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# What's new in sedation strategies?

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#### Introduction

Sedation constitutes an essential component of intensive care [1]. Having been accepted as an undisputable need for many years, research in the last two decades has clearly indicated that sedation affects the course of critical illness. Over-sedation, even for short periods [2, 3], has been associated with prolonged mechanical ventilation and intensive care unit (ICU) length of stay, higher rates of delirium, and death [1, 4]. While for selected indications pharmacological sedation is unavoidable, achieving patient comfort, particularly during mechanical ventilation, does not necessarily rely on sedative drugs (Fig. 1) [1, 5].

## Strategies to minimize sedation: less is more!

Minimizing sedation during mechanical ventilation has been associated with multiple benefits (Fig. 1), including improved survival rates [1–4]. Two recent studies showed that avoidance of or lightening sedation as early as during the first 48 h after intubation may be essential to maximize these benefits [2, 3]. The mortality effects of light sedation appear to persist after discharge from the hospital up to 180 days [6]. Long-term psychiatric outcomes may be positively affected by reducing the sedation depth [7]. Further benefits provided by minimizing sedation during mechanical ventilation comprise facilitation of spontaneous breathing as well as early physical and occupational therapy (Fig. 1, electronic supplementary material), interventions which have been associated with improved short- and longterm outcomes [8, 9]. Interestingly, it is not the illness acuity or the presence of life support measures but the level of sedation which determines the ability of the patient to participate in early physical therapy [10, 11]. Accordingly, the 2013 practice guidelines from the American College of Critical Care Medicine for the management of pain, agitation, and delirium in adult ICU patients recommend that sedative medications be titrated to maintain a light rather than a deep level of sedation, unless clinically contraindicated (level of recommendation: 1B) [12].

Different strategies to minimize sedation have been evaluated: (1) daily sedation interruption [4]; (2) sedation protocols based on validated sedation scales (managed by nurses) [13]; and (3) a symptom-based approach focusing on pain and delirium control while avoiding sedation [14]. Based on the current evidence, no strategy is superior. A North American multi-centered randomized controlled trial including 423 mechanically ventilated critically ill patients compared protocolized sedation with protocolized sedation plus daily sedation interruption. Benzodiazepines were the sedative agents applied in 80 % of patients. No difference in the time to successful extubation, rates of delirium, or the duration of ICU and hospital stay was observed between groups. Mean midazolam doses [102 (SD 326) vs. 82 (287) mg/patient/day; p = 0.04] and nurse workload (p = 0.001) were higher in the interruption group [15]. These results were supported by a recent Cochrane review which did not find that daily interruption alters the duration of mechanical ventilation, mortality, or length of ICU or hospital stay [16]. Of note,



reduced costs of care and improved resource utilization

Fig. 1 Goals of sedation and benefits of minimizing sedation in critically ill patients

the effect of daily sedation interruption on the duration of mechanical ventilation depended on the study country of origin, suggesting that geographic differences in ICU organization and practice may influence the effects of daily sedation interruption on patient outcome [16]. A Danish single-center study, including 140 mechanically ventilated critically ill patients, compared a symptombased approach focusing on pain and delirium control while avoiding sedation with a sedation protocol including daily sedation interruption [14]. Patients in the nosedation group experienced shorter durations of mechanical ventilation, and ICU and hospital stay. The protocol of avoiding sedation had to be deviated in 18 % of patients in the intervention group (n = 10), who received continuous propofol sedation on more than two occasions. Agitated delirium was more frequent in the intervention group than in the control group, likely because of enhanced recognition in these non-sedated patients, rather than an increased prevalence.

#### **Choice of sedative agents**

As the majority of studies evaluating strategies to minimize sedation did not differentiate between the types of sedative agents applied, one may assume that the goal to minimize sedation in critically ill patients is of greater importance than the choice of sedative agents. Yet, a recent meta-analysis including six trials enrolling 1235 patients reported that, compared to a benzodiazepine sedative strategy, a non-benzodiazepine strategy was associated with a shorter ICU length of stay and duration of mechanical ventilation with similar short-term mortality [17]. Another possible advantage to non-benzodiazepine sedation is a more favorable cost-effectiveness ratio, which was reported in a study from the United States [18]. Using propensity score analysis, Lonardo et al. [19] found a significantly lower mortality rate in critically ill patients sedated with continuous propofol compared with midazolam or lorazepam; durations of mechanical ventilation and ICU stay were also shorter in propofol-treated patients. The 2013 practice guidelines recommend that sedation strategies using non-benzodiazepine sedatives (propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (midazolam or lorazepam) in mechanically ventilated critically ill patients (level of recommendation: 2B) [12].

To date, only one sufficiently powered trial has compared a propofol- versu s a dexmedetomidine-based sedation strategy in 500 mechanically ventilated ICU patients [20]. No between-group differences were observed for the time at target sedation, duration of mechanical ventilation, incidence of delirium, length of ICU and hospital stay, or mortality. Patients sedated with dexmedetomidine were more arousable, more cooperative, and could better communicate their level of pain than patients receiving propofol. While there were no between-group differences in bradycardia or hypotension, patients receiving dexmedetomidine had a higher incidence of atrioventricular block. A meta-analysis suggested specific benefits of dexmedetomidine in mechanically ventilated cardiac surgery patients [21]. A new sedative option which has received little attention so far is the use of inhalational anesthetics; in a randomized trial of 47 mechanically ventilated ICU patients, sevoflurane decreased wake-up and extubation times, reduced post-extubation morphine consumption, and improved awakening quality compared with midazolam or propofol [22].

## **Conclusions**

The current evidence strongly indicates that excessive sedation and over-sedation, even as early as during the first 48 h after intubation, is associated with poor clinical

outcomes in mechanically ventilated critically ill adult patients. Different strategies to minimize sedation have been evaluated but none have proved to be superior. Such strategies could be complementary and combined for cultural and/or practical reasons. When daily interruption of sedation is not implemented, indications to continue sedation as well as the level of sedation must be systematically and carefully checked in all patients at least on a daily basis. The use of non-benzodiazepine sedatives appears to be associated with clinical benefits. No differences in relevant outcome variables have so far been detected between the short-acting sedative agents, propofol and dexmedetomidine.

Conflicts of interest None to disclose.

#### References

- 1. Reade MC, Finfer S (2014) Sedation and delirium in the intensive care unit. N Engl J Med 370:444-454
- 2. Tanaka LM, Azevedo LC, Park M et al (2014) Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. Crit Care 18:R156
- 3. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, McArthur C, Seppelt IM, Webb S, Weisbrodt L (2012) Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 186:724-731
- 4. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471-1477
- 5. Chlan LL, Weinert CR, Heiderscheit A, Tracy MF, Skaar DJ, Guttormson JL, Savik K (2013) Effects of patientdirected music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilator support: a randomized clinical trial. JAMA 309:2335-2344
- 6. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, Khoo TM, Ali SB, Saman MA, Shaltut A, Tan CC, Yong CY, Bailey M, Sedation Practice in Intensive Care Evaluation (SPICE) Study Group Investigators (2013) Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med 39:910-918

- 7. Treggiari MM, Romand JA, Yanez ND, 11. Mendez-Tellez PA, Dinglas VD, Deem SA, Goldberg J, Hudson L, Heidegger CP, Weiss NS (2009) Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 37:2527-2534
- 8. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW (2008) Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. Lancet 371:126-134
- 9. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP (2009) Early physical and occupational therapy in mechanical ventilated, critically ill patients: a randomised controlled trial. Lancet 373:1874-1882
- 10. Pohlman MC, Schweickert WD, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister K, Hall JB, Kress JP (2010) Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. Crit Care Med 38:2089-2094

- Colantuoni E, Ciesla N, Sevransky JE, Shanholtz C, Pronovost PJ, Needham DM (2013) Factors associated with timing of initiation of physical therapy in patients with acute lung injury. J Crit Care 28:980-984
- 12. Barr J, Fraser GL, Puntillo K, Ely WE, Gélinas C, Dasta JF, Davidson JÉ, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R, AmericanCollegeof Critical Care Medicine (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 41:263-306
- 13. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH (1999) Effect of a nursingimplemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 27:2609-2615
- 14. Strom Martinussen T, Toft P (2010) A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomized trial. Lancet 375:475-480
- 15. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, Herridge M, Ferguson N, Devlin J, Tanios M, Dodek P, Fowler R, Burns K, Jacka M, Olafson K, Skrobik Y, Hébert P, Sabri E, Meade M, SLEAP Investigators, Canadian Critical Care Trials Group (2012) Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 308:1985-1992

- 16. Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S (2014) Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Database Syst Rev Rev 7:CD009176
- 17. Fraser GL, Devlin JA, Worby CP, Alhazzani W, Barr J, Dasta JF, Kress JP, Davidson JE, Spencer FA (2013) Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and metaanalysis of randomized trials. Crit Care Med 41:S30–S38
- Bioc JJ, Magee C, Cucchi J, Fraser GL, Dasta JF, Edwards RA, Devlin JW (2014) Cost effectiveness of a benzodiazepine vs. nonbenzodiazepinebased sedation regimen for mechanically ventilated, critically ill adults. J Crit Care 29:753–757

- 19. Lonardo NW, Mone MC, Nirula R, Kimball EJ, Ludwig K, Zhou X, Sauer BC, Nechodom K, Teng C, Barton RG (2014) Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. Am J Respir Crit Care Med 189:1383–1394
- 20. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J, Dexmedetomidine for Long-Term Sedation Investigators (2012) Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 307:1151–1160
- 21. Lin YY, He B, Chen J, Wang ZN (2012) Can dexmedetomidine be a safe and efficacious agent in post-cardiac surgery patients? A meta-analysis. Crit Care 16:R169
- 22. Mesnil M, Capdevila X, Bringuier S, Trine PO, Falquet Y, Charbit J, Roustan JP, Chanques G, Jaber S (2011) Longterm sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. Intensive Care Med 37:933–941