SYSTEMATIC REVIEW

Role of Sedation and Analgesia during Noninvasive Ventilation: Systematic Review of Recent Evidence and Recommendations

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Abstract

Aim: This systematic review aimed to investigate the drugs used and their potential effect on noninvasive ventilation (NIV).

Background: NIV is used increasingly in acute respiratory failure (ARF). Sedation and analgesia are potentially beneficial in NIV, but they can have a deleterious impact. Proper guidelines to specifically address this issue and the recommendations for or against it are scarce in the literature. In the most recent guidelines published in 2017 by the European Respiratory Society/American Thoracic Society (ERS/ATS) relating to NIV use in patients having ARF, the well-defined recommendation on the selective use of sedation and analgesia is missing. Nevertheless, some national guidelines suggested using sedation for agitation.

Methods: Electronic databases (PubMed/Medline, Google Scholar, and Cochrane library) from January 1999 to December 2019 were searched systematically for research articles related to sedation and analgosedation in NIV. A brief review of the existing literature related to sedation and analgesia was also done.

Review results: Sixteen articles (five randomized trials) were analyzed. Other trials, guidelines, and reviews published over the last two decades were also discussed. The present review analysis suggests dexmedetomidine as the emerging sedative agent of choice based on the most recent trials because of better efficacy with an improved and predictable cardiorespiratory profile.

Conclusion: Current evidence suggests that sedation has a potentially beneficial role in patients at risk of NIV failure due to interface intolerance, anxiety, and pain. However, more randomized controlled trials are needed to comment on this issue and formulate strong evidence-based recommendations.

Keywords: Analgesia, Analgosedation, Discomfort, Noninvasive ventilation, Respiratory failure, Sedation, Sedoanalgesia.

Abbreviations: ACPE, acute cardiogenic pulmonary edema; AECOPD, acute exacerbation of the chronic obstructive pulmonary disease; AHRF, acute hypercapnic respiratory failure; ALI/ARDS, acute lung injury/acute respiratory distress syndrome; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; EAdi, electrical activity of the diaphragm; ERS/ATS, European Respiratory Society/American Thoracic Society; ETI, endotracheal intubation; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; NAVA, neurally adjusted ventilatory assist; NIV, noninvasive ventilation; PSV, pressure support ventilation; PVD, patient-ventilator dyssynchrony; RCT, randomized controlled trial.

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Introduction

Over the last decades, noninvasive ventilation (NIV) has gained wide acceptance in different subsets of patients with acute respiratory failure (ARF). The addition of NIV to standard care for acute hypercapnic respiratory failure (AHRF) in patients with chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema (ACPE) has now become the gold standard of care with proven benefits.[1,2]

The official European Respiratory Society/American Thoracic Society (ERS/ATS) clinical practice guidelines recommended using NIV in patients with AECOPD to prevent endotracheal intubation (ETI) and invasive mechanical ventilation (IMV) in patients with mild to moderate acidosis and respiratory distress.[3] The guidelines found strong evidence for the NIV use for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH $\leq$ 7.35) due to COPD exacerbation. Bi-level NIV is known to improve related

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symptoms, reduce hospital stay and intubation rate, and reduce the mortality rate.[3,4]

These successful endpoints are only achieved by appropriate patient selection and tolerance of NIV. The occurrence of pain, pressure sores, agitation, stress, discomfort, or claustrophobia leads to low tolerance and thereby acceptance of NIV.[5] The acceptance of NIV could be related to the patient-device interface and accompanying air leak, the severity of disease condition, agitation, and also the mode as well as settings of NIV being used. These factors may influence the need for sedation. Alternatively, NIV rarely requires or might not require sedation at all. NIV treatment outcomes were found to be more favorable in awake COPD patients having a strong cough.[6,7] Ongoing delirium and agitation are also relative contraindications to the use of NIV.[8]

Even though sedation is not mandatory during NIV therapy, the addition of a small amount of analgosedation may help selected patients to better tolerate NIV, which can help to achieve the desired outcomes. The choice of use of sedative and/or analgesia during NIV therapy, however, remains controversial with absent guidance. The present review was aimed to search the current evidence and formulate recommendations in this aspect.

Methodology

Electronic databases (PubMed, Google Scholar, and Cochrane library) were searched systematically for sedation during NIV. The medical literature published from January 1, 1999, to December 31, 2019, was included to analyze and formulate the conclusion and recommendation. Index words "Noninvasive ventilation," "Sedation," and "Analgosedation" were used. The PubMed advanced search was used for index word combination of ((((("noninvasive ventilation") OR "continuous positive airway pressure") OR "bi-level positive airway pressure") AND "sedation") OR "analgosedation" as the primary search strategy. Only clinical studies, clinical trials, comparative studies, or controlled clinical trials reported in the English language were included. Abstracts from conferences and unpublished data were excluded.

Studies that included human participants of any age and gender and were conducted in the intensive or critical care units were eligible for inclusion. Studies reporting sedation with NIV in the operating room, procedural like bronchoscopy, emergency department, or sedation in patients receiving high-flow nasal cannula were also excluded. Sedation-related outcomes, like the degree and effectiveness of sedation provided by different pharmacological agents, feasibility, and tolerability of NIV, complications, and NIV success, were assessed.

Further, we have reviewed the literature, including the reviews and meta-analysis available on the topic from the last two decades related to the use of analgosedation in context to both the drugs used, their side effects, and impact on NIV. We have also analyzed recent guidelines by different critical care societies for their views and evidence and discussed the same while formulating our recommendations. In a scenario where literature was insufficient to draw evidence-based solid recommendations, an expert opinion was formulated.

Results

The search strategy flow chart for the literature is presented in Flowchart 1. Only five observational studies (Table 1), six retrospective studies (Table 2), and five randomized controlled trials (RCTs) were eligible as per our criteria. Two guidelines were also included for literature review, analysis of evidence, and formulating recommendations.

Most studies displayed variation in the design, drugs used, their doses, and the outcomes. Most RCTs were conducted over the last decade, and the most common drug compared was dexmedetomidine with either midazolam or placebo. Even the dexmedetomidine dose and regimen used were variable. Two studies used a loading dose of 0.1 µg/kg/hour, followed by infusion. The maintenance dose was mostly titrated up to 0.7 µg/kg/hour. However, one study titrated the dose up to 1.3 µg/kg/hour, and

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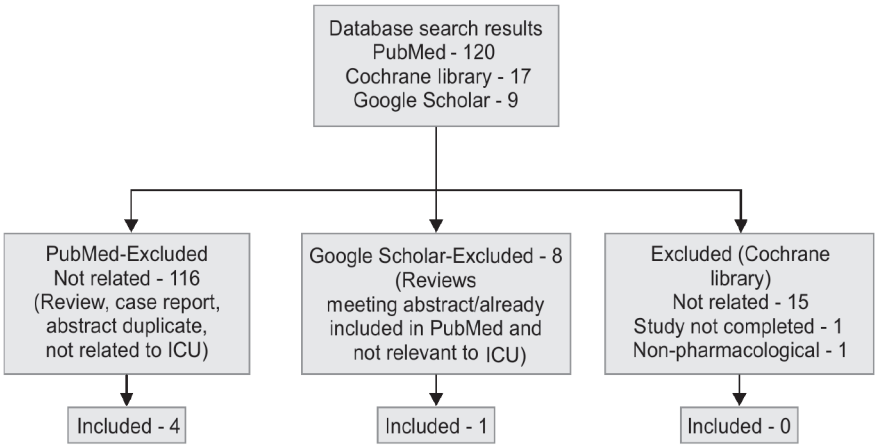
Flowchart 1: Diagram showing the search strategy for randomized trials for the present systematic review



this study reported bradycardia and pressor requirements in three out of 20 patients (Table 3). However, the sedation level was not excessive.

Shutes et al. retrospectively reviewed dexmedetomidine infusion for >24 hours and analyzed their infusion discontinuation patterns, relationship with patients' hemodynamics, and incidence of withdrawal.[9] The majority (71.5%) of patients did not require the addition of another sedative and were included in the analysis. They found that dexmedetomidine as a sedative had a predictive hemodynamic effect and caused bradycardias in 75% and hypotension in 30% during escalation. Only 19 (4.9%) patients developed withdrawal resulting from the cumulative dose from prolonged infusion, but symptoms were managed easily with short duration oral clonidine. In a similar study including pediatric patients, Venkatraman et al. evaluated dexmedetomidine infusion during NIV therapy within 48 hours of ICU admission.[10] They found that dexmedetomidine infusion provided effective sedation as the single agent; however, dose titration was frequently required to prevent cardiorespiratory adverse events. Piastra et al. also performed another retrospective analysis of 40 pediatric patients who received NIV to manage ARF.[11] They analyzed the effectiveness of dexmedetomidine infusion as a sedative and found that early initiation of dexmedetomidine infusion was safe and effective in reducing patient-ventilator dyssynchrony (PVD).

Ni et al.[12] evaluated the role of sedation and/or analgesia as rescue therapy during NIV in 80 adult patients with interface intolerance after extubation and found that sedation and/or analgesia can decrease NIV failure rate, hospital mortality rate, and length of stay (LOS) in ICU patients.

Dexmedetomidine has been recently reported to facilitate NIV in patients with blunt chest trauma.[13] Dexmedetomidine could facilitate the acceptance and tolerance of the first session of NIV and could lead to comfortable ventilation and a longer duration of NIV session compared to placebo in patients who were found to be challenging to manage because of the pain and agitation due to chest trauma. Despite improving NIV tolerance, dexmedetomidine did not alter pain scores or cumulative morphine consumption.[13]

The Use of Sedation during NIV

To date, there are no principles or algorithms to guide the use of sedation during NIV.[14] Observational studies and clinical trials have assessed the potential use of sedative or analgesic drugs to avoid patients' discomfort and prevent or treat NIV intolerance.[15] However, there is a lack of robust data to formulate any standard guideline, and the choice of the drug selected is mainly based on the physicians' clinical preference.

Low NIV acceptance is multifactorial, and any decision to resort to sedation must be taken as the last stage with a careful evaluation of the causes of actual or pending failure,[14] as showed in Figure 1. The acceptance of NIV varies according to the type of interface used and increases with the least constricting interfaces (i.e., helmet) and declines with more intrusive forms (i.e., oronasal mask). Further, the model and pattern of ventilation used can influence the patient's compliance. In most cases, positive pressure ventilation will lead to patient discomfort, especially with higher ventilation settings. This will necessitate sedation for tolerance, whereas spontaneous breathing seldom requires sedation unless it is too rapid and distressing. Even though numerous non-pharmacological strategies can be employed to avert/reduce NIV failure, some patients will still fail NIV due to PVD. In this situation, careful administration of sedation and/or analgesia should be tried in a rescue attempt to improve PVD. The approach may be worthy before considering escalation to intubation and initiating IMV. However, oversedation may lead to untoward adverse effects, and it is still unclear whether sedation and/or analgesia can benefit these patients and improve the outcomes resulting from NIV intolerance.

In a retrospective study on patients who received NIV after extubation and had an intolerance to NIV interface in seven intensive care units (ICUs),sedation and/or analgesia were used in 41 out of 80 patients (analgesia in 17, sedation in 11, and both in 13) at some time during NIV therapy. Those who received sedation and/or analgesia showed reduced NIV failure rate (15 vs 38%, $p = 0.015$), mortality (7 vs 33%, $p = 0.004$), and length of ICU stay after extubation.

Side Effects of Sedation

Sedatives and analgesics are routinely used to improve patient comfort and NIV tolerance. Titration of these drugs can be challenging because of variations in pharmacokinetics, pharmacodynamics, and local hospital guidelines, resulting in resistance and tolerance. Thus, sedation and/or analgesia should be administered under continuous monitoring by experienced staff using the minimum doses required to achieve NIV tolerance while avoiding adverse

Table 1: Observational studies included for review and analysis and their characteristics

Author	*Study intervention*	*Sedative dose*	*Sample size*	*Study population*	*Inclusion criteria*	*Sedation goal*	*Outcome measure*	*Results*	*Side effects of sedation*
Clouzeau et al. (2010)	Target controlled infusion (TCI) of propofol	Initially 0.4 µg/mL, increments of 0.2 µg/mL	10 pts	Pts with acute respiratory failure under NIV	NIV failure due to pt. refusal to continue NIV sessions because of discomfort, claustrophobia, or marked agitation	OAA/S level of 4 or 3	The primary outcome: the need for ETI and mechanical ventilation at any time Secondary outcome: development of complications	3 pts (30%) required ETI 2 pts died Gas analysis improved: • mean Pa/FiO_2 ratio increased • mean $PaCO_2$ decreased • mean pH increased	One episode of oversedation with significant respiratory depression
Constantin et al. (2007)	Remifentanil	0.025 µg/kg/min increasing the infusion rate by 0.025 µg/kg/min every minute to a maximum of 0.15 µg/kg/min	13 pts	Pts with acute respiratory failure under NIV	NIV failure due to pt. refusal to continue the NIV sessions (due to discomfort), and marked agitation	Ramsay scale 2–3	ETI need	4 pts (31%) required ETI, all during the first NIV session and all due to an inability to maintain a PaO_2/FiO_2 ratio above 85 mm Hg	No pts demonstrated gastric aspiration in the airways No other side effects recorded
Rocco et al. (2010)	Remifentanil	0.025 µg/kg/min increasing rate by 0.010 µg/kg/min every min to a max 0.12 µg/kg/min	36	Hypoxemic acute respiratory failure (HARF) pts, 13 chest trauma PaO_2/FiO_2 lower than 200	Pts refusing to continue NIV for intolerance to two different interfaces	Ramsay scale 2–3	ETI need	14 pts (39%)	
Akada et al. (2010)	Dexmedetomidine	3 µg/kg/hr over 5 min, followed by continuous infusion at a dosage range of 0.2–0.7 µg/kg/hr	10	Pts with acute respiratory failure who were given NIV	Pts receiving NIV who were subsequently uncooperative/ agitated	Ramsay scale 2–3		All pts were successfully weaned from NIV, All survived	No respiratory or hemodynamic side effects recorded
Rocker et al. (1999)	Morphine and midazolam		10 12 occ.	Pts with acute lung injury (ALI) or ARDS	Acute exacerbation of COPD and ALI	Sedation measurement was not a primary objective		66% success rate (avoidance of intubation during 72 hr of initiation of NIV)	Pts were provided sedation while receiving NIV. The effect of the drugs used was not compared

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ETI, endotracheal intubation; NIV, noninvasive ventilation

Table 2: Retrospective studies included for review and analysis and their characteristics

Author	*Sedation used*	*Sample size*	*Study population*	*Inclusion criteria for sedation*	*Sedation goal*	*Outcome measures and results*	*Side effects of sedation*
Venkatraman et al. (2017)	Dexmedetomidine infusion	202	Pediatric pts with ARF and initiation of NIV	NIV with dexmedetomidine	SBS score of 0 to −1	ETI 2.5% NIV weaning 96% Efficacy of sedation: target sedation level 80% of time 83%	Significant Bradycardia (13%) Hypotension (20%) Hypopnea (5%)
Piastra et al. (2018)	Dexmedetomidine infusion	40	Pediatric pts with ARF and managed with NIV for >8 hr	Uncooperative due to young age, RASS +1 or more Comfort-B 22 or more		Efficacy of sedation: Comfort-B score and RASS significantly decreased Gas exchanges while on NIV: Significant P/F ratio increase ETI 10% NIV discontinuation Due to intolerance 0% Mortality 0%	No pt. developed severe bradycardia or hypotension
Shutes et al. (2018)	Dexmedetomidine infusion	382	Pediatric pts managed with NIV			Hemodynamic effects: Bradycardia 28% Hypotension 2% Hypertension 33%	Escalation phase: Bradycardia and hypotension were 75 and 30%
Matsumoto et al. (2015)	Continuous sedatives: Dexmedetomidine 15%, Midazolam 9%, or Propofol 13% Morphine 19% Intermittent: Risperidone 43% Haloperidol 73% Other 9%	120/3506 (3.4%) Intermittent 72 pts Switched to cont 37 Continuous 11 pts	Adult pts receiving NIV	When pts could not continue NIV due to agitation RASS +1 or more	RASS −2 and 0	NIV failure due to agitation 4% of all ETI (non-DNI group): Intermittent 29% Continuous 27% Mortality: Non-DNI group 18% DNI group 68%	Oversedation 3 pts Hypotension 2 pts Delirium 1 pt Ileus 1 pt
Muriel et al. (2015)	Multiple drugs, most commonly midazolam and morphine	165/842 pts (19.6%) Analgesics or sedative drugs 88 pts Analgesia 44 pts sedatives 33 pts Both	Adult pts receiving NIV	Not specified	Not specified	NIV failure: Sedation group 47% All 31% Mortality: Sedation group 27% All 23%	Not specified
Ni et al. (2017)	Sedatives: Propofol and dexmedetomidine Analgesics: fentanyl and sufentanil	41/80 (51%) Analgesia 17 pts Sedation 11 pts Both 13 pts	Adult pts receiving NIV after extubation	Interface intolerance	Not specified	NIV failure: A/S vs none 15% vs 38% Mortality: A/S vs none 7% vs 33% NIV duration: A/S vs none 46.5 vs 70 hr $p = 0.041$ ICU LOS: 5 vs 8 days $p = 0.030$	Not specified

ARF, acute respiratory failure; DNI, do not intubate; ETI, endotracheal intubation; NIV, noninvasive ventilation

Table 3: Randomized controlled trials included for review and analysis and their characteristics

Author	*Study intervention*	*Sedative dose*	*Sample size*	*Study population*	*Inclusion criteria*	*Sedation goal*	*Outcome measure*	*Results*	*Side effects of sedation*
Senoglu et al. (2010)	Dexmedetomidine (D) vs Midazolam (M)	D: 1 µg/kg load. 0.5 µg/kg/hr maint. M: 0.05 mg/kg load. 0.1 mg/kg/hr maint.	40 pts D: 20 M: 20	Pts with ARF	Pts who were uncooperative: 1 on the RSS and ≥1 on the RSAS	RSS of 2 to 3, an RSAS score of 3 to 4, and a BIS level >85	Primary outcome: RSS, RSAS, and BIS scores Secondary outcome: heart rate (HR), blood pressure (BP) ABG values NIV failure	2 pts in M group did not achieve RSS ≥2 and RSAS ≤5; BIS higher in group D; D required fewer adjustments in dosing vs M HR and BP not significantly different NIV failure 0%	No severe respiratory or cardiovascular side effects in either group 1 pt Oversedated
Huang et al. (2012)	Dexmedetomidine (D) vs Midazolam (M)	D: 0.2–0.7 µg/kg/hr M: 0.05–0.1 mg/kg/hr	62 pts D: 33 M: 29	Pts with cardiogenic ARF under NIV	NIV failure due to pt. refusal to continue NIV because of discomfort, claustrophobia, or agitation	Ramsay scale 2–3	Primary outcome: ETI Secondary outcomes: ICU LOS ICU mortality NIV duration	20 pts (32%) required ETI M vs D 44.8%:21.2%, $p = 0.043$ Duration of NIV D vs M (57.5 ± 7.9 hr vs 93.4 ± 12.4 hr, $p = 0.01$ ICU LOS M vs D (4.9 ± 4.3 hr vs 8.5 ± 4.6 hr, $p = 0.042$ ICU mortality similar	No recorded serious adverse events D: M Bradycardia (18.2% vs 0, $p = 0.016$) – no interruption of study drug
Devlin et al. (2014)	Dexmedetomidine vs placebo	0.2 mg/kg/hr titrated by 0.1 every 30 min to 0.7 mg/kg/hr	33 pts D: 16 P: 17	Adults with ARF and within 8 hr of starting NIV	Adults with ARF and within 8 hr of starting NIV	SAS 3–4	Primary outcome: tolerability of NIV as Assessed by an NIV Tolerance Score Secondary outcome: Percentage of time spent at desired sedation goal	D did not improve NIV tolerance nor helped to maintain sedation at the desired goal SAS 3–4 100% both groups Duration NIV D vs M 37 hr vs 12 hr ETI D vs M 31 vs 29%	Severe bradycardia or hypotension did not develop in any pt. in either group.
Allam et al. (2016)	Dexmedetomidine (D) vs Midazolam (M)	D: 1 µg/kg load. 0.2–0.7 µg/kg/hr maint. M: 0.05 mg/kg load. 0.05–0.1 mg/kg/hr maint.	200 pts D: 100 M: 100	Adults with signs and symptoms of acute respiratory distress		RASS 2–3	ETI mortality Sedation efficiency NIV tolerance		Postsedation delirium D vs M 8 vs 21 Bradycardia D vs M 20 vs 9 Hypotension 2 in each group

(Contd...)

Table 3: *(Contd...)*

Author	*Study intervention*	*Sedative dose*	*Sample size*	*Study population*	*Inclusion criteria*	*Sedation goal*	*Outcome measure*	*Results*	*Side effects of sedation*
Deletombe et al. (2019)	Dexmedetomidine vs placebo	0.7 µg/kg/hr titrated by 0.2 µg/kg/hr every 60 min (up to a maximum dose of 1.3 µg/kg/hr)	20 pts Cross-over design	Significant blunt chest trauma with TTSS higher than 6 and if they required NIV		RASS 0–3	The primary outcome: the duration of NIV session to reflect comfort and NIV tolerance	D prolonged the duration of NIV vs placebo: 280 min (118–450) vs 120 min (68–287), intraindividual increased NIV duration by 96 min (12–180) ($n = 19$ pts; $p = 0.03$) D lower RASS score vs placebo: 0.8 (1.0;0.0) vs 0.0 (0.5;0.0), respectively ($n = 19$ pts; $p < 0.01$) No pt required ETI	Under D one episode of bradycardia and five episodes of arterial hypotension 3 pts required the concomitant infusion of norepinephrine No episode of excessive sedation under D

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; BIS, Bi-spectral Index; COPD, chronic obstructive pulmonary disease; ETI, endotracheal intubation; LOS, length of stay; NIV, noninvasive ventilation; RASS, Richmond's agitation scale

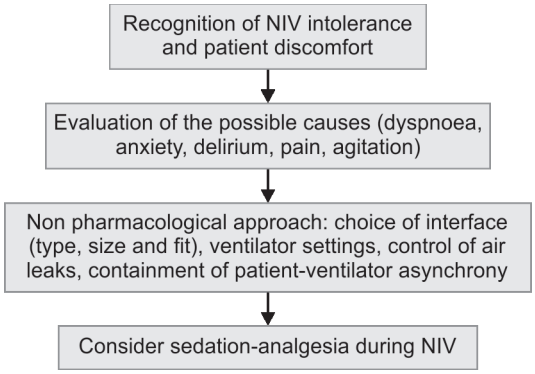


Fig. 1: Steps to follow for administering pharmacological sedoanalgesia for noninvasive ventilation

effects. Several sedation scales are in vogue, which may help titrate the dosing to ensure the desired level of sedation without causing harm to the patients.[16] Because NIV is not the prerogative of the ICUs or high-dependency units (HDU), particular attention must be paid to the use of these drugs in less intensively monitored areas.

Furthermore, it is not clear whether sedation is a factor that contributes to the success or failure of NIV.[14] Even though sedation can improve the patients' NIV acceptance and tolerance, there is no robust evidence to support that its use will have a formidable impact in patients where NIV response is inadequate since initiation. Adding sedation may be disadvantageous by obscuring a failure of NIV due to the underlying pathology and thus delaying necessary intubation.[17]

Matsumoto and colleagues retrospectively evaluated sedation's role to manage agitated patients undergoing NIV.[18] In a total of 120 patients, both intermittent and continuous infusion of sedatives were found to affect NIV favorably and potentially avoid NIV failure. They also noted that sedation is helpful even in patients with a history of poor therapeutic evidence of NIV. Muriel et al. assessed the impact of analgesic and/or sedative drugs on NIV failure incidence (defined as the need for initiation of IMV).[19] They studied patients who received at least 2 hours of NIV as the first-line therapy in an observational study carried out in 322 ICUs patients from 30 countries. Using a marginal structural model analysis, they did not find any deleterious effect of either sedation or analgesia on NIV outcomes when used alone. However, their combined use resulted in significantly higher NIV failure, ICU mortality, and 28-day cumulative mortality. They found that sedation and analgesia were administered in only about 20% of patients on NIV. Their outcomes corroborated with the previously conducted web survey from the North America and Europe.[20] In that survey, opioids alone were seen as more likely to be used in European countries, whereas benzodiazepines were the preferred agent in the United States. It indicated that not only sedation is infrequently used in NIV, but also the choice of sedatives varied widely based on the patients' configuration, geographical areas, and clinical experience with different sedative agents.[20]

Drugs Used for NIV

Evidence to recommend a specific sedative drug during NIV is lacking.[14] In the quest for the "ideal" drug, some following criteria should be considered: preserving ventilatory drive, the avoidance of delirium, the promotion of sleep, the effects on airways patency, the hemodynamic impact, and anxiolysis. No specific drug fully satisfies all these criteria, so the choice should be tailored to an individual patient's need and circumstances.[14]

Data obtained from patients managed with IMV suggest caution against using propofol and opiates as sedatives during NIV due to their potential for respiratory depression. By measuring the electrical activity of the diaphragm (EAdi), Vaschetto et al.[21] showed in intubated patients that propofol significantly interferes with the patient-ventilator synchrony during pressure support ventilation (PSV) at sedative doses. During the use of neurally adjusted ventilatory assist (NAVA) and PSV, propofol was found to reduce neural respiratory drive and effort without significantly affecting the respiratory timing.

On the contrary, continuous infusion of opioids did not reduce the respiratory drive but did show detrimental effects on respiratory timing during testing of airway occlusion pressure at 0.1 seconds (P0.1)[22,23] and measurement of EAdi.[24] In addition to providing sedation and analgesia, opioids effect on decreasing the perception of dyspnea leads to reduced respiratory rate and can improve discomfort and thereby increase NIV acceptance, especially in patients with COPD[25,26] and ACPE. NIV guidelines from the British Thoracic Society suggest using intravenous boluses of morphine (2.5–5 mg) for symptomatic relief to improve NIV tolerance as a good practice in agitated, distressed, and/or tachypneic patients.[27]

From a pharmacological perspective, benzodiazepines should be avoided during NIV as their use has been shown to increase delirium. Dexmedetomidine seems to have the most suitable overall ideal pharmacological profile (i.e., the absence of respiratory side effects, beneficial effect on prevention and delirium management, and much lesser hemodynamic adverse impact in sedative dose range). However, more data are required before we can convincingly and routinely start using it. There are few studies relating to the use of dexmedetomidine during NIV, which are mostly plagued with relatively smaller sample sizes and conflicting results.

Sengoku et al. compared 24 hours infusions of dexmedetomidine vs midazolam in 40 uncooperative patients receiving NIV to manage ARF due to AECOPD.[28] Though no patient experienced NIV failure, patients receiving dexmedetomidine required fewer dosing adjustments to maintain the desired sedation level ($p < 0.01$) compared to midazolam. However, this study evaluated only the first 24 hours of NIV and did not provide valuable information on any other outcome variables.

An RCT on 200 patients divided into two equal groups analyzed the sedative and side effects of dexmedetomidine and midazolam over 3 days of NIV therapy and assessed the weaning success and failure on the fifth day.[29] They reported that dexmedetomidine was a better agent for sedation and resulted in significantly higher weaning success and lower failure rates of NIV.

Huang et al.[30] randomized 62 hypoxemic ACPE patients refusing to use NIV because of discomfort in two groups received either midazolam or dexmedetomidine. None of the patients developed any serious adverse events or dropped out of the study protocol. The dexmedetomidine group reported more bradycardia (18.2 vs 0%, $p = 0.016$), but lower NIV failure (21 vs 45%, $p = 0.043$). The overall NIV failure (those requiring ETI) rate was 32%. Dexmedetomidine helped to achieve a more desired level of awake sedation, shortened the duration of mechanical ventilation, and the length of ICU stay. Devlin et al. enrolled 33 adult patients with ARF within 8 hours after starting NIV and divided them into two groups to receive either dexmedetomidine (preventive approach) or placebo up to 72 hours.[31] Patients having agitation and/or pain were also allowed to receive intravenous rescue boluses of midazolam or fentanyl. After initiation of NIV, the administration of dexmedetomidine neither prevented PVD occurrence nor helped to maintain the adequate level of sedation. The Devlin et al. study's unique feature is that they started the infusion early during NIV without the indication of NIV intolerance or acceptance. In most of the studies discussed in this review, sedation was started after low NIV acceptance documentation. Further, failure to achieve the desired sedation might also explain the failure to improve NIV tolerance in this study.[31]

Several studies investigated the use of ketamine for procedural sedation[32–34] but there are hardly any data related to NIV therapy. Ketamine does not usually lead to respiratory depression at dose ranges used to provide analgesia or procedural sedation.[32] Furthermore, it decreases airway resistance and hyperreactivity, improves dynamic compliance, and preserves the lung volumes while retaining the protective upper airway reflexes.[33] Ketamine can, however, lead to hypersalivation, bronchorrhea, and emergence delirium.[33] Because of its indirect stimulating effects on the sympathetic nervous system, ketamine is better avoided in patients with decompensated heart failure. Analgosedation effect of low-dose ketamine infusion might be useful in NIV patients having pain and anxiety. However, ketamine is too tricky to titrate to avoid its typical adverse effects. Also, its use outside ICU and HDU is not entirely safe unless there is round-the-clock monitoring. Moreover, ketamine infusion, even in low doses, is potentially addictive and may impact cognition.

A retrospective study including 79 ICU patients on all types of mechanical ventilation evaluated the effect of ketamine-based analgosedation on delirium and coma and compared them with non-ketamine-based analgosedation.[35] The study found that sustained ketamine-based sedation was associated with an increased rate of observed coma.[36] Another retrospective study, including data of 160 concomitant analgesic-sedative infusions in 104 patients, evaluated the effect of ketamine infusion as an adjuvant analgosedation in all mechanically ventilated patients. The study found that adjunctive continuous ketamine infusion promotes non-ketamine analgesic and sedative dose-sparing effects.[36] However, both of these studies did not specify the type of mechanical ventilation used, and any patients on IMV preclude us from extrapolating this outcome into patients having NIV.

A mini-review published in 2013, including six non-RCTs and two RCTs published between 1999 and 2012, analyzed sedation during NIV.[37] The sedative drugs used in those studies were morphine, midazolam, remifentanil, dexmedetomidine, and propofol. The author concluded that sedation and analgesia titrated to the level of conscious sedation reduced patient discomfort during NIV without affecting hemodynamics, respiratory drive, and pattern. Although the analysis indicated final preferences toward dexmedetomidine and remifentanil as the preferred sedatives for NIV, the evidence was not strong enough to recommend that practice routinely.

Discussion

The analysis results fail to firmly answer the benefit of sedation and the safest drug choice during NIV therapy. No major RCT provided conclusive guidance on sedation use and the type of sedative to be used during NIV provision. Over the last decade, five RCTs compared dexmedetomidine, midazolam, placebo, and/or fentanyl and found both dexmedetomidine and midazolam as effective sedatives and improved arterial blood gases and respiratory rate.[30] Dexmedetomidine had a better profile for NIV failure, LOS in ICU, and mortality. However, dexmedetomidine failed to benefit both for maintaining desired sedation and NIV tolerance when the infusion was started early during NIV.[31] Our analysis from this

review and the published RCTs indicates the safety and efficacy of dexmedetomidine as a sedative for NIV. Nevertheless, the evidence is yet not enough to strongly recommend it.

A survey published in 2007 indicated that the use of sedation for NIV was, in fact, infrequent, and the practices of use of sedation vary widely within and between different specialities and geographic regions.[20] A recent Swedish survey evaluating sedation practices during NIV indicated that propofol and dexmedetomidine were the preferable agents for short- and long-term sedation, with the most common (88%) indication for dexmedetomidine being NIV.[38] We failed to find any recent trial evaluating or comparing propofol and dexmedetomidine during NIV. However, the PRODEX trial evaluated propofol and dexmedetomidine intending to maintain sedation, reduce mechanical ventilation duration (including NIV), and patients' communication ability.[39] The study reported that dexmedetomidine was not inferior to propofol in maintaining mild to moderate sedation and improved patients' ability to communicate while reducing mechanical ventilation duration in ICU patients who received prolonged ventilation.

The routine use of sedation during NIV is not essential but can benefit some subset of patients. The present evidence is confusing and unclear in this context. In critically ill patients who were mechanically ventilated (either IMV or continued on NIV after extubation), no sedation as compared to interrupted sedation resulted in a shortened length of ICU and hospital stay.[40] The clinical practice guidelines for preventing and managing pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU indicated sedation in selective patients, although this was not specific to patients having NIV.[41] Nevertheless, the finding indicated that sedation could alleviate agitation[18,27] and pain.[13] Thereby, agitated patients and patients with pain are likely to benefit from titrated sedation, and this can potentially improve NIV tolerance and shorten LOS in ICUs.

Indian Society of Critical Care Medicine Guideline for the use of NIV in ARF in adult ICUs patients recommends using a non-pharmacological approach to calm the patient (reassuring the patient, proper environment) administrating analgosedation.[42] The guideline also states that sedation may be used with close monitoring in patients on NIV and only in an ICU setting with a lookout for NIV failure signs. However, these recommendations were based on expert opinion due to the lack of evidence and categorized them as valuable practice points. Further, as NIV is now frequently used outside ICUs, sedation might be required in those setups. The guideline also states that sedation in patients on NIV, if used appropriately and with the correct precautions, improves patient comfort and reduces NIV failure. However, the guideline could not indicate a preference for any drug specifically for the use in patients with ARF on NIV.[42]

Although the present analysis is based on a systematic search, we have not searched large databases, like Embase and Scopus, and included only the English literature. It might have an impact on our result and interpretation.

Conclusions

Current evidence suggests that sedation in patients receiving NIV has a potential beneficial role when used with appropriate monitoring in selected patients who are at risk of NIV intolerance. Pharmacological sedation should only be chosen when initial non-pharmacological strategies fail and should be carefully titrated. No single sedative agent is currently available that fulfills all the criteria to be an ideal agent. Dexmedetomidine is emerging as the sedative agent of choice based on the most recent trials. However, we need more RCTs to firmly comment on this issue to formulate the standard guideline and recommendation benefitting such patients.

Recommendations

- Pharmacological sedation should be chosen if non-pharmacological strategies fail. However, this should be considered after optimizing ventilatory support, selecting the best interface for the patient, and a proper interface rotational program to prevent the development of a pressure sore and related NIV intolerance.
- Pharmacological sedative agents should be used in NIV therapy patients with pain, agitation, risk of NIV intolerance, and failure.
- Dexmedetomidine appears to be a safe and relatively better choice for pharmacological sedation. However, further RCTs are required for knowing the proper impact on NIV outcomes.
- When using sedation, patients should be closely monitored and the level of sedation should be carefully titrated to prevent oversedation.

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