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The Future ICU

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Future Strategies in Sedation and Analgesia

From massive sedation in the past, through current patient-centred sedation protocols, the future may further improve sedation in the ICU.

Introduction

The concepts for an optimal sedation in the intensive care unit (ICU) should include:

- Definition of the optimal depth of sedation;
- The need for agents with on/off effects;
- The need for agents with dedicated effects on hypnosis, pain, and confusion;
- Continuous supervision and adequate monitoring.

In the ICU patients, sedation is used according to two different goals. For the patients with acute respiratory distress syndrome (ARDS) and/or intracranial hypertension, the goal is to obtain a perfect adaptation to ventilator; thus, a deep level of sedation is required, i.e. enough to obtain no response to external stimuli. To achieve such level of sedation, hypnotics and opioids are both required. Muscle relaxant agents can be added if muscle contractions do not allow efficient mechanical ventilation or intracranial pressure control.

In the other patients, the only goal of sedation, if required, is patient comfort. The patient should always be interactive, quiet and cooperative. Non-benzodiazepine hypnotics and non-opioid analgesics are the best choice, but no sedation remains the first option (Chanques et al. 2017).

Different scales are used to measure the depth of sedation. The Richmond Agitation-Sedation Scale (RASS) ranges from -5 (no response to voice or physical stimulation) to +4 (overtly combative or violent; immediate danger to staff). In patients requiring deep sedation, the RASS score is targeted at -4, while in those requiring comfort sedation, it is targeted around 0. Unfortunately, the monitoring of sedation level remains unsatisfactory in most ICUs (Leone et al. 2012; Payen et al. 2007).

Post-intensive care syndrome (PICS) depicts disorders including physical impairment, cognitive impairment and psychiatric impairment occurring in ICU survivors. There is an association between prolonged immobilisation and sedation and the development of PICS. Thus, we have moved from a utilitarian view of sedation to a global management of patients, aiming at reducing the burden of distress after ICU hospitalisation.

Current Practices

The ABCDEF bundle (Jackson et al. 2010; Pandharipande et al. 2010) recommends a daily check of the following items:

A: Assessment, prevention and manage ment of pain.
B: Both spontaneous awakening trials and spontaneous breathing trials.
C: Choice of sedation and analgesia.
D: Delirium assessment, prevention and management.
E: Early mobility and exercise.
F: Family engagement and empowerment.

Sedation and analgesia are playing a key role at every step of this bundle. Most recent guidelines are mainly drawn from these six items (Devlin et al. 2018). Experts suggest using comfort sedation in place of deep sedation in the ICU mechanically ventilated patients only if indicated. Comfort sedation is associated with shorter time to extubation (Bugedo et al. 2013; Shehabi et al. 2013; Treggiari et al. 2009) and lower tracheostomy rates (Tanaka et al. 2014; Treggiari et al. 2009), as compared with deep sedation. Daily sedation interruption protocols and nurse-protocolised targeted sedation are both safe and make it possible to reach a targeted level of sedation (Mehta et al. 2012; de Wit et al. 2008).

Regarding the choice of drugs, propofol and dexmedetomidine have interesting pharmacokinetic and pharmacodynamic profiles (Sahinovic et al. 2018; Weerink et al. 2017). Propofol use has been associated with shorter durations of sedation and mechanical ventilation, as compared with benzodiazepines (Mesnil et al. 2011; Zhou et al. 2014). The SEDCOM study (Safety and Efficacy of Dexmedetomidine COmpared with Midazolam), a robust randomised clinical trial (RCT), showed that dexmedetomidine reduced time to extubation and delirium rates (Riker et al. 2009). Moreover, associated harm with either propofol or dexmedetomidine was deemed to be minimal and not clinically significant. No significant differences were reported between propofol and dexmedetomidine. Nevertheless, propofol infusion syndrome limits the use of propofol as the main agent for sedation for longer than two days or at a dose above 4 mg/kg/h (Bray 1998).

In the ICU, up to 90% of patients receive opioids (Arroliga et al. 2005; Payen et al. 2007; Wøien et al. 2012) and these agents are associated with increased morbidity and mortality (Kamdar et al. 2017). The opioids crisis (Volkow and Collins 2017), although not discussed in the setting of ICU, should be kept in mind by intensivists. If required, opioids should be used at the lowest effective dose and the timing of administration should coincide with noxious stimuli. Acetaminophen, paracetamol, nefopam, ketamine and non-steroidal anti-inflammatory drugs (within the restrictions of use) can be used to decrease opioid needs in the ICU patients (Devlin et al. 2018). Multimodal analgesia should become a standard of care, since several alternatives to opioids have been studied and have been proven to be efficient in the ICU patient.

Future of Sedation

Target-controlled infusion

Intermittent boluses or continuous infusion are not optimal methods in the ICU setting. Indeed, intermittent boluses expose the patient to cycles of under-dosage and over-dosage and increase the load of work for the nursing staff. If continuous infusion is used, there is a delay to obtain the target; thereafter there is a risk of exceeding this target by a mechanism of drug accumulation.

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The aim of target-controlled infusion (TCI) is to obtain the desired "target" concentration of an intravenous agent at the effector site (or in plasma), without delay. It also makes it possible to maintain the concentration at the target level by adapting the infusion rate to the predicted tissue or plasma concentration. TCI is based on predictive mathematical models, the computer calculating the amount of drug required to reach a desired target according to the patient features, including age, body mass index, and gender (Struys et al. 2016). TCI is widely used in the operating room due to the high precision of models, allowing an excellent quality of anaesthesia with fast onset and recovery. The principle of TCI is of particular interest in the ICU since the level of stimulation of an ICU patient changes over time. With TCI, concentration targets could be set in real-time, according to the stimulation provided to the patient.

Few studies have assessed TCI-delivered sedation in the ICU. In a small RCT, TCI was used to infuse sufentanil and ketamine, both of them combined with midazolam. The model was quite robust for sufentanil, but prediction was disappointing for ketamine and midazolam (Bourgoin et al. 2005). In an observational study, use of a TCI of propofol, which was used for sedation of neurosurgical patients, resulted in a bias of -34.7% and precision of 36% (Cortegiani et al. 2018). It seems that pharmacokinetic models are not suitable for the ICU patients. Indeed, admission to the ICU is associated with significant pharmacokinetic changes requiring to be considered in more complex models than those developed for the "standard" surgical patients. Those variables are, for example, creatinine clearance, liver function, distribution volume, concomitant medication, organ failure, SIRS, shock, etc.

Closed-loop systems

In a philosophy of time-sparing methods in ICU, strategies based on closed-loops systems are of particular interest. Indeed, light sedation requires frequent monitoring of sedation levels to maintain the patient in the optimal range of sedation. Those are time-consuming and prone to human error. A closed-loop system may facilitate this process, if clinically relevant variables have been targeted based on a robust monitoring, which should not be subject to artefacts.

In the ICU patient, the selection of the best variables is challenging since many of them are taken into account. For example, haemodynamic variables interplay with consciousness level since sedation will affect both systems. The challenge to use closed-loop control technology for the sedation of ICU patients is to identify the best variables to control several systems simultaneously. The most commonly used target for sedation control is the bispectral index. Bispectral index monitoring, albeit a low level of evidence, seems to reduce the amount of sedative drugs. However, artefacts are possible; ketamine, for instance, increases the bispectral index level due to its excitatory effects on the EEG (Johansen 2006). Ideal monitoring control should include, for instance consciousness, respiratory rate and blood pressure or cardiac index (Haddad and Bailey 2009).

A closed-loop system requires a reliable algorithm that insures to obtain the desired target value. The algorithms are therefore complex and use modern mathematical and statistical processes. We can cite for example the dynamic learning strategy or fuzzy logic system (Le Guen et al. 2016), Bayesian networks and probability theory to extend deterministic rule-based expert systems (Gholami et al. 2012), or deep machine learning. The later one has been used to assess sedation levels and ICU delirium (Sun et al. 2019).

Today, to advance in this field, more data are needed for the elaboration of ICU-dedicated pharmacokinetic models, as well as the selection of best target values and the development of adaptive algorithms.

Regional analgesia

In the operating room, the development of regional analgesia was associated with improved outcomes in moderate to high-risk surgeries (Guay et al. 2014). One should note that poor pain control can be responsible for confusion and agitation. Regional analgesia is probably the best strategy for pain control, and depending on the way to administer it, the haemodynamic effects can be quite limited. The development of regional analgesia should be under the responsibility of an anaesthesiologist, experts in this field. This highlights the interplay between the practice in operating room and ICU (Tankel et al. 2019). Thus, regional anaesthesia should also be used when feasible. A recent multicenter retrospective cohort study showed a diminution of mortality in acute pancreatitis patients admitted to ICU receiving epidural analgesia (Jabaudon et al. 2018), without significant harm (Jabaudon et al. 2015). Regional analgesia makes it possible to introduce early rehabilitation in the ICU patients by reducing the level of pain and the use of opioids.

Conclusion

In the past, ICU patients received massive sedation for long period of time. We already are in an era of drug-sparing methods to improve short and long-term outcomes of our patients. Guidelines recommend the use of short-acting agents and a daily assessment of the opportunity to decrease or stop sedation. Opioids are also to be spared with the use of multimodal and regional analgesia. The first option should always be to avoid sedation. With the development of powerful computing capabilities, the future will bring ICU-specific target-controlled infusions within adaptive closed-loop systems, to keep improving ICU outcomes.

Conflicts of interests

Marc Leone declares fees from MSD, Pfizer, Orion, Octapharma, Aspen, Aguettant, Amomed. Bruno Pastene has no conflicts of interests to declare. ■

Key Points

- In the ICU patients, sedation is used according to two different goals - deep sedation in patients with ARDS and/or intracranial hypertension; and comfort sedation in other patients.
- There is an association between prolonged immobilisation and sedation and the development of post-intensive care syndrome.
- Experts suggest using comfort sedation in place of deep sedation in the ICU mechanically ventilated patients only if indicated.
- Opioids should be used at the lowest effective dose and the timing of administration should coincide with noxious stimuli.
- Regional analgesia makes it possible to introduce early rehabilitation in the ICU patients by reducing the level of pain and the use of opioids.
- Guidelines recommend the use of short-acting agents and a daily assessment of the opportunity to decrease or stop sedation.

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