What Is the Best Sedative Agent for NIV Intolerance?

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Introduction

Respiratory failure is a common cause of emergency department (ED) presentation in both pediatric and adult patients. Invasive ventilation is associated with multiple hemodynamic, infectious, and respiratory complications that require sedation and ICU admission. Noninvasive ventilation (NIV) provides respiratory support by applying positive pressure to conscious patients, often avoiding intubation.[1] However, one of the risk factors for NIV failure is intolerance. It was reported that about 5% of patients on NIV experienced intolerance which is associated with higher rate of intubation and mortality.[2]

There are multiple factors that contribute to NIV intolerance, including the type and severity of respiratory failure, the underlying disease, interface (mask) tolerance, hemodynamic instability, neurological status deterioration, and poor patient–ventilator synchrony.[3] A prospective, international, multicenter study showed that about 20% of patients received analgesic or sedative drugs during NIV.[4] Sedation and analgesia can mitigate the effects of psychological stress and pain thus potentially improving NIV tolerance. But data on sedative or analgesic agent use in NIV remains limited. Agent selection is really at the physician's judgement.

Neurocognitive disorders such as developmental delay and delirium can present additional challenges in managing NIV tolerance as well. In this article, we discuss a hypothetical case of a patient with concomitant neurodevelopment and respiratory distress requiring NIV, emphasizing pearls and pitfalls.

Case presentation

A 24-year-old man with a history of autism and morbid obesity presented to the ED in respiratory distress. His SpO2 was 85% on 6L NC so additional airway support was needed but he was unable to tolerate NRB or BiPAP due to agitation. He was given haloperidol 5mg IV and lorazepam 2mg IV with minimal improvement. During shift change he removed the mask, desaturated and suffered a hypoxic cardiac arrest.

What went wrong?
First, let us review the current sedative options and their evidence.

Opioids

Summary: Opioid infusion seems to work but respiratory rate and mental status need to be carefully monitored. Buyer beware.

Opioids remain the mainstay of pharmacologic management of dyspnea that is refractory to disease-modifying treatment because of their ability to suppress respiratory drive.[5] Opioids are commonly used in mechanically ventilated patients in the ICU and are one of the most commonly used sedative/analgesic drugs during NIV.[4] The combined effects of analgesia and sedation make it easier for physicians to use them if the cause of NIV intolerance is unclear. However, respiratory depression and hemodynamic effects are less desirable in NIV, a modality that is dependent on respiratory drive. Newer machines have backup ventilation, but it is not a consistently reliable feature. Several opioids were studied in the past to facilitate NIV tolerance, including morphine, fentanyl, remifentanil, and sufentanil.[4] Intravenous morphine infusion was found to be effective in improving NIV compliance in acute pulmonary edema caused by heart failure.[6] Two European studies found that remifentanil improved NIV tolerance safely in patients with respiratory failure.[7,8] One study showed sufentanil helped induce awake sedation without significant adverse effects but did not comment on whether it improved NIV tolerance.[9] There is currently no evidence suggesting fentanyl can improve NIV tolerance. None of the studies went into detail about adverse effects.

Ketamine

Summary: Limited evidence but theoretically a good choice. Patients should mentally travel to their happy places.

Ketamine, a phencyclidine derivative, acts as a dissociative agent primarily by blocking the N-methyl-D-aspartate (NMDA) receptor. It provides both analgesic and sedative effects and can provide amnesia depending on dosing. In contrast to opioids, ketamine preserves pharyngeal and laryngeal protective reflexes, lowers airway resistance, increases lung compliance, and is less likely to produce respiratory depression. Hemodynamically, ketamine results in increased heart rate and blood pressure due to its sympathomimetic effect which may provide additional advantage in managing respiratory failure patients with hypotension.[10] Emergence reaction, however, may trigger anxiety if the patient is not mentally prepared when ketamine is administered. There are currently two available case reports discussing ketamine use during NIV - one in asthma exacerbation and another in acute decompensated heart failure.[11,12] Currently there are no studies comparing ketamine with other sedatives.

Dexmedetomidine

Summary: Theoretically and in-practice a good choice if the heart rate and blood pressure can tolerate it.

Dexmedetomidine acts as an α2 adrenoreceptor agonist with anxiolytic, sedative, and some analgesic effects. Like ketamine, dexmedetomidine does not cause respiratory depression. The main adverse effects of dexmedetomidine are bradycardia and hypotension, so it should be used cautiously in patients with hemodynamic instability. Multiple studies have demonstrated that dexmedetomidine can be used safely in pediatric respiratory failure patients to facilitate NIV tolerance.[13-16] In adults, there are reports of successful use of dexmedetomidine to improve ventilator-patient

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synchronization among patients with acute respiratory failure.[17-19] Compared to midazolam, dexmedetomidine seems to be superior in terms of maintaining sedation with fewer dose adjustments.[20,21] In addition to common medical etiologies of respiratory failure, dexmedetomidine was also found to improve NIV tolerance in blunt chest trauma patients.[22] One study failed to show improvement of NIV tolerance with dexmedetomidine, although the sample size was small (n=33) and both arms could receive midazolam and fentanyl, which probably negated the effects of dexmedetomidine.[23] Overall, it seems that dexmedetomidine is safe and probably effective during NIV.

Benzodiazepines

Summary: Often used, barely studied. Get the endotracheal tube ready if adding to opioids.

Benzodiazepines are anxiolytics that bind to GABA receptors. Despite being the most used sedative/analgesic drugs during NIV (particularly midazolam),[4] benzodiazepines do not have an analgesic effect and increase the risk of delirium. There is very limited data on benzodiazepine use during NIV to facilitate tolerance. One case report showed successful use of lorazepam in severe asthma exacerbation requiring NIV.[24] It is unclear if the benefit of benzodiazepines outweighs the risks. Benzodiazepines such as midazolam might be a good choice if the cause of NIV intolerance is clearly identified as anxiety and the patient's respiratory status can be closely monitored.

Propofol

Summary: Milk of amnesia is well known for hypotension and apnea; it requires very careful observation.

Propofol activates central GABA receptors and is an intravenous anesthetic that is commonly used for sedation of agitated adult ICU patients. Propofol is well known to cause hypotension and apnea. However, there are a few studies showing potential safe use of propofol in adult patients to facilitate NIV at very low infusion doses.[25,26]

Antipsychotics

Summary: Theoretically helpful but no evidence.

Antipsychotics are usually dopamine antagonists that are commonly used to treat agitation in the ICU and ED. Despite their potential (and likely frequent off-label use for NIV), currently there is no data evaluating whether antipsychotics can improve NIV tolerance. Theoretically they would slow psychomotor activity without reducing respiratory drive. Of note, antipsychotics can cause extrapyramidal effects which could potentially worsen NIV tolerance.

Combination of sedatives and analgesics

Summary: Not a good idea.

Current available data suggest that single use of analgesic or sedative during NIV does not have an apparent effect on outcome. However, in a study comparing analgesic only, sedative only, and combined use during NIV, the combined had higher mortality.[4]

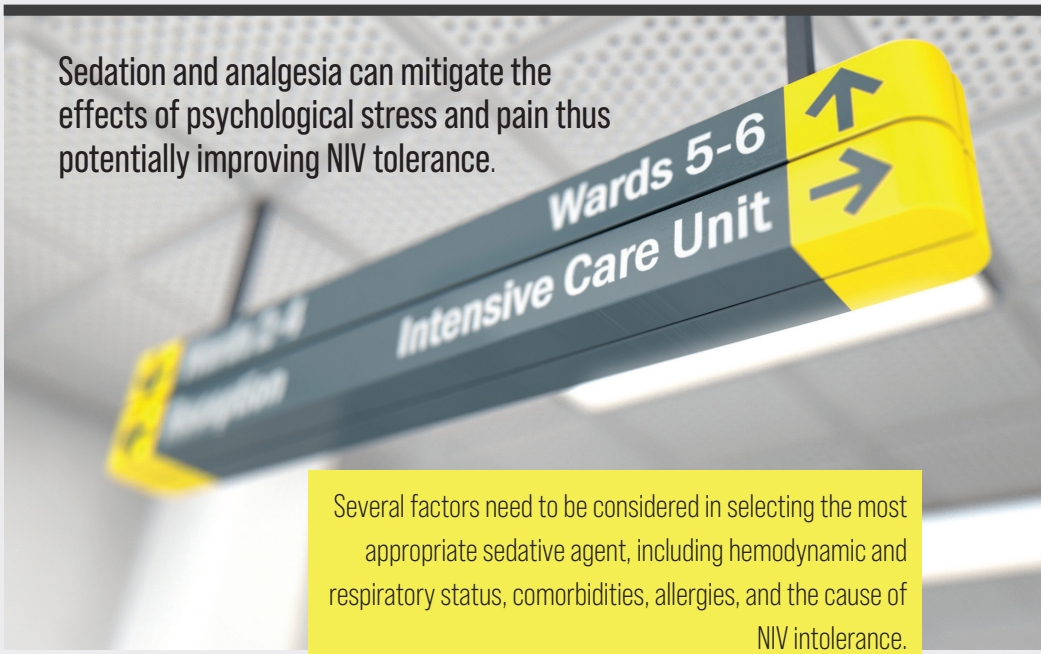
So, what is the best sedative agent?

The answer is there is no single sedative agent that is optimal for every patient.[27] Several factors need to be considered in selecting the most appropriate sedative agent, including hemodynamic and respiratory status, comorbidities, allergies, and the cause of NIV intolerance. The ideal agent should be able to improve NIV tolerance without further respiratory deterioration.

Case conclusion

Is there a better sedation option than the B-52?

Probably ketamine or dexmedetomidine, but no matter which agent, an infusion rather than bolus injection. The combined use of haloperidol and lorazepam might be associated with increased mortality and there are no data supporting antipsychotic use to facilitate NIV. Given that the patient had been hemodynamically stable but with severe hypoxemia, efforts could have been made to achieve adequate sedation without compromising respiratory status. ●



Sedation and analgesia can mitigate the effects of psychological stress and pain thus potentially improving NIV tolerance.

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