Intensive Care Med (2015) 41:1688–1691
DOI 10.1007/s00134-015-3935-6

EDITORIAL

Gilles Hilbert
Paolo Navalesi
Christophe Girault

# Is sedation safe and beneficial in patients receiving NIV? Yes

Received: 1 June 2015
Accepted: 17 June 2015
Published online: 7 July 2015


For a contrasting viewpoint, please go to
doi:10.1007/s00134-015-3915-x.

G. Hilbert (✉)
Division of Medical Intensive Care, University Hospital, Service de Réanimation Médicale, Hôpital Pellegrin, 33076 Bordeaux Cedex, France
e-mail: gilles.hilbert@chu-bordeaux.fr
Tel.: 33 5 56 79 98 29

P. Navalesi
Department of Translational Medicine, Anesthesia and Intensive Care, Sant'Andrea Hospital, Università del Piemonte Orientale (UPO), CRRF Mons. L. Novarese, Moncrivello (VC), Novara Vercelli, Italy

C. Girault
Department of Medical Intensive Care, Institute for Biomedical Research and Innovation, Charles Nicolle University Hospital and UPRES EA 3830-IRIB, Rouen University, 76031 Rouen Cedex, France

Compared with medical therapy, noninvasive ventilation (NIV) improves outcome and reduces complications in selected patients with acute respiratory failure (ARF) [1–3].

Mask intolerance because of pain, discomfort, or claustrophobia may lead the patient to refuse ongoing NIV, causing its discontinuation and subsequent requirement for endotracheal intubation with rates of 9–22 % [4]. For some of these patients, sedation during NIV could be a valuable option to avert the need for intubation.

In the present issue, Muriel et al. aimed to assess the impact of analgesic and/or sedative drugs on the risk of NIV failure [5]. They conducted an ancillary study from a previous prospective international multicenter observational trial of mechanically ventilated patients carried out in 322 intensive care units (ICU) from 30 countries [6]. They selected patients who received at least 2 h of NIV as first-line ventilatory support at ICU admission, and NIV failure was defined as the need for invasive mechanical ventilation. The authors reported that less than 20 % of patients (165/842) received sedation–analgesia during NIV. Using a specific marginal structural model (MSM) analysis, they showed no deleterious effect on NIV outcome when sedation or analgesia was used alone, but their combination was significantly associated with NIV failure, ICU mortality, and 28-day mortality.

The study has limitations, most of which the authors properly discuss. Some of these limitations, however, warrant further comments and some others need to be also considered. First we do not know whether analgesics and/or sedatives were always given with respect to the interface tolerance or also administered for associated causes not strictly depending on NIV, such as agitation, pain, dyspnea, or tachypnea unrelated to NIV. Also, it is unclear whether analgesics and/or sedatives were administered to prevent or treat NIV intolerance. In addition, it is uncertain for how long the patients underwent NIV before being sedated. Noteworthy, the study cannot differentiate among the route of administration (intravenous, intramuscular, oral, subcutaneous), type of drugs (short acting vs. long lasting), modality of administration (continuous versus bolus), duration of sedatives and/or analgesics administration, or specific protocols used.

In addition to the present trial [5], several observational studies [7–11] and three randomized trials comparing midazolam and dexmedetomidine or placebo [12–14] have assessed the potential use of sedative and/or analgesic drugs to reduce discomfort and risk of NIV failure. The main characteristics and results of these studies are

**Table 1** Clinical studies assessing the use of sedation/analgesia during NIV

| References | Type | Patients (*n*) | Reason for NPPV (*n*) | Reason for sedation/ analgesia | Sedative and/or analgesic drugs used (*n*) | NIV tolerance/ sedation | NPPV success rate (%) |
|---|---|---|---|---|---|---|---|
| Rocker et al. [7] | Prospective observational | 9/12 | Hypoxemic ARF (ALI/ARDS) | Preventive NIV intolerance | Midazolam (6)/morphine (8) | Adequate tolerance | 50 |
| Constantin et al. [8] | Prospective observational | 13 | Hypoxemic (10) or hypercapnic ARF (3) | Curative NIV intolerance | Propofol (3)/ remifentanil (13) | Adequate tolerance | 69 |
| Akada et al. [9] | Prospective observational | 10 | Hypercapnic ARF | Curative NIV intolerance | Dexmedetomidine | Adequate tolerance | 100 |
| Rocco et al. [10] | Prospective observational | 36 | Persistent hypoxemic ARF | Curative NIV intolerance | Remifentanil | Adequate tolerance | 61 |
| Clouzeau et al. [11] | Prospective observational | 10 | Hypoxemic (7) or hypercapnic ARF (3) | Curative NPPV intolerance | Propofol | Adequate tolerance | 70 |
| Senoglu et al. [12] | Prospective randomized double-blind | 40 | Hypercapnic ARF (COPD) | Curative NIV intolerance | Dexmedetomidine (20) vs midazolam (20 | Adequate tolerance/ sedation | 100 vs 100 (during first 24 h) |
| Huang et al. [13] | Prospective randomized | 62 | Hypercapnic ARF (CPE) | Curative NIV intolerance | Dexmedetomidine (33) vs midazolam (29) | Adequate tolerance/ sedation | 79 vs 55 ($p = 0.043$) |
| Devlin et al. [14] | Prospective randomized double-blind | 33 | Hypercapnic ARF | Preventive NIV intolerance | Dexmedetomidine (16) vs placebo (17) ±midazolam (agitation) and/or fentanyl (pain) | No adequate tolerance/sedation | 69 vs 71 |

*NIV* noninvasive ventilation, *ARF* acute respiratory failure, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *CPE* cardiogenic pulmonary edema, *preventive NIV intolerance* at start of NIV to prevent NIV intolerance, *curative NIV intolerance* for poor tolerance (pain, discomfort, agitation, refusing to continue) during NIV

reported in Table 1. Even if different medications have been used, the aims of sedation and/or analgesia were similar: allowing moderation of patient discomfort and obtaining the desired level of sedation, either to prevent or to treat NIV intolerance. Whatever the drugs used, the goal was to achieve a level of sedation to a point where patients were awake, arousable, and comfortable. Pilot studies have suggested that continuous infusion of a single sedative agent may decrease patient discomfort, with no significant deleterious effects on respiratory drive, respiratory pattern or hemodynamics, and with improvement in gas exchanges [7–11].

The first randomized controlled trial compared 24-h infusions of dexmedetomidine and midazolam in 40 uncooperative patients receiving NIV for ARF due to acute exacerbations of chronic obstructive pulmonary disease [12]. Though no patient experienced NIV failure during the study period, compared to midazolam, dexmedetomidine required fewer dosing adjustments to maintain adequate sedation ($p < 0.01$). This study, however, considers only the first 24 h of NIV and does not provide valuable information on any outcome variable.

Another randomized controlled study enrolled 62 hypoxemic patients with acute pulmonary edema failing NIV because of discomfort leading the patients to refuse continuing NIV [13]. Except that bradycardia occurred more with dexmedetomidine (18.2 % vs. 0, $p = 0.016$), there were no serious adverse events, and none of the patients interrupted the study protocol. The main outcome variable was the rate of failure, i.e., endotracheal intubation, which was overall 32 %. In the dexmedetomidine group of patients NIV failure was lower (21 %) than in the midazolam group (45 %), $p = 0.043$. In addition, dexmedetomidine led to a more desired level of awake sedation, shortened the duration of mechanical ventilation, the length of ICU stay, and further reduced the prevalence of nosocomial infection.

Devlin et al. randomized 33 adult patients with ARF within 8 h after starting NIV to receive dexmedetomidine (preventive approach) or placebo up to 72 h [14]. Patients with agitation or pain could also receive a bolus of midazolam or fentanyl by intravenous administration, as needed. They found that administering dexmedetomidine soon after NIV initiation neither prevented the occurrence of NIV tolerance nor helped maintain sedation at the desired goal.

Taken together, the results of these studies are encouraging [7–13]. Overall, the use of sedation during NIV appears feasible and safe. The "curative" use of sedation–analgesia, i.e., applied for treating discomfort leading to NIV intolerance, seems to be able to avoid intubation in 55–70 % of cases [8–13], while ensuring the desired level of awake sedation. By contrast, the "preventive" administration of sedation–analgesia, i.e., at initiation of NIV to prevent discomfort leading to intolerance, has so far not shown encouraging results [14].

The present study adds valuable information indicating that (1) the use of a single sedative or analgesic drug should help to improve NIV tolerance in the vast majority of patients, and (2) in the case of failure of one drug, the association of sedative and analgesic drugs is unable to further improve NIV tolerance and may be deleterious [5].

While we believe that benzodiazepines should certainly be avoided and dexmedetomidine could have the most suitable overall profile [15], further studies are definitely needed to determine the "ideal" sedative or analgesic drug to be used during NIV, as well as the "best" route and modalities of administration.

Finally, before considering sedation–analgesia to improve patient comfort, clinicians should always first consider the other factors known to improve NIV tolerance and patient cooperation, such as the choice of the interface (type, size, and fit), ventilator settings, control of air leaks, and containment of patient–ventilator asynchrony. Furthermore, as frequent dose adjustments are required to apply sedation–analgesia during NIV, a safe environment and close monitoring are necessary, which restricts its use to the ICU setting.

Is sedation safe and beneficial in patients receiving NIV? Yes, definitely. The ideal indication for sedation during NIV is unknown but could be when mask intolerance and/or lack of cooperation may lead the patient to refuse ongoing NIV. Thus, the objective is clearly to avoid intubation. While awaiting further randomized controlled trials clarifying the role, modalities, and indications, we believe it is wise to suggest the separate use of sedative or analgesic agents to treat NIV intolerance due to discomfort.

## References


1. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, Isabey D, Harf A (1995) Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 333:817–822
2. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP (2001) Noninvasive ventilation for treatment of acute respiratory failure in immunosuppressed patients with pulmonary infiltrates and fever, a randomized trial. N Engl J Med 344:481–487
3. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti R, Passariello M, Meduri GU (2001) Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multicenter study. Intensive Care Med 27:1718–1728

4. Hilbert G, Clouzeau B, Nam Bui H, Vargas F (2012) Sedation during non-invasive ventilation. Minerva Anestesiol 78:842–846
5. Muriel A, Peñuelas O, Frutos-Vivar F, Arroliga AC, Abraira V, Thille AW, Brochard L, Nin N, Davies AR, Amin P, Du B, Raymondos K, Rios F, Violi DA, Maggiore SM, Soares MA, González M, Abroug F, Bülow HH, Hurtado J, Kuiper MA, Moreno RP, Zeggwagh AA, Villagómez AJ, Jibaja M, Soto L, D'Empaire G, Matamis D, Koh Y, Anzueto A, Ferguson ND, Esteban A (2015) Impact of sedation and analgesia during non-invasive positive pressure ventilation on outcome: a marginal structural model causal analysis. Intensive Care Med. doi:10.1007/s00134-015-3854-6
6. Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Peñuelas O, Abraira V, Raymondos K, Rios F, Nin N, Apezteguía C, Violi DA, Thille AW, Brochard L, González M, Villagomez AJ, Hurtado J, Davies AR, Du B, Maggiore SM, Pelosi P, Soto L, Tomicic V, D'Empaire G, Matamis D, Abroug F, Moreno RP, Soares MA, Arabi Y, Sandi F, Jibaja M, Amin P, Koh Y, Kuiper MA, Bülow HH, Zeggwagh AA, Anzueto A (2013) Evolution of mortality over time in patients receiving mechanical ventilation. Am J Respir Crit Care Med 188:220–230
7. Rocker GM, Mackenzie MG, Williams B, Logan PM (1999) Non invasive positive pressure ventilation: successful outcome in patients with acute lung injury/ARDS. Chest 115:173–177
8. Constantin JM, Schneider E, Cayot-Constantin S, Guerin R, Bannier F, Futier E, Bazin JE (2007) Remifentanil based sedation to treat noninvasive ventilation failure: a preliminary study. Intensive Care Med 33:82–87
9. Akada S, Takeda S, Yoshida Y, Sakamoto A (2008) The efficacy of dexmedetomidine in patients with non invasive ventilation: a preliminary study. Anesth Analg 107:167–170
10. Rocco M, Conti G, Alessandri E, Morelli A, Spadetta G, Laderchi A, Di Santo C, Francavilla S, Pietropaoli P (2010) Rescue treatment for noninvasive ventilation failure due to interface intolerance with remifentanil analgosedation: a pilot study. Intensive Care Med 36:2060–2065
11. Clouzeau B, Bui HN, Vargas F, Grenouillet-Delacre M, Guilhon E, Gruson D, Hilbert G (2010) Target-controlled infusion of propofol for sedation in patients with non-invasive ventilation failure due to low tolerance: a preliminary study. Intensive Care Med 36:1675–1680
12. Senoglu N, Oksuz H, Dogan Z, Yildiz H, Demirkiran H, Ekerbicer H (2010) Sedation during noninvasive mechanical ventilation with dexmedetomidine or midazolam: a randomized, double-blind, prospective study. Curr Ther Res Clin Exp 71:141–153
13. Huang Z, Chen YS, Yang ZL, Liu JY (2012) Dexmedetomidine versus midazolam for the sedation of patients with non-invasive ventilation failure. Intern Med 51:2299–2305
14. Devlin JW, Al-Qadheeb NS, Chi A, Roberts RJ, Qawi I, Garpestad E, Hill NS (2014) Efficacy and safety of early dexmedetomidine during noninvasive ventilation for patients with acute respiratory failure: a randomized, double-blind, placebo-controlled pilot study. Chest 145:1204–1212
15. Longrois D, Conti G, Mantz J, Faltlhauser A, Aantaa R, Tonner P (2014) Sedation in non-invasive ventilation: do we know what to do (and why)? Multidiscip Respir Med 9:56