The goals of analgesia and sedation at the intensive care unit (ICU) are to facilitate mechanical ventilation, prevent patient and caregiver injury, and avoid the psychological and physiologic consequences of inadequate treatment of pain, anxiety, agitation, and delirium.

Most ICU patients, especially the surgical and trauma ones, routinely experience pain at rest and with routine procedures. Treating pain in ICU patients depends on a clinician’s ability to perform a reproducible pain assessment and to monitor patients over time to determine the adequacy of therapeutic interventions to treat pain. Implementation of behavioral pain scales improves ICU pain management and clinical outcomes, including better use of analgesic and sedative agents and shorter durations of mechanical ventilation and ICU stay. Opioids are the primary medications for managing pain in critically ill patients. Multimodal approach to pain management in ICU patients has been recommended.

Sedatives are commonly administered to ICU patients to treat agitation and its negative consequences. Sedation strategies using nonbenzodiazepine sedatives (propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients. It is recommend daily sedation interruption or a light target level of sedation be routinely used in adult intensive care patients using mechanical ventilation. Delirium affecting up to 80% of mechanically ventilated adult ICU patients.

ICU protocols that combine routine pain and sedation assessments, with pain management and sedation-minimizing strategies, along with delirium monitoring and prevention, may be the best strategy for avoiding the complications of oversedation.

Protocolized pain, agitation and delirium assessment (PAD ICU), is significantly associated with a reduction in the use of analgesic medications, ICU length of stay, and duration of mechanical ventilation.

Key words: pain, intensive care unit, analgesia, sedation

INTRODUCTION

ICU (Intensive Care Unit) patients often suffer from undertreated and unrecognized pain, with potentially serious physical and psychological effects. The accurate assessment of pain in ICU is very difficult. ICU patients are less able to communicate their pain to us than non-ICU patients and they are frequently sedated. Pain management is an essential component of the delivery of quality care for a critically ill patient. Being ill in an ICU is nearly always very frightening and may require a number of painful or uncomfortable procedures.

The reasons why do we need pain control and sedation are: patient comfort, early mobilization, facilitate patient-ventilator synchrony, optimize oxygenation, delirium and delusional memories influence the likelihood of patients having long term psychological effects, judicious use of sedative agents, decrease length of mechanical ventilation, reduce ICU length of stay (LOS), and, pain therapy is basic human right. But, how much do we really think about ICU patient’s personality?

Pain, agitation, and delirium are all extremely common in ICU patients that they’ve been termed the “ICU triad” (Fig. 1). No one knows exactly how common each is, because ICU patients are often too delirious to complain of pain; or their agitation hides their delirium; or their unidentified pain may cause their agitation.
PAIN IN ICU PATIENT

According to numerous studies up to 70% of patients complained moderate or severe pain after surgery and up to 50% of patients complained traumatic memory of their ICU stay. Most ICU patients, especially the surgical and trauma ones, routinely experience pain at rest and with routine ICU procedures. Adequate analgesia should be a fundamental part of this approach. Sedation should never be given as a substitute for analgesia. Unrelieved pain has serious side-effects, therefore the containment of such a stressor is vital. The chronic activation of the catabolic process of the stress response can ultimately cause multiple system dysfunction. The physiological changes of unrelieved pain have an impact on the cardiovascular, gastrointestinal, respiratory, genitourinary, musculoskeletal and immune systems. Increased heart and breathing rates facilitate the increasing demands of oxygen and other nutrients to vital organs. The physiological changes that take place can also induce vomiting and potentially can pre-empt chronic pain conditions. Psychological and cognitive adverse effects are also relatively common. Good acute pain management, including an expert knowledge of analgesic drugs and an understanding of the physiological effects of pain, is an essential element of ICU pain management.

PAIN ASSESSMENT

Routine pain assessments in adult ICU patients are associated with improved clinical outcomes. Pain assessment, especially if protocolized, has been significantly associated with a reduction in the use of analgesic medications, ICU length of stay (LOS), and duration of mechanical ventilation. Pain assessment is essential for appropriate treatment, especially when part of a comprehensive pain management protocol. Although the quality of evidence is moderate, a strong recommendation for performing routine pain assessments in all ICU patients is appropriate, as the benefits strongly outweigh the risks.

Physiological indicators such as hypertension and tachycardia correlate poorly with more intuitively valid measures of pain, but pain scales such provide structured and repeatable assessments and they are currently the best available methods for assessing pain. The Behavioral Pain Scale (BPS) and the CriticalCare Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain scales for monitoring pain in medical, postoperative, or trauma (except for brain injury) adult ICU patients who are unable to self-report, and in whom motor function is intact and behaviors are observable, according to the available evidence. The BPS has three categories of behavior: the patient’s facial expression, the movement of their upper limbs, and their compliance with mechanical ventilation. The BPS provides descriptions of different behaviors which may be observed and assigns a score to each one. Higher scores are associated with greater pain. An overall pain score is then calculated, ranging from three (no pain) to twelve (worst possible pain). CPOT is very similar to the BPS, but includes vocalisation as an additional category of behavior.

TREATMENT OF PAIN

Treating pain in ICU patients depends on a clinician’s ability to perform a reproducible pain assessment and to monitor patients over time to determine the adequacy of therapeutic interventions to treat pain. Implementation of behavioral pain scales improves ICU pain management and clinical outcomes, including better use of analgesic and sedative agents and shorter durations of mechanical ventilation and ICU stay.

Opioids are the primary medications for managing pain in critically ill patients because of potency, concomitant mild sedative and anxiolytic properties, and their ability to be administered by multiple routes. The optimal choice of opioid and the dosing regimen used for an individual patient depends on many factors, including the drug’s pharmacokinetic and pharmacodynamic properties. Recommended opioids include fentanyl, remifentanil, morphine and hydromorphone. The choice of intermittent vs. continuous IV strategies may depend on drug pharmacokinetics, frequency and severity of pain and the patient’s mental status.

Several other types of analgesics or pain-modulating medications, such as local and regional anesthetics (e.g., bupivacaine), nonsteroidal anti-inflammatory medications (e.g., ketorolac, ibuprofen), IV acetaminophen, and anticonvulsants, can be used as adjunctive pain medications to reduce opioid requirements (Table 1). However, their safety profile and effectiveness as sole agents for pain management have not been adequately studied in critically ill patients. Regional or neuraxial modalities may also be used for postoperative analgesia following selected surgical procedures. Adverse effects of epidural analgesia are more common with morphine than fentanyl. The incidence of respiratory depression is equivalent with epidural and intravenous morphine.

Complementary, nonpharmacologic interventions for pain management, such as music therapy and relaxation techniques, may be opioid-sparing and analgesia-enhancing; they are low cost, easy to provide, and safe. Few studies have been published on the effectiveness of nonpharmacologic interventions in these patients.

It is suggested that for other types of invasive and potentially painful procedures in adult ICU patients, preemptive analgesic therapy and/or nonpharmacologic interventions may also be administered to alleviate pain.

Multimodal approach to pain management in ICU patients has been recommended.

AGITATION AND SEDATION

Agitation and anxiety occur frequently in critically ill patients and are associated with adverse clinical outcomes. Sedatives are commonly administered to ICU patients to treat agitation and its negative consequences. A small percentage of critically ill patients requires deep sedation. Patients undergoing mechanical ventilation...
usually receive some degree of pharmacologic sedation, because of the anxiety and discomfort that are widely attributed to the experience.\textsuperscript{10} ICU patients have historically been oversedated, unnecessarily extending ventilator days and ICU stays. Only a minority of critically ill patients require deep sedation, for conditions such as severe respiratory failure (e.g., ARDS), intracranial hypertension, refractory status epilepticus, and those receiving neuromuscular blocking agents. Patients undergoing mechanical ventilation usually receive some degree of pharmacologic sedation, be-

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset after IV loading dose</th>
<th>Metabolism/Elimination</th>
<th>Adult dose (IV)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>2-5 min</td>
<td>Liver oxidation via CYP450; metabolism impeded by other drugs metabolised by CYP450</td>
<td>Bolus dose 1-5mg (0.03mg/kg/h)</td>
<td>Continuous infusion not recommended; increase in context sensitive half-life</td>
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<td></td>
<td></td>
<td>Active metabolite</td>
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<tr>
<td></td>
<td></td>
<td>1-hydroxymethyl-midazolam</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Extensive protein binding</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Half-life 3–11 hr</td>
<td></td>
<td></td>
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<tr>
<td>Lorazepam</td>
<td>15-20 min</td>
<td>Liver glucuronidation to inactive metabolites</td>
<td>Bolus dose 2-4 mg every 2-4 h</td>
<td>Independent risk factor for developing delirium. Propylene glycol accumulation with prolonged use leading to metabolic acidosis and hyperosmolality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life 8–15 hr</td>
<td></td>
<td></td>
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<tr>
<td>Diazepam</td>
<td>2-5 min</td>
<td>Metabolized by hepatic desmethylation and hydroxilation</td>
<td>Bolus 1-5 mg</td>
<td>Respiratory depression, hypotension, phlebitis</td>
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<tr>
<td></td>
<td></td>
<td>Half-life 20–120 hr</td>
<td></td>
<td></td>
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<tr>
<td>Propofol</td>
<td>1-2 min</td>
<td>Conjugation in liver to inactive metabolites</td>
<td>0.5-3 g/kg/h</td>
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<td></td>
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<tr>
<td>Dexmedetomidine</td>
<td>5-10 min</td>
<td>Complete biotransformation in liver Half-life 1.8–3.1 hr</td>
<td>Loading dose 1μg/kg over 10 min. Maintenance 0,05-0,7μg/kg/h</td>
<td>Biphasic cardiovascular effect: transient hypertension and bradycardia with loading dose; hypertension and bradycardia is then seen, especially in hypovolemic patients; loss of airway reflexes</td>
</tr>
<tr>
<td>Morphine</td>
<td>15-20 min</td>
<td>Hepatic metabolism - 80% morphine-3-glucuronide with no analgesia - 20% morphine-6-glucuronide with potent analgesia</td>
<td>Loading dose 1-1.5 mg iv every 5 min. Max 0.5 mg/kg. Maintenance 2-4 mg/h. Infusion lead to prolonged elimination half-life</td>
<td>Respiratory depression. Histamine release with hypotension</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2-5 min</td>
<td>Hepatic metabolism to non-active metabolites Accumulation due to organ-dependent metabolism</td>
<td>Loading dose 0.5-1μg/kg iv every 5 min. Max 2μg/kg. Infusion 5-10μg/kg/h titrated at 1-2 μg/kg/h increments</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>1 min</td>
<td>Metabolised by non-specific esterase in plasma, red blood cells and interstitial tissue</td>
<td>Starting infusion 6-9 μg/kg/h. Titrate 1.5μg/kg/h</td>
<td>Respiratory depression. Hypotension</td>
</tr>
</tbody>
</table>
cause of the anxiety and discomfort that are widely attributed to the experience. Of the sedation scales described, The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients. For the majority of patients undergoing mechanical ventilation in an ICU, an appropriate target is a score of 3 to 4 on the Riker Sedation–Agitation Scale (which ranges from 1 to 7, with scores of <4 indicating deeper sedation, a score of 4 indicating an appearance of calm and cooperativeness, and scores of =5 indicating increasing agitation) or a score of -2 to 0 on the Richmond Agitation–Sedation Scale (which ranges from -5 to +4, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation, and with 0 representing the appearance of calm and normal alertness). Sedatives that are commonly used in the ICU are the benzodiazepines midazolam and lorazepam (and to a lesser extent, diazepam), the short-acting intravenous anesthetic agent propofol, and dexmedetomidine. Sedation strategies using non-benzodiazepine sedatives (propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients. Propofol infusion syndrome is an adverse drug event associated with high doses (>4 mg/kg per hour or >67 µg/kg per minute) and long-term (>48 hours) use of propofol.

It is recommended daily sedation interruption or a light target level of sedation be routinely used in adult intensive care patients using mechanical ventilation and it is suggested that analgesia-first sedation be used in mechanically ventilated adult ICU patients. Benzodiazepines are associated with an increased duration of mechanical ventilation and ICU length of stay when compared with propofol or dexmedetomidine, and may be associated with a greater incidence of delirium. It is suggested non-pharmacological sedation therapy: Good communication with regular reassurance from nursing staff; Environment control such as humidity, lighting, temperature, and noise; Explanation prior to procedures, touching and message; Management of thirst, hunger, constipation, and full bladder; Variety for the patient (e.g. radio).

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**TABLE 2**

"ICU PAIN, AGITATION, AND DELIRIUM (PAD) CARE BUNDLE" ADAPTED FROM BARR j. (3)

**Pain**
- ICU patients routinely experience pain at rest and with ICU care. Procedural pain is common in ICU patients
- Assess and treat pain first, then sedate (analgo-sedation)
- The BPS and CPOT are the most valid and reliable behavioral pain scales (B)
- Threat significant pain: NRS ≥ 4, BPS ≥ 6, or CPOT ≥ 3
- Use appropriate pain management strategies (patient specific)
- Administer pre-procedural analgesia
- Multimodal therapy should be considered

**Agitation/Sedation**
- Minimize sedative use, avoid over-sedation
- Sedation goals: patient is responsive, aware and able to purposely follow command* (RASS = 0 to -2 or SAS = 3 to 4)
- Maintaining lighter levels of sedation in ICU patients is associated with improved clinical outcomes (B)
- Choose sedatives than minimize side effects (patient-specific)

**Delirium**
- Delirium risk factors include: pre-existing dementia, HTN, history of alcoholism, and a high severity of illness at baseline; coma; and benzodiazepine use
- Routinely monitor ICU patients for delirium. The CAM-ICU and ICDSC are the most valid and reliable instruments for this purpose
- When sedation is required in delirious ICU patients, suggest using dexmedetomidine rather than benzodiazepine infusions for sedation in these patients.

* Performs 3 out of 5 commands: open eyes, maintains eye contact, squeezes hand, sticks out tongue, wiggles toes.
**DE LIR IUM**

Cognitive impairment after anesthesia and surgery (postoperative cognitive dysfunction) is a recognized clinical phenomenon. As early as 1955, it was described by Bedford in the Lancet under the designation “adverse cerebral effects of anaesthesia on old people”.

Delirium, as a manifestation of acute brain dysfunction, is an important independent predictor of negative clinical outcomes in ICU patients, including increased mortality, hospital LOS, cost of care, and long-term cognitive impairment consistent with a dementia-like state. Acute central cholinergic deficiency is one of the most widely-accepted explanatory theories and decreased GABA-ergic activity.

Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: preexisting dementia; history of hypertension and/or alcoholism; and a high severity of illness at admission. Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients.

ICU personnel often underestimate the presence of delirium in patients because it frequently presents as hypoactive rather than hyperactive delirium. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools in adult ICU patients.

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**FIGURE 1.** CAUSES AND INTERACTIONS OF PAIN, AGITATION, AND DELIRIUM (PAD) [ADAPTED FROM READE MC].
CONCLUSION

The goals of ICU analgesia and sedation are to facilitate mechanical ventilation, prevent patient and caregiver injury, and avoid the psychological and physiologic consequences of inadequate treatment of pain, anxiety, agitation, and delirium. Optimal analgo-sedation strategy in the critically ill should achieve effective analgesia, targeted sedation and reduced risk of delirium and agitation. Protocolized pain, agitation and delirium (PAD) assessment, is significantly associated with a reduction in the use of analgesic and sedative medications, ICU length of stay, and duration of mechanical ventilation.

SUMMARY

ANALGEZIJA I SEDACIJA U JEDINICI INTENZIVNE TERAPIJE (ICU)

Cilj analgosedacije u Jedinki intenzivne terapije (ICU) je da se olakša pacijentima mehanička ventilacija, spreče dodatna oštećenja i izbegnu psihološke i fiziološke posledice usled neadekvatno lećenog boli, anksioznosti, agitacije ili delirijuma. Većina pacijenata u jedinici intenzivnog liječenja (ICU), posebno hirurški i traumatizovani pacijenti, obično osećaju bol u miru, ali i prilikom izvođenja rutinskih procedura. Terapija bila veoma je bitna komponenta kvalitetne nege i terapije kritično bolesnih pacijenata. Lećenje boli kod pacijenata u ICU zasnovan je na osnovi mogućnosti kliničara da adekvatno proceni bol, da sve vreme prati bolne reakcije pacijenata, na osnovu čega se određuje adekvatnost primenjene analgetike i sedativa. Korišćenje bihejvioralnih skala za procenu bol a, uznemirenosti i delirijuma u ICU (PAD integracija) značajno je povezana sa smanjenjem upotrebe analgetika i sedativa, trajanjem mehaničke ventilacije i dužinom boravka u ICU.

REFERENCE: