ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 26(2); April 2022 DOI: 10.35975/apic.v26i2.1809

CORRESPONDENCE CORONA EXPERIENCE

Requirement and response pattern for sedatives in COVID-19 patients requiring non-invasive ventilation: A pilot observation

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Key words: Sedatives; COVID-19; Ventilation, non–invasive
Citation: Nayak P, Karim HMR. Requirement and response pattern for sedatives in COVID-19 patients requiring non–invasive ventilation: A pilot observation. Anaesth. pain intensive care 2022;26(2):260–262;
DOI: 10.35975/apic.v26i2.1809

Received: , Reviewed: , Accepted:

Patients in a critical care unit (CCU) are exposed to multiple external stimuli and an unfamiliar environment, in addition to the rigors of their primary disease; all of these are the stress factors for the patient. Titrated sedation has a pivotal role in easing the stress. Sedation also helps patients better tolerate procedural pain and discomfort.[1]

Continuous monitoring sedation level and its various physiological effects is equally important for a better outcome. For example, inadequate sedation will result in unpleasant feelings or create hemodynamic instability due to increased sympathetic drive. Similarly, over-sedation will lead to hypotension, decrease cognition and increase the need for ventilatory support or prolong the length of stay in CCU. Various international sedation guidelines recommend that mechanically ventilated patients are kept awake or easily aroused, with adequate pain control.[2]

Many pharmacological and non-pharmacological methods of sedation are currently available. Studies showed the relevance of titrated sedation in patients with the ongoing COVID-19 pandemic. Helms et al. studied 58 ICU patients with COVID-19 infection, of which 40 (69%) developed delirium in the absence of muscle relaxation and sedation.[3] The study by Pun BT et al. showed that patients with COVID-19, kept in deep sedation for prolonged periods, had significantly higher delirium.[4] Unlike other encephalopathies, COVID-19 encephalopathy manifests itself as a hyperactive delirium state. Therefore, it becomes prudent to study the pattern of the sedation required in COVID-19 patients, especially those on noninvasive ventilation (NIV).

In this prospectively collected pilot data set, we aimed to find the response pattern of the patients receiving different pharmacological agents for sedation and to define an optimal approach.

Out of 58 patients admitted during the observation period of 15 days, 16 patients were included in the analysis and were observed for 40 sedation days. Out of these 2 (12.5%) were females. The mean (± SD) age was 58.37 ± 6.96 y. Thirteen of the 16 patients had comorbidities; diabetes mellitus and hypertension were common. The median days of illness on the commencement of observations were 6, and median NIV days for observation were 2 (Table 1). A majority (68.75%) of the patients required pharmacological sedation. Only midazolam (Mezolam® from Neon Laboratories Ltd. Mumbai, India) and dexmedetomidine (Dextomid® from Neon Laboratories Ltd. Mumbai, India) were used in the observed cohort in our set-up. The midazolam infusion was started at 0.05 mg/kg/h and titrated up to 0.1mg/kg/h. Dexmedetomidine 1 µg/kg bolus over 20 min was followed by infusion at 0.2 µg/kg/h, titrated up to 0.7 µg/kg/h. The second drug was added when the highest infusion rate was achieved for the first one. However, the initial drug to be started was under the consultant's discretion. Although the target sedation achieved by dexmedetomidine was higher (80%), the difference from midazolam (50%) was not significant ($p = 0.52$). The sample is, however, small. None of the patients experienced over-sedation or hemodynamic instability attributable to sedatives. All patients on recruitment were tachypneic with a median respiratory rate of 34 breaths/min.

On commencement of NIV, the mean (± SD) PaO_2 and $PaCO_2$ were 96.92 ± 18.58 and 42.0 ± 7.36 mmHg, respectively. Only 4 (25%) patients were weaned off from mechanical ventilators.

Table 1: Sedation and NIV-related data in the cohort. [N = 16].

Parameters	n (%)
Pharmacological sedation required	**11 (68.75)**
Single drug	9 (81.8)
Two drugs	2 (18.2)
Midazolam infusion	4 (36.36)
Dexmedetomidine infusion	5 (45.45)
Midazolam + Dexmedetomidine	2 (18.2)
Target RASS achieved	**7 (63.64)**
With Single drug	6 (66.67)
With 2 drugs	1 (50.0)
NIV Intolerance noted	4 (25.0)
Day of intolerance 1st/2nd	2/2
Days of illness on starting day of observation	6.5 (IQR 4-8; Range 2-16)
Days of NIV therapy observed	2 (IQR 1-2; Range 1-7)
RASS score	0 (IQR 0-0; Range 0-2)

Sedation is frequently required in COVID-19 patients requiring artificial respiratory support to ensure patient comfort and ventilator synchrony. Although intolerance to NIV is indicated to start pharmacological sedation, in COVID-19 patients, it is the anxiety that plays a crucial role. Only 25% developed NIV intolerance in our cohort, but 68.75% of patients required sedation. Unusually high numbers of COVID-19 patients requiring sedation have been found in other studies too.[5] The use of an inhalational anesthetic agent has also been advocated.[5,6] However, limited evidence is directly derived from COVID-19 patients using different agents or their combinations.

In our pilot study cohort, the most commonly used drug was dexmedetomidine, followed by midazolam, followed by a combination of both. Current expert opinion and consensus recommendations advocate mild sedation when the patient is on NIV.[7] However, we observed that 4 (36.36%) out of 11 patients did not achieve adequate depth of sedation with 0.075-0.1 mg/kg/h midazolam or 0.7 µg/kg/h dexmedetomidine and even a combination of both. It indicates toward the higher levels of anxiety and more requirement of sedation in COVID-19 patients.

Surviving Sepsis Campaign suggests continuous deep sedation when there is persistent ventilator asynchrony in COVID-19 patients.[8] Patient-ventilator asynchrony can even happen in NIV; however, deep sedation in patients in NIV might lead to respiratory compromise. Nevertheless, all these recommendations are based on low-quality evidence and extrapolated from the information from acute respiratory distress syndrome patients of non-COVID-19 causes. Therefore, it is impossible to recommend a specific drug over another for sedation at this point. Analgosedation using either dexmedetomidine, ketamine, or fentanyl might be preferred as the initial step. There was no difference in the sedation target achieved between dexmedetomidine and midazolam in our observation. However, the literature consensus and experience indicate that a single drug is inadequate to achieve the target sedation. In our observation, 3 out of 9 (33.33%) patients who received a single drug did not achieve the target sedation of RASS score 0 to -1.

To conclude, our pilot observation indicates that sedation requirements are higher in COVID-19 patients, and a single drug is usually inadequate to achieve the target sedation level. Therefore, assessing the sedation level at frequent intervals and titrating and escalating to multimodal regimens based on the sedative agents' individual properties and side effect profiles and patient characteristics can be regarded as an excellent clinical strategy.

Financial support: The support for the infrastructure, human resources, and equipment was from the institute. No other financial support has been obtained for this study.

Conflicts of interest: None

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