for the patients with hemodynamic instability, multiorgan disfunction and abnormal mental status. From this point of view, it can be said that NIPPV is less comfortable than HFNC. Some meta analysis and randomized controlled trials are demonstrated that mortality rate and ICU length of stay are higher with NIPPV than conventional oxygen therapy and HFNC. However, the results of the same studies comparing the intubation rates of NIPPV and HFNC are contradictory. Frat et al showed that 50% of patients with hypoxic respiratory failure who received NIPPV required intubation. In the patients with MERS, NIPPV therapy had a failure rate as high as 92.4%. The use of NIPPV for other pandemic respiratory infection is also controversial, for example most guidelines do not recommended using NIPPV as first-line therapy in the patients with H1N1. Therefore, data on the effect of NIPPV strategies on intubation rate, mortality and morbidity in the patients with COVID19 is still insufficient.

The combination of HFNC and NIPPV in post-extubation patients may reduce the re-intubation rate comparing HFNC alone. Especially if weakness is significant, alternating NIPPV and HFNC may be a good option, so that while NIPPV provides more ventilation assistance, HFNC also provides better tolerance and humidification.

Risks of non-invasive positive pressure ventilation and preventions

Although non-invasive positive pressure ventilation treatment may contribute clinical improvement with its many positive effects especially in selected
patients, it also causes some negative situations. One of the main determinants of treatment success is patient-ventilator compliance. For example, the patients with claustrophobia may poorly tolerated NIPPV administration. If the mask does not fit the patients’ face tightly, both the effectiveness of the treatment decreases and the viral spread increases. It is also important that understanding the technical features of the non-invasive ventilator and masks by the user to increase the success of NIPPV. Care should be taken due to the risk of aspiration, aerosol transmission and self-induced lung injury.

One of the underlying concerns the controversy about non-invasive treatment is that NIPPV may worsen lung injury due to increased transpulmonary pressure and high tidal volumes. As a result, the risk of pulmonary edema is further increased, especially in lung already damaged by COVID19. The lung damage leads to increased work of breathing and a vicious circle. Therefore, it should be kept in mind that lung damage may worsen with the effect of excessive negative pressure during NIPPV administration.

Aerosol generated by the use of NIPPV increases the risk of infection for healthcare professionals compared with HFNC, standard oxygen and even invasive mechanical ventilation (excluding intubation period). The most important barrier to prevent transmission of COVID19 during NIPPV is the wearing of personal protective equipment (PPE). Personal protective equipment includes respirator masks (N95 respirators, FFP2 or functionally equivalent), eye protection (goggles or full face shield), gown and gloves. The use of negative pressure rooms, HEPA filters and full PPE for healthcare providers are recommended. Therefore, negative pressure rooms are one of the most effective protective methods especially in pandemic control. It is recommended for use when performing aerosol-generating procedures such as tracheal intubation, bronchoscopies, NIPPV or HFNC to prevent cross-contamination and reduce the risk of infection for health worker and other patients. The main purpose of using negative air pressure is to keep the pathogen in the room and prevent its spread from room to room. If there is no negative pressure rooms, according to WHO guidance on COVID19, the rooms should be naturally ventilated at least 160 L/second/patient. HEPA filters should be used and change every 24 hours. The risk of viral spread via aerosol with NIPPV can be significantly decreased with the using HEPA filter on the expiratory circuit and prevention of interface leak. Another option is to use portable HEPA filter device in the patients’ room, if possible. In addition, the presence of unnecessary medical personnel in the room should be avoided. To reduce aerosol formation, the mask should place before turning NIV on and remove after turning NIPPV off.
Cooperation between experienced healthcare professionals (intensivists, infectious diseases and respiratory therapists) and availability of adequate equipment increase the success of treatment. The use of old ventilators or anesthesia machine and the use of a single device for more than one patient are among the problems during NPPV therapy. The most common reason for these problems is equipment limitations caused by the pandemic.

Non-invasive positive pressure ventilation with Helmet

Helmet masks are generally preferred in the patients with pressure ulcers on the face area or leakage with the other masks. Non-invasive ventilation with Helmet masks have several advantages including better tolerability and less leakage.

The least aerosol-generating mask (helmet, full face mask, oronasal mask, nasal mask, respectively) for NIPPV during pandemics should be considered and so, using the helmet mask is suggested due to safety of health-care personnel. Therefore, NIPPV with a helmet mask would be a correct approach in the patients with COVID19 pneumonia.

Helmet mask allows positive pressure ventilation without pressure on the face and thus without pain and device-related pressure necrosis. Another advantage of the Helmet mask is to increase patients comfort, the patients can read and talk during NIPPV with Helmet. However, the use of helmet masks is limited because they are more expensive than the other masks and they are not available in every center. Moreover, claustrophobic patients may have difficulty in adaptation to the Helmet mask.

Sedation for non-invasive positive pressure ventilation therapy

After evaluating all factors may cause NIPPV intolerance, sedation and analgesia may be applied to increase the success rate. Conscious sedation by titrating analgesic and sedative agents improves patient tolerance without significant effect on respiratory pattern, respiratory drive and hemodynamics. Short-acting agents such as dexmedetomidine, propofol or midazolam can be used successfully in case of patient-ventilator asynchronie.

Considerations during non-invasive positive pressure ventilation therapy

Insistence on NIPPV in COVID19 pandemic may result in increased the need for intubation, morbidity and mortality rates. If NIPPV fails, ‘delayed intub-
tion’ may be associated with an increase in complications due to urgent procedure (unstable intubation, increase the risk of aerosol transmission to the healthcare workers, etc). Therefore, selection of the appropriate patient is very important. Bellani et al demonstrated that using of NIPPV was associated with higher mortality in the patients with a PaO2/FiO2 ratio (Harovitz index) of less than 150 mmHg.

Patients receiving NIPPV should be monitored closely, especially the first 1-2 hours are important. Increased respiratory rate and work of breathing, the use of accessory respiratory muscles should suggest the possibility of intubation. Therefore, specialized healthcare professionals are more needed than standard oxygen therapy and HFNC.

CONCLUSION

In selected patients with COVID19, the use of non-invasive ventilation modalities may be considered after the balance between benefit and harm is carefully calculated. Especially when resources are limited for practicing invasive mechanical ventilation, non-invasive ventilation strategies are crucial. However, high failure rate, the possibility of delayed intubation and the increased risk of aerosolization due to poor mask fit should be kept in mind. And routine use of NIPPV should be avoided in the patients with COVID19. The patients should be closely monitoring during non-invasive ventilation therapy for worsening of respiratory condition and clinical deterioration. Intubation should be considered if inability to maintain PaO2/FiO2 rate > 150 mmHg, no reduction in respiratory rate (≥ 30 breath/minute), FiO2 > 80% after 1 hour of CPAP therapy.

REFERENCES


