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EDITORIAL

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Is sedation safe and beneficial in patients receiving NIV? No

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This editorial is not meant to be a firm statement against the use of sedation and analgesia for noninvasive ventilation (NIV), but aims to better understand when, why, and how these drugs should be avoided during an NIV attempt.

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Sedation is not used in the large majority of patients

Sedation and analgesia are commonly used in the ICU to improve patient comfort and tolerance, to minimize reactions to painful stimuli and the physiologic stress response, and to modulate patient respiratory effort, drive, or timing. Although intolerance is commonly perceived as an important reason for NIV failure that should respond to sedation and analgesia, recent studies suggest that they are not used very often for that indication. Muriel et al. [1] found that sedation and analgesia were used in "only" about 20 % of patients using NIV, confirming the results of an earlier web-survey performed in North America and Europe [2]. Therefore, the large majority of patients (approximately 80 %) treated with NIV for acute respiratory failure do not receive any form of sedation and yet tolerate NIV and usually succeed with it [1].

Do not sedate your patients unless non-pharmacologic approaches to achieving patient tolerance have been tried first

There are other measures that can be applied to improve tolerance of NIV before consideration of sedation or analgesia. Improvements in interface technology have enabled us to choose between numerous different mask types and sizes and employ the so-called rotation strategy, avoiding intolerance due to excessive use of a single mask type [3]. Furthermore, advances in software technology offer newer algorithms that enhance interactions (and synchrony) between the patient and the ventilator [4]. They also have led to improved ventilator monitoring capabilities and graphics that permit analysis of flow and pressure tracings on ventilator screens that may be of help in "fine tuning" the ventilator [5]. Successful application of these enhancements also depends on the expertise of the NIV team, which performs better as it gains more experience in the administration of NIV [6]. This expertise not only enables the team to efficiently make appropriate adjustments in equipment and ventilator settings but also imparts a feeling of confidence to the patient, both factors that are likely to contribute to success. Thus, numerous approaches may be employed to avert NIV failure before considering sedation and analgesia. Nonetheless, we acknowledge that some patients remain intolerant and uncooperative with poor patient–ventilator synchrony despite application of the aforementioned non-pharmacological strategies; under these circumstances, administration of analgesia and sedation in an attempt to reverse the situation may be worthwhile before resorting to intubation.

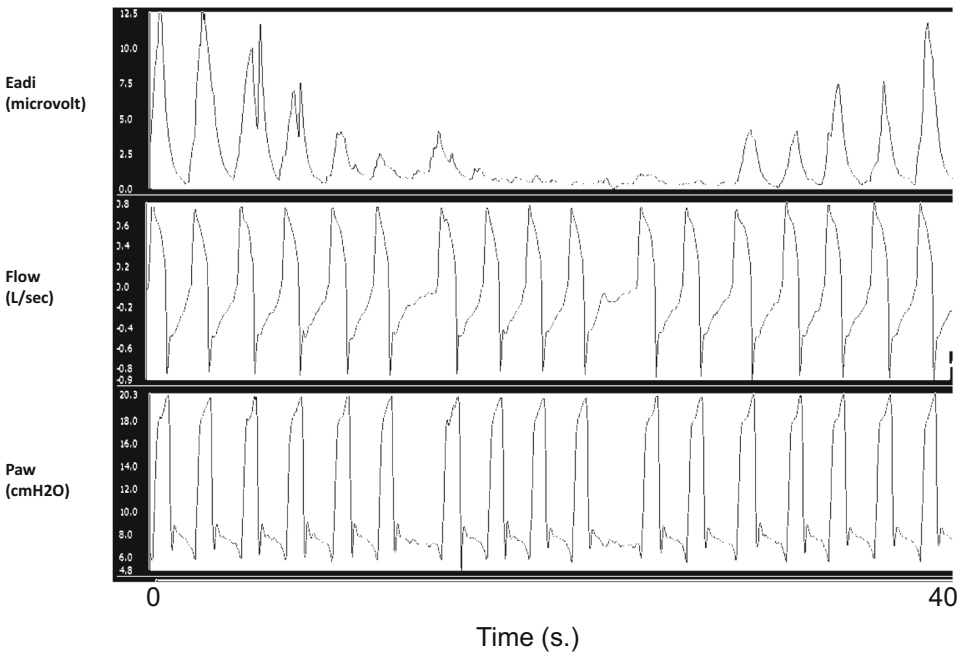

Fig. 1 Depicts the depressant effects on drive, causing asynchrony (as assessed by EAdi tracing) in a patient with postoperative pneumonia receiving NIV (PSV 12, PEEP 8 cmH_2O) through a face mask under propofol moderate sedation (RASS-3)

Do not use analgesia and sedation for NIV without appropriate monitoring by experienced staff

Intensivists and nurses working in ICUs are very experienced with the administration of sedative and analgesic drugs. Dosing of these drugs can be very challenging because of the different sensitivities and rates of metabolism between patients. For example, chronic users of benzodiazepines or opiates may have high tolerance to these drugs and require high doses, whereas naïve users, especially those with respiratory failure and chronic CO_2 retention, may exhibit profound respiratory depression, even with relatively small doses. Intravenous bolus dosing may be particularly hazardous in this regard. Considering that we are seeing fewer COPD patients with acute respiratory failure admitted to the ICU [7] and more use of NIV on regular medical/surgical wards [8], we must be particularly cautious about the use of sedation and analgesia in these less intensively monitored environments. Such applications may not only be dangerous for patients but may also have legal implications if there are adverse outcomes, at least in litigious countries.

Thus, sedation and analgesia should be administered by experienced staff using the minimum doses required to achieve tolerance, avoiding oversedation. This should be in a setting where, at the very least, electrocardiogram and oximetry tracings can be monitored continuously. Several sedation scales are available that may be helpful in ensuring that level of sedation is minimized; but, once again, application of these requires trained staff.

Dangerous side effects of sedation

The depressant effects of sedation and analgesia on respiratory function vary between individuals depending on the choice and dose of the drug, its sedative or analgesic effects, and sensitivity and metabolic capabilities of the recipient [9–12]. In the (few) studies examining the clinical use of sedatives in patients receiving NIV [13–17] or more correctly in patients failing NIV for interface intolerance, two classes of drugs have been used most often: GABAergic agonists (usually midazolam or propofol) or opiates (usually morphine or remifentanil). Both classes of drugs may blunt the output of the respiratory center. The electrical activity of the diaphragm (EAdi) provides a direct assessment of respiratory drive and timing close to respiratory centers, permitting a better understanding of patient–ventilator interaction.

By adopting EAdi monitoring, Vaschetto et al. [18] showed in intubated patients that propofol significantly interferes with patient–ventilator synchrony in pressure support ventilation (PSV) at doses producing deep sedation. Both during PSV and neurally adjusted ventilator assistance (NAVA), propofol reduced neural drive and effort, while not significantly affecting respiratory timing.

Figure 1 depicts the depressant effects on drive, causing asynchrony in a patient with postoperative pneumonia receiving NIV under propofol sedation.

Conversely, a continuous infusion of opiates has not been shown to reduce respiratory drive, but has shown detrimental effects on respiratory timing both when airway occlusion pressure at 0.1 s (P0.1), a surrogate of

EAdi, was assessed [11, 12] or when EAdi was directly measured [19].

A randomized study on the physiologic effects of a continuous infusion of remifentanil at increasing rates (no infusion, 0.03, 0.05, 0.08, 0.1 μg kg^{-1} min^{-1}) assessed respiratory pattern, drive, timing, and gas exchange in a group of critically ill patients receiving partial ventilatory support with both PSV and NAVA. Compared to baseline remifentanil infusion at a rate of 0.08 μg kg^{-1} min^{-1} significantly reduced $Ti/Ttot_{neu}$ (neural respiratory time), but did not affect the amplitude of EAdi (i.e., respiratory drive). Conversely, both during PSV and NAVA, remifentanil doses above 0.05 μg kg^{-1} min^{-1} significantly prolonged Te_{neu} and Te_{mec}, confirming that remifentanil does not affect respiratory drive, VT, or VE, but prolongs the Te_{neu} and consequently reduces the $Ti/Ttot_{neu}$ [19].

Although these data were obtained during invasive ventilation, the results suggest caution when applying the same sedation strategies and dosages during NIV, also in view of the absence of data on other side effects of sedation, specifically the hemodynamic instability that may be a serious problem in COPD patients who usually are older and have important co-morbidities such as cor pulmonale or other cardiovascular diseases.

An alternative approach could be the use of dexmedetomidine, which is an alpha-2 adrenoreceptor agonist with a different mechanism of action, providing sedation and anxiolysis via receptors in the locus coeruleus, analgesia via receptors at the spinal cord level, and attenuation of the stress response in the absence of significant respiratory depression [20]. This absence of respiratory side effects could be of interest in patients receiving noninvasive positive pressure ventilation (NPPV) but more data are needed as only few studies, with reduced sample sizes, have been dedicated to this aspect, with conflicting results [21, 22].

Compliance with ethical standards

Conflicts of interest SN has no conflict of interest to declare on this subject. NH received research funding and continuing medical education speaker honoraria from Hospira. GC received in the last five years honoraria for educational activities from Orion Pharma. The Catholic University of Rome received research grants from Orion Pharma.

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