Review Article

Sedation for adult ICU patients: A narrative review including a retrospective study of our own data

ABSTRACT

The optimization of patients' treatment in the intensive care unit (ICU) needs a lot of information and literature analysis. Many changes have been made in the last years to help evaluate sedated patients by scores to help take care of them. Patients were completely sedated and had continuous intravenous analgesia and neuromuscular blockades. These three drug classes were the main drugs used for intubated patients in the ICU. During these last 20 years, ICU management went from fully sedated to awake, calm, and nonagitated patients, using less sedatives and choosing other drugs to decrease the risks of delirium during or after the ICU stay. Thus, the usefulness of these three drug classes has been challenged. The analgesic drugs used were primarily opioids but the use of other drugs instead is increasing to lessen or wean the use of opioids. In severe acute respiratory distress syndrome patients, neuromuscular blocking agents have been used frequently to block spontaneous respiration for 48 hours or more; however, this has recently been abolished. Optimizing a patient's comfort during hemodynamic or respiratory extracorporeal support is essential to reduce toxicity and secondary complications.

Key words: Analgesia, benzodiazepines, delirium, dexmedetomidine, mechanical ventilation opioids sedation, neuromuscular blockade, pain, propofol

Background

Early deep sedation is associated with adverse outcomes and constitutes an independent predictor of hospital mortality in mechanically ventilated patients.[1] So, the new objective today is to go from full to light sedation with daily short cessations to reduce the risk of mortality induced by the drugs.

In 1846, a London dentist, James Robinson, demonstrated the administration of the anesthetic gas ether for the first time in England. This was also done a couple of months earlier by William Morton on the other side of the Atlantic Ocean in Boston. A few years earlier, in 1843, John Snow had experimented with ether for promoting anesthesia through respiration in his self-made research laboratory.[2] Ether gave John Snow the opportunity to bring his laboratory experience and clinical work to bear on a potent chemical whose properties were still mysterious.

Chloroform was introduced in 1847 by an Edinburgh obstetrician, James Young Simpson. John Snow studied chloroform as much as he had studied ether. He soon realized

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that accuracy of delivery and patient monitoring were even more important when administering chloroform than when administering ether because chloroform was much more potent.

Anesthesia at that time was still dangerous with many risks and unpredictable effects. It took a lot of time to make new safer forms of anesthesia with less overall risks. In 1952, Copenhagen was struck by a severe epidemic of poliomyelitis that included a large number of bulbar polio cases resulting in respiratory paralysis.[3] During the period from August to December, about 3,000 patients with polio were admitted, and of these, about 1,250 had some type of paralysis. During the first 3 weeks of the epidemic, 27 of 31 patients with bulbar polio died, 19 of them within 3 days of admission. Henry Lassen, the chief physician at the hospital stated: "Although we thought we knew something about the management of bulbar and respiratory poliomyelitis, it soon became clear that only very little of what we did know at the beginning of the epidemic was really worth knowing".[3] The introduction of manual bag ventilation early in the epidemic thanks to the anesthesiologist Bjørn Ibsen helped the patients with respiratory paralysis. Earlier in 1952, Ibsen had been involved in the treatment of a child with tetanus who was curarized and ventilated manually through a tracheostomy.[3] It is interesting to note that this early mechanical ventilation in the early 1950s was made using very light sedation. It was somewhat the precursor of modern sedation in ICU.

Drugs

In this review, drugs will be evaluated first by their pharmacology and then through the studies published. Sedative drugs will be evaluated first, then analgesic drugs, and finally neuromuscular blocking agents [Table 1].

Sedation

Sedation drugs used in the ICU include three main drug classes: benzodiazepines, propofol, and a-2 adrenoreceptor agonists. Sevoflurane and isoflurane, as a volatile anesthetic has also been used in the ICU. Drugs will be illustrated here below but evaluation of sedation will be studied further in our review.

Benzodiazepines

Lorazepam and midazolam are the two main benzodiazepines used for sedation in the ICU. They are drugs that enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_a$ receptor, resulting in a sedative with hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties.

Lorazepam has been used in the ICU for sedation in mechanical ventilation and to help patients with neurological problems including alcohol withdrawal syndrome or epilepsy. Early guidelines have proposed that lorazepam should usually be used in continuous intravenous (IV) infusion from 1 to 10 mg/h as per sedation level testing using the Richmond Agitation-Sedation Scale (RASS).[4,5]

Midazolam is now the most commonly used benzodiazepine for moderate sedation, has a fast onset of 1–5 min and 1–2.5 h duration of action, unlike other longer acting benzodiazepines.[6]

Both these benzodiazepines display dose-dependent kinetics and are eliminated by the kidneys and as such, dose reduction is required in case of renal failure.

Nowadays, ICU physicians try to reduce the use of benzodiazepines as this may prolong the induced coma. Therefore, light sedation with propofol and dexmedetomidine are preferred even with the need of light support of noradrenaline. Sometimes, sevoflurane is used as a surrogate as well with alfentanil or other opioids.

Remimazolam is a novel ultrashort-acting intravenous benzodiazepine sedative-hypnotic that significantly reduces

Table 1: Drugs for analgesia, sedation, and neuromuscular blockade[86]

Class	Agent	Time to onset	Loading dose	Half-life	Maintenance dose
Hypnotics	Midazolam	2-5 min	0.01-0.05 mg/kg	3-11 h	0.02-0.1 mg/kg/h
	Propofol	1-2 min	5 mcg/kg in 5 min	3-12 h*	5-50 mcg/kg/min
	Dexmedetomidine	5-10 min	1 mcg/kg in 10 min	1.8-3.1 h	0.25-0.75 mcg/kg/h
Analgesic	Morphine	5-10 min	2-4 mg	3-4 h	2-30 mg/h
	Sufentanil	5 min	0.5 mcg/kg	1.33 h	5-20 mcg/h
	Tramadol	10-15 min	100 mg	6 h	50-100 mg every 6 h
	Acetaminophen	5-10 min	1000 mg	2-4 h	1000 mg every 6 h
	Ketamine	30-40 sec	1-4 mg/kg	2.5 h	0.1-0.5 mg/min
NMBA	Cisatracurium	2-3 min	0.15-0.20 mg/kg	22 min	1-2 mcg/kg/min
	Rocuronium	1-2 min	0.6-1.0 mg/kg	60-70 min	9-12 mcg/kg/min

NMBA: neuromuscular blocking agents

the times to sedation onset and recovery.[7] In a recent trial that was conducted to confirm the recovery time from anesthesia of remimazolam-flumazenil versus propofol in patients undergoing endotracheal surgery under rigid bronchoscopy, remimazolam-flumazenil allows for faster recovery from anesthesia than propofol and is better tolerated hemodynamically.[7]

Propofol

Propofol is a short-acting medication approved in the late 80s that results in a decreased level of consciousness and a lack of memory for events and is believed to work at least partly via a receptor for GABA. Common side effects of propofol include hemodynamic instability and heart rate modification especially bradycardia. As it has a phospholipid vehicle, a long-term high-dose use could induce hypertriglyceridemia. Propofol has a rapid onset (1 min) and a short duration of sedation. This can be interesting in neurological patients when a clinical examination is necessary. Recovery is fast but can be delayed after more than 12 hours of use.[8] The maximal recommended dose is 4 mg/kg/h to impede a propofol infusion syndrome.[9]

Alpha-2 agonists

Clonidine and dexmedetomidine are the two main alpha-2 agonists used in the ICU (with dexmedetomidine being the most used one).

Clonidine stimulates presynaptic alpha-2 adrenoreceptors within the brainstem, decreasing norepinephrine release while enhancing parasympathetic activity. The sedative, analgesic, and anxiolytic effects of clonidine may be due to its effects on the locus coeruleus.[10] A systematic review and meta-analysis investigated the efficacy and safety of clonidine as a sedative in critically ill patients requiring invasive mechanical ventilation, but data remain insufficient to support the routine use of clonidine as a sedative in the mechanically ventilated population.[11]

Dexmedetomidine is an alpha-2 adrenoreceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus coeruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression.[12]

Both drugs have side effects including a dose-dependent risk of hypertension followed by hypotension and bradycardia. It is cleared by hepatorenal pathways and should be dose-adjusted in patients with hepatic or renal dysfunction.

Even if not common in the Unites States, a single agent for moderate sedation could be alpha-2 adrenoreceptor agonists.

Inhaled sevoflurane

Inhaled anesthetics may be ideal sedatives for the ICU because of their pulmonary elimination, limited amount of metabolism, bronchodilation, and cardioprotective effects. However, inhaled anesthetics are not widely used for sedation in the ICU and most modern ICU ventilators do not readily accommodate an anesthetic vaporizer. It is now possible to use an anesthetic conserving device that uses a syringe pump to deliver inhaled anesthetic in liquid form into the breathing circuit of a standard ICU ventilator.[13] It is the so-called anaconda system. The target is to keep end-tidal sevoflurane concentration between 1% and 1.5% minimum alveolar concentration. Sevoflurane has also the advantage to have no weaning issue in contrast with benzodiazepines for instance. One drawback is the initiation of nephrogenic diabetes insipidus.[14]

Comparing drug groups

Important questions were asked in the scientific literature to figure out whether the use of propofol, benzodiazepines, alpha-2 adrenoreceptor agonists, or even sevoflurane is advantageous for ICU sedation compared with the other sedatives.

The use of propofol in ICU sedation was compared to the use of benzodiazepines in 12 trials. They showed that, with propofol, patients had a shorter time to light sedation and a shorter time for extubation than with a benzodiazepine.[15] When looking at the data of large trials, we acknowledge that the use of propofol sedation allowed for a more rapid tracheal extubation than with midazolam, but this did not result in an earlier ICU discharge.[16] These data allow us to notice that using propofol for ICU sedation probably outweighs the usefulness of benzodiazepine sedation.

Randomized control trials compared dexmedetomidine and benzodiazepines for three main parameters: the duration of mechanical ventilation, the length of the ICU stay, and the prevalence of delirium. They globally included a little less than 3,000 patients. When looking at the studies with the lowest risk of biases, it appears that patients receiving dexmedetomidine had shorter periods for extubation and lower risks of delirium with patients receiving a benzodiazepine infusion instead.[17] Therefore, it seems that using dexmedetomidine for ICU sedation probably outweigh the advantages of benzodiazepine use, and thus, a conditional recommendation favoriting dexmedetomidine was issued.

Three other studies compared the use of dexmedetomidine with the use of propofol in the ICU. They showed no difference in extubation time. Even if there was no other

primary end point in these studies, they did not show any difference concerning the side effects like bradycardia or hypotension between patients sedated with propofol and the others with dexmedetomidine.[18]

Finally, comparing inhaled sevoflurane to IV drugs were covered by 15 trials. Volatile sedation administered through an anaconda system shortened the awakening time but did not show any difference in the lengths of the ICU and the hospital stay.[19]

Analgesia

Drugs used for analgesia are mainly opioids, used with or without other classes of analgesics.

Opioids

Opioids are the first category of drugs used to treat pain in ICU patients. This class of drugs is mainly used for mechanical ventilation, postoperative or post-traumatic pain, and technics (placement of catheters,…). We know however that these drugs can sustain disturbances of consciousness, prolong mechanical ventilation, and ICU stay.[20] High doses and long-term use can induce opioid-induced hyperalgesia. Long-term opioid use can also induce tolerance, physical dependence, and opioid withdrawal syndrome. Thus, it is obvious that optimal dosing is primordial to protect patients from all these possible side effects of opioids.[21] Support from pharmaceutical drugs and nonpharmaceutical management can be useful in these circumstances. Optimalisation of ICU pain management including opioid use has been summarized by the Society of Critical Care Medicine in 2018.[15]

Major opioid drugs include morphine, hydromorphone, meperidine, fentanyl, sufentanil, remifentanil, and methadone. In Europe, the type of opioid drugs used changes from country to another, and the opioids most used are morphine, fentanyl, and sufentanil (Morphine was preferred over fentanyl and sufentanil in Norway, UK, Ireland, Sweden, Switzerland, the Netherlands, Spain, and Portugal. Fentanyl was preferred in France, Germany, and Italy. Sufentanil was preferred in Belgium, Luxemburg, and Austria).[22]

Morphine is the oldest opioid drug used in medicine (the first time being more than 200 years ago). Its dose depends on several main points including the patient's tolerance and the metabolism and the excretion of the drug and its metabolites.[23] Its onset starts after 5 to 10 minutes and its half-life lays between 3 and 4 hours. It is used mainly on a continuous IV route but we can also titrate the IV or oral dose.[24] In postoperative and polytraumatized ICU patients, intrathecal morphine just prior to surgery has also been used.[25]

Hydromorphone has a low oral bioavailability, so the IV route remains the best for efficiency. Its onset and half-life are similar to morphine but its metabolites are inactive on pain. It has mainly been used for postoperative pain management in patients with renal impairment or a renal transplant because of the effects of the metabolites.[26]

Meperidine has a faster onset and a lower duration of action than morphine because it is more lipophilic. However, it is seldomly used in ICU mainly because of its decreased analgesic potency.[4]

Fentanyl, remifentanil, and sufentanil are the three liposoluble opioids. Fentanyl is 50 to 100 times more potent than morphine and has a rapid onset with a half-life of 2-3 hours.[27] Remifentanil, a fentanyl derivative has a much shorter half-life (2-3 minutes) due to the metabolization by unspecific esterases instead of being biotransformed by the liver. Sufentanil, on the other hand, is 5 to 10 times more potent than fentanyl but has roughly the same onset of action and duration time. The three drugs have been used in the ICU. Twenty years ago, the three drugs were compared in fast-track cardiac anesthesia. There were no significant statistical differences in postoperative ICU ventilation time, ICU stay, and hospital stay between the three drugs.[27] However, another study on patients under mechanical ventilation showed that remifentanil was associated with significantly less time spent on mechanical ventilation and in the ICU compared to sufentanil.[28] The difference was significant for patients ventilated no longer than four days but insignificant for patients ventilated more than four days.[28] When comparing the patients' comfort using either remifentanil or fentanyl in the ICU, no significant difference was seen.[29]

Alfentanil, being used mainly in short-term analgesia and in sedation with propofol, has not been used to maintain patients under sedation.[30]

Piritramide is a μ-agonist with similar properties to morphine. It is mainly used for postoperative pain relief. It has been used for patient-controlled intravenous analgesia and for continuous infusion in mechanically ventilated patients. The context-sensitive half-time of piritramide is lower than predicted from bolus kinetics, making the drug a suitable candidate for ICU analgesia.[31]

Methadone is the last opioid on our list to be used in the ICU. It has a very long duration of action with a half-life of 22 hours. Its onset of action starts after around 30 minutes with a peak effect after 2.5 hours. It can be used either to decrease the doses of the opioids used or in patients with a

resistance to other opioid drugs. One must be cautious about the QT interval increase, sometimes leading to Torsade de Pointes[32] and inducing auriculo-ventricular blocks.[33]

Other drugs

Acetaminophen, nefopam, ketamine, lidocaine, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used as adjuvant drugs to opioids. It also seems possible to use them without or with a reduced dose of opioids.

Acetaminophen is one of the most used drugs in pain management. It has been used in addition to opioid drugs; however, no data exist on the use of acetaminophen alone for pain management in the ICU. An interesting study has recently shown new data on its metabolism. Acetaminophen was mainly seen as an inhibitor of cyclooxygenase enzymes, but with the new data on the subject, the new analgesic mechanism includes its metabolization to N-acylphenolamine, which then acts on the transient receptor potential vanilloid 1 and cannabinoid 1 receptors in the brain.[34] We should be careful in its use in patients with liver failure.

Nefopam is a nonopioid analgesic that exerts its effect by inhibiting dopamine, noradrenaline, and serotonin recapture in both the spinal and supra-spinal spaces. A 20-mg dose has an analgesic effect comparable to 6 mg of morphine administered intravenously.[35]

Ketamine is an N-methyl-D-aspartate antagonist with emerging evidence assessing its use as a continuous infusion agent to provide concomitant analgesia and sedation. The role of ketamine as adjunctive therapy in mechanically ventilated patients is unclear. It has been used to reduce the dose of opioid drugs and their possible hyperalgesia side effect. Low doses were usually used with a loading dose of 0.5 mg/kg followed by a continuous IV dose of 1-2 μg/kg/h. No difference in side effects was seen when used with opioids versus with opioid use alone.[36] Lately, ketamine has shown potential benefit in several disease states including pain, alcohol withdrawal syndrome, status epilepticus, and acute agitation.[37] One must be careful with its use in patients with hypertension and/or coronary artery disease because of hypertensive side effects.

Lidocaine is a sodium channel blocker classified as a type Ib antiarrhythmic and is an amide local anesthetic. It has also been used to treat both acute and chronic pain conditions including postoperative pain hyperalgesia, presumably by affecting mechano-insensitive nociceptors.[38] Lidocaine as an adjunctive agent in the treatment of acute pain may help ICU patients who are refractory to opioids or those in whom opioid-induced respiratory depression is a concern.[39] It has also recently been used in the ICU after cardiac surgery with good results.[40] One must be aware of the possible hemodynamic alterations associated with lidocaine.

The last category of nonopioid drugs used in analgesia are NSAIDs. The main research in the ICU was its use in postoperative pain especially after cardiac surgery. Although a nonsignificative reduction in pain was demonstrated, one should remain cautious as adverse effects include acute renal injury and excessive bleeding.[41,42]

Regional anesthesia can, with single or continuous dosing, using neuraxial and peripheral catheters, play an important role in multimodal analgesia for pain management in the ICU. It provides superior pain control when compared to systemic treatments and it is associated with a lower risk of side effects. They are seldom used systematically for postoperative and trauma patients in the ICU, although injured patients could benefit from these techniques.[43]

Finally, we should be prudent and know the exact dosing and the risks of adverse effects when giving medications for IV, per os or intrathecal use.[15]

Nonpharmacologic pain therapy

Hypnosis, cybertherapy, music, relaxation technics, massage, and cold therapies have been proposed to decrease opioid drugs in pain management in ICU patients. Even if there are many studies looking at these therapies for ICU patients, effects of nonpharmacologic interventions in patients unable to self-report remain unknown.

Music therapy sessions were found to be effective for decreasing anxiety and promoting relaxation, as indicated by decreases in the bispectral index, heart rate, blood pressure, and respiratory rate over the intervention period in intubated patients during the weaning phase.[44]

Neuromuscular blockers

The first description of neuromuscular blocking agents (NMBA) use was shown in 1932 when it was given to control muscular spasms in tetanus.[45] Blockade drugs have been used in the ICU mainly for intubation but has been maintained for mechanical ventilation (in up to 90% of the patients[46]) as shown in a review 30 years ago.[47] They have also been used to stop shivering during therapeutic hypothermia following cardiac arrest, in elevated intracranial pressure and in status asthmaticus. Consequently, it seems essential to look at evidence-based data regarding the most appropriate use of neuromuscular blocking drugs in the ICU. More than 20 years later, the use of blockades was

shown to improve adjusted survival in acute respiratory distress syndromes (ARDS) at 90 days (Hazard ratio 0.68, confidence interval$_{95}$ 0.48-0.98, $P < .04$) in a 340-patient multicenter double-blind trail.[48] This was put to question 10 years later when, in the same pathology (moderate to severe ARDS), a multicenter trial enrolling 1,006 patients showed no significant difference in the 90-day mortality rate between the group receiving 48 hours of continuous IV administration of cisatracurium and the others receiving a placebo.[49]

Depolarizing agents

Depolarizing agents such as succinylcholine, which compete with acetylcholine, are mainly used for intubation because of its very short delay of action (30 seconds) and short half-life (5-10 minutes). However, succinylcholine can trigger malignant hyperthermia and it also increases plasma potassium levels; therefore, we must be cautious in its use especially with patients suffering from sepsis, burns, acute or chronic renal failure, prolonged immobility, stroke, or spinal cord injury.[50]

Amino-steroidal agents

Amino-steroidal agents include rocuronium, vecuronium, and pancuronium.

Rocuronium, an intermediate acting drug is very interesting as it can mimic, at high doses (4 x ED$_{95}$), succinylcholine action in rapid muscle paralysis for tracheal intubation. It is not associated with histamine release nor hemodynamic instability.

Vecuronium, an intermediate acting drug, and pancuronium, a long-acting drug, were not proposed as a NMBA in the ICU. This is due to vecuroniums and pancuroniums active metabolites inducing prolonged duration of action, ICU-acquired weakness, renal and hepatic failure, and tachycardia.

Benzylisoquinolinium drugs

Benzylisoquinolinium drugs include actracurium, cisatracurium, and mivacurium.

Mivacurium is a short-acting drug but without the potential to quickly induce a neuromuscular blockade. Like other drugs from the same family, it is degraded by the patient's body pH and temperature through the Hofmann elimination. This produces laudanosine which can induce seizures.

Cisatracurium (used during mechanical ventilation) and atracurium are intermediate-acting drugs. A recent observational study compared cisatracurium to vecuronium in ARDS patients under mechanical ventilation and showed that cisatracurium was associated with an increase in ventilator-free days and a decrease in the ICU stay but without any difference in the mortality rate.[51]

Drug interactions with NMBAs

Drug interaction has two main risks in the use of NMBA: resistance and prolonged action. The main drugs associated with resistance to neuromuscular blocking drugs include antiepileptic drugs (such as phenytoin and carbamazepine), ranitidine, theophylline, and calcium. Much more drugs are associated with the prolonged action of NMBA. In the ICU, these include cardiovascular drugs (such as furosemide, b-blockers, calcium blockers, quinidine, and procainamide), antibiotics (including aminoglycosides, tetracycline, clindamycin, and vancomycin), immunosuppressive drugs (such as corticosteroids and cyclosporine), potassium, magnesium, and lithium.

Drug monitoring

Monitoring the use of NMBA in the ICU by determining the level of neuromuscular blockade is essential to limit prolonged muscular paralysis. The monitoring is so important because repeated clinical qualitative and quantitative values of the depth of neuromuscular blockade may result in a decrease of the administrated dose of NMBA, and thus, decreasing the complications of these agents. This is shown in a limited number of studies which have demonstrated the clinical benefice of NMBA monitoring in the ICU.[52]

Drug reversal

Reversal agents are mainly used in operating theaters to restore baseline function and reduce the risk of postoperative residual paralysis. In the ICU, the use of reversal agents is limited. The two main classes are acetylcholinesterase inhibitors and sugammadex.

The main acetylcholinesterase inhibitor is neostigmine. It is mainly used in the train-of-four levels more than 3. It is used in association with glycopyrrolate to avoid bronchoconstriction and bradycardia induced by the acetylcholine increase.[53]

Sugammadex can antagonize rocuronium (seemingly being the most important amino-steroidal agent used in the ICU) and vecuronium. Sugammadex could be useful when the necessity of rapidly stopping the muscular blockade is needed for clinical evaluation as it has the ability of reversing deep neuromuscular blockades swiftly. Although it is rarely used in the ICU, as a rescue therapy for residual blockades and promoting enhanced recovery protocols in the ICU.[54]

Finally, NMBAs can prove to be lifesaving in patients with acute problems in the ICU. The best use is probably limited

in time during the ICU stay. Seeing their risks and their drug interactions, clinicians should understand the pharmacology, the monitoring, and the reversal for reducing the risks in multimodal sedation in complicated patients.

Evaluation of Sedation

Evaluation of sedation in ICU patients is very important nowadays (this was not really the case 20 years ago). A careful and thorough evaluation of the appropriate titration of sedative drugs is mandatory. The patient's comfort should be the primary goal in the ICU but achieving an appropriate sedation is challenging. Sedation scores seem to be one of the most interesting ways to realize this challenge. The most valid sedation scores are the Sedation-Agitation Scale (SAS) from the Ricker study and the RASS (Table 2 shows the two different scales).[55] The RASS has been evaluated in the ICU and also compared with the SAS but without any significant differences for patients.[5,56] It has been used to evaluate multiple sedatives. The last study compared dexmedetomidine and propofol in mechanically ventilated patients with sepsis who were being treated with recommended light-sedation approaches. The outcomes in the group receiving dexmedetomidine did not differ with the outcomes of the propofol group.[57]

Bi-Spectral Index (BIS) analysis, based on the processing of electroencephalographic signals, may overcome the restraints of the sedation scales and provide a more reliable and consistent guidance for the titration for an appropriate sedation depth.[58] Unfortunately, there is not sufficient evidence to systematically use the BIS monitoring for sedation in critically ill and mechanically ventilated adults.

Pain

The vast majority of ICU patients suffer from pain due to the underlying source of illness and the necessary procedures performed for the monitoring and care.[59]

It is often underestimated in the critically ill, especially among those who cannot self-report, so accurate assessment and management continue to be essential in their care. It is thus necessary to check if the patient is in pain through validated methods of pain assessment whether the patient is conscious or not. In conscious critically ill patients, self-reporting scales such as the Numeric Rating Scale is probably the best available way to estimate pain. This has been shown in 3 major studies.[60-62] In unconscious patients on the other hand, two main scales have been reported, the Critical Care Pain Observation Tool (CPOT) and the Behavioral Pain scale (BPS). These two scales have demonstrated the greatest reliability and validity for monitoring pain (their clinical assessments are shown in Table 3A and 3B).[63,64]

Drugs for pain management in the ICU have been described earlier in this review. Optimizing pain treatment is essential as pain pathways are closely interconnected

Table 2: Evaluation of sedation in ICU

	RASS term	RASS Description	SAS term	SAS Decription
+7			Dangerous agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
+6			Very agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT
+5			Agitated	Anxious or physically agitated, calms to verbal instructions
+4	Combative	Overtly combative or violent; immediate danger to staff	Calm and cooperative	Calm, easily arousable, follows commands
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
+2	Agitated	Frequent non-purposeful movement or patient–ventilator desynchrony	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands
+0	Alert and calm	Spontaneously pays attention to caregiver		
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice		
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice		
-3	Moderate sedation	Any movement (but no eye contact) to voice		
-4	Deep sedation	No response to voice, but any movement to physical stimulation		
-5	Unarousable	No response to voice or physical stimulation		

Table 3A: Behavioral Pain Scale (BPS)

Main Item	Clinical feature	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limb movement	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Mechanical ventilation compliance	Tolerating movement	1
	Coughing but tolerating	2
	Fighting the ventilator	3
	Unable to control	4

PBS ranges from 3 (no pain) to 10 (maximum pain)[63]

Table 3B: Critical Care Pain Observation Tool (CPOT)

Main Item	Clinical feature	Score
Facial expression	Relaxed	0
	Tense	1
	Grimacing	2
Body movement	No movement	0
	Protection	1
	Restlessness	2
Muscle tension	Relaxed	0
	Tense	1
	Very tense or Rigid	2
Mechanical ventilation compliance	Tolerating	0
	Coughing but tolerating	1
	Fighting the ventilator	2
Vocalization (extubated patients)	Talking or no sound	0
	Signing or moaning	1
	Crying out or sobbing	2

CPOT ranges from 0 (no pain) to 10 (maximum pain)[62]

to the systematic nervous system.[59] This means that pain can have physiological signs such as tachycardia, hypertension, and diaphoresis. Uncontrolled pain can lead to persistent adrenergic activation. This can worsen an already precarious metabolic energy expenditure. Furthermore, the postintensive care syndrome frequently (33% to 77%) includes chronic or post-ICU pain.[65] Consequently, it is very important to optimize treatment pain management in the ICU, but one must be careful as both pain and analgesic drugs can perpetuate the eventual presence of delirium.[66]

Delirium

Delirium is common in ICU patients. Even if delirium is a clinical diagnosis, the best way to diagnose it is to use screening tools such as the Confusion Assessment Method for the ICU (CAM-ICU).[67] We know that delirium is associated with a worsened patient outcome and increased ICU and hospital cost; it is therefore important to diagnose it quickly. Risk factors exist such as the use of benzodiazepines, blood transfusions, age, prior coma, dementia, and increased APACHE and ASA scores.[68] Confusion assessment method for the ICU (CAM-ICU), with its 9 evaluated items, has shown to have a high sensibility and specificity.[67] Testing patients regularly will help with the diagnosis. The outcomes are different depending on the delirium evolution. A positive delirium screening in ICU patients is associated with longer hospital stays and cognitive impairment at 3 and 12 months after discharge.[69] When delirium is rapidly reversible, long-term outcomes are the same as the outcome of patients without delirium.[70] Pharmacological prevention of delirium does not seem to help patients. Treating ICU patient suffering from delirium with dexmedetomidine has been studied especially in mechanically ventilated patients and it can help those patients by decreasing the time of extubation but not the length of the ICU or hospital stay.[71]

Finally, delirium is the most common manifestation of acute brain dysfunction in critically ill patients. It is associated with both poor short-term outcomes and adverse long-term sequelae related to the ICU stay.[72] However, seeing the multifactorial etiology, a multicomponent therapy will probably be the most adapted to reduce the risk of delirium in the ICU, but more research is needed. This is another reason to avoid benzodiazepines for sedation in the ICU.

Long-Term Evolution

After their ICU stay, patients frequently have prolonged and poorly understood forms of cognitive dysfunction characterized by new deficits in executive function or global cognition.[73] We know that the rate of long-term cognitive dysfunction after the ICU stay is increasing, probably due to the larger number of acutely ill patients treated in ICUs. It is even more severe with older patients, in whom cognitive dysfunction is associated with an increase in institutionalization and secondary hospitalization.[74] In conclusion, cognitive impairment after critical illness is very common and, in some patients, it persists for at least a year. Post-ICU patients with a longer duration of delirium are more likely to have cognitive deficits than those with a shorter duration of delirium.[75]

Evolution in our Hospital

Since the year 2000, the beginning of my ICU work, sedation of patients has changed a lot in the ICU. In the beginning, patients were sedated with a benzodiazepine and a morphine derivate (sufentanil) in association with a neuromuscular blocking agent. Stopping sedation needed some time before the patient was sufficiently awake to be able to be

extubated. The duration between the sedation cessation and extubation could be long, especially in patients with hepatic or renal failure. Since 2010, with the whole medical team and in collaboration with nurses and pharmacists, we started proposing a systematic handling of ICU patients for sedation. This permitted us to propose a sedation protocol in our three ICUs using mainly morphine as an analgesic and midazolam as a sedative (the proposed protocol is shown in Figure 1a). NMBA was proposed to be used only in ARDS and in postcardiac arrests but not in every mechanically ventilated patients.[47] A simplified sedation evaluation score was used: the Brussels Sedation score.[76] Five years later, there was a revision in the sedatives used in our ICUs. We changed our anesthesia drugs only keeping midazolam for patients with epilepsy or patients with recreational drug or ethanol intoxication.[77] For all the other patients, sedation was attained with propofol or dexmedetomidine.[57,78] Analgesia was maintained especially with morphine and sufentanil, otherwise (WHO Level 1 and 2) analgesia was proposed with acetaminophen, ketamine, lidocaine, and NSAIDs (the new protocol in 2015 is shown in Figure 1b). This proposition was followed by an evaluation of drug consumption as from 2014, to see if our changes in ICU sedation could have an impact on the quantities of drugs used annually in the following years after protocol change (as shown in Figure 2a [sedation] and b [analgesia]). The new protocol caused a decrease in the sedative drugs used before with an important decrease in midazolam use over the years to be able to focus on propofol and dexmedetomidine. The purpose was to be able to evaluate and decrease sedation rapidly. The use of opioids and especially morphine was reduced considerably and, furthermore, it was used in direct IV dosing if needed instead of continuous IV dosing. Finally, family visits seem to help patients in their evolution. In the future, an organization structured on the needs of the patient and their family is mandatory in designing a new ICU. The main aims in the design of a new department should be patient-centered care, safety, functionality, innovation, and a future-proof of concept.[79]

Discussion

Taking care of severely ill ICU patients pushes us to use sedative drugs with analgesics and sometimes neuromuscular blocking agents. The actual question in the literature is whether deep sedation, light sedation, or no sedation should be used for these critically ill patients. The way it is induced is also a very important question. Must we systematically add opioids or can other analgesic drugs be used instead or together with opioids? Are NMBAs useful in the ICU and, if yes, for which patients? All these questions need to be answered for an ideal patient care in the ICU.

The first question, we ask ourselves, is: what the best sedation level for patients in the ICU is. We know that the aim of sedation is to minimize oxygen consumption and facilitate a patient's ability to remain comfortably connected to a ventilator, although the exact dose to do this is unknown. As said before, it has been recognized that deep and prolonged sedation can increase the duration of mechanical ventilation, the delay in the weaning, the risk of neuromuscular function impairment, and it can produce delirium, have side effects specific to certain sedative drugs, and increase the mortality rate.[80] Daily interruption of sedation was the first change in patient care as compared to full sedation used 20 years ago. This interruption was associated with a decrease in the duration of mechanical ventilation.[81]

When going further in the research of the best way to handle severe ICU patients, proposing light sedation could be a logical concept. Even if the exact levels of RASS for light sedation are not really known, a RASS between -2 and +1 seems logical in the studies that have approached the concept of light sedation. Measures of the levels of sedatives in the plasma or subjective clinical assessments of the patient's wakefulness should not be considered a part of the definition of levels of sedation.[15] Studies comparing light versus deep sedation, whatever the drugs used, looked at outcomes such as 90-day mortality, time to extubation, delirium, tracheostomy, cognitive and physical functional decline, depression, and post-traumatic stress disorder. They show that light sedation was associated with a shorter time for extubation and a reduced tracheostomy rate but no decrease in the 90-day mortality rate nor a reduction in the incidence of delirium or self-extubation.[82-85] No study evaluated the impact of light versus deep sedation on cognitive or physical functioning.

One step beyond is to compare light versus no sedation in severe ICU patients even if omitting sedation for mechanical ventilation is complicated due to the reluctance of caregivers to nurse patients who are agitated or in pain.[80] In a recent trial comparing mechanically ventilated ICU patients with light sedation versus no sedation at all in a multicenter trial, there was no significant difference in the mortality rate at 90 days between those assigned to a plan of no sedation and those lightly sedated patients with daily interruptions.[86] This led to questioning. First, the PaO_2/FiO_2 ratio was low and could lead to forego sedation. Second, nearly 15% of the patients declined to participate in the trial. Furthermore, they observed that the nonsedation group had 1 more day free from coma or delirium than the sedation group, but because of the lack of adjustment for multiple comparisons, no inferences could be made from this result. Although more events of accidental extubations occurred in

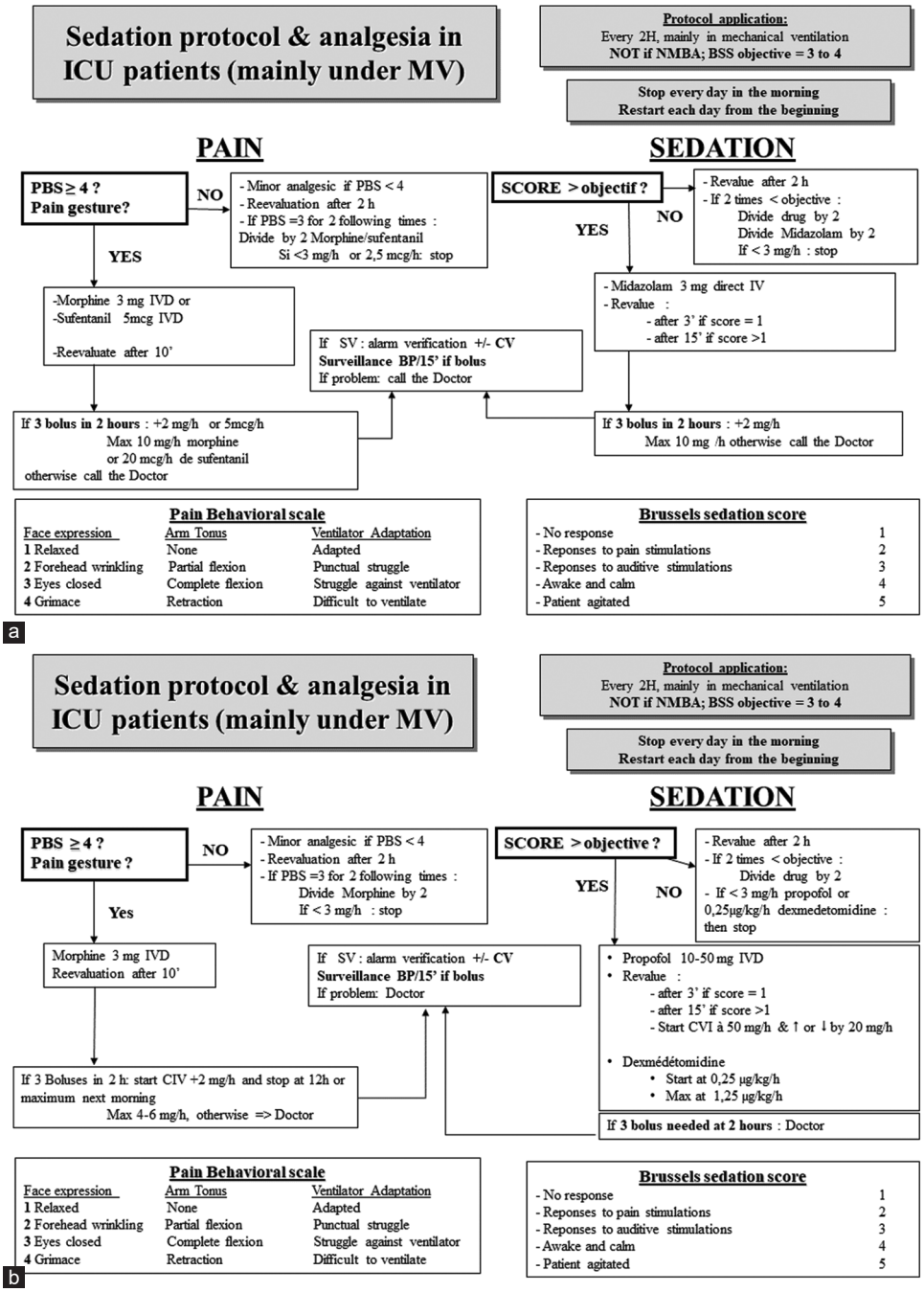

Figure 1: (a and b) Proposed sedation protocol in ICU patients in 2010 and 2015. (a) 2010 (b) 2015

the nonsedation group in the trial, few led to reintubations within 1 hour. Besides, more than a quarter of the patients in the nonsedation group received sedation during the first 24 hours after randomization. In addition to that, when looking at the Kaplan–Meier estimates of survival at 90 days, we see that survival curves change at day 15 and that patients without sedation decrease their survival after ICU discharge. Finally, the trial may have been underpowered because it depended on the outcomes from the preliminary trial to calculate the power to detect a difference in the mortality rate. In conclusion, we should reinforce the need to monitor sedation clinically aiming the discontinuation as soon as possible or at least interrupting it daily.[80] Furthermore, the possible occurrence of post-traumatic stress disorder should be taken into account before totally stopping sedation in ICU patients under mechanical ventilation.[87]

Conclusion

Sedation in ICU patients has evolved a lot in the last 20 years. Decreasing the use of benzodiazepines and replacing them by propofol and/or dexmedetomidine has been proposed

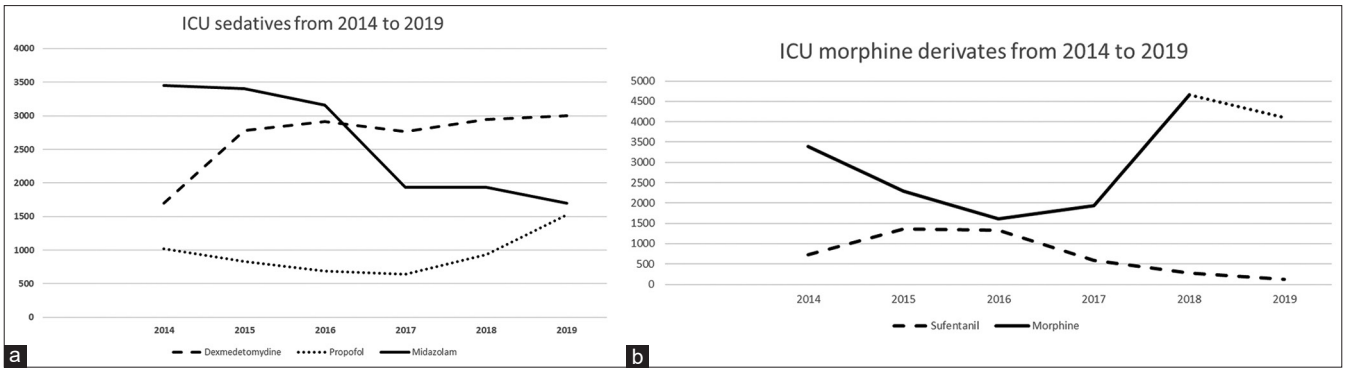

Figure 2: (a and b) Change in drug use in the last 5 years in our ICU. (a)Sedation (b) Opioids use for analgesia

to try to decrease post-ICU delirium. It permits us to daily evaluate patients to be able to wean them from mechanical ventilation. Analgesia is used with opioids when necessary but continuous IV drugs are less used to adequate the drugs with the pain and wean continuous IV analgesia. Other analgesics rather than opioids are preferred whenever possible. Neuromuscular blocking agents are only used in postcardiac arrest and less used in ARDS seeing the new literature on the subject. Finally, optimizing family visits permits a social impact on patients and family and a possible decrease in the needed drugs and in the ICU stay.

Abbreviations

IV: Intra-Venous
ICU: Intensive Care Unit
GABA: Gamma-Amino-Butyric Acid
RASS: Richmond Agitation-Sedation Scale
ACD: Anaconda system
MAC: Minimum Alveolar Concentration
ARDS: Acute Respiratory Distress Syndrome
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
NMBA: Neuro-Muscular Blocking Agents
SAS: Sedation-Agitation Scale
CPOT: Critical care Pain Observation Tool
BIS: Bispectral index
BPS: Behavioral Pain Scale
CAM-ICU: Confusion Assessment Method for the ICU
PTSD: Post-Traumatic Stress Disorder

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Our thoughts are also with Professor David de Bels (first author) who passed away at the age of 56 years (in April 2022) before the submission of this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Highlights

Sedation in the intensive care unit (ICU) has changed a lot during the last 20 years. Patients, who were fully sedated and under mechanical ventilation and neuromuscular blockades, are nowadays awake under very low sedation. Evaluating the side effects of the different drugs used in the ICU, including sedation pain and delirium, and searching for alternative ways to take care of the patients will help us minimize the negative implications of a long ICU stay, use the best possible medication at the lowest effective dose, and better the quality of life of these people after hospitalization.

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Conflicts of interest

There are no conflicts of interest.

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