Pain Management in Critically Ill Patient

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3.1 Introduction

Staying in intensive care units (ICUs) has been described as a dramatic human experience, and pain is a major contributor. Indeed, pain is commonly reported by patients admitted to ICUs [1]. Surgery, invasive devices or baseline conditions may all contribute to its onset or exacerbation. Among many factors, tracheal intubation, mechanical ventilation and nursing are reported as major sources of pain or discomfort in those patients [2].

Pain is not only unacceptable as a human experience but is also a major contributor to morbidity of ICU patients, both in terms of increased incidence of delirium and requirements of sedative/analgesics with their side effects. Thus, prevention and treatment of pain are morally mandated and part of a good medical practice in ICUs [3–5].

An appropriate pain control allows to reduce the sympathetic burden of the patient, reducing oxygen consumption and insulin resistance and possibly contributing to immune modulation [6]. In critically ill patients, control of pain is a prerequirement of agitation control, i.e. an agitated patient should be assessed for the need of analgesia prior to be sedated. This approach, the so-called analgo-sedation, has proven efficacious in reducing the use of sedatives in ICU, thus contributing to a reduced rate of delirium, shorter length of stay and better outcomes [7]. Finally, incidence of long-term pain, which can occur in ICU survivors, can be reduced by an optimal pain control during the ICU stay [5].

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3.2 Physiology

The "physical feeling of pain" originates in tissues and travels to the brain via a simple neural network:

- The first sensitive neuron ("pseudo-unipolar") senses the local release of mediators of tissue damage such as bradykinin, substance P, prostaglandins, potassium and others through its dendritic ends and activates the second sensitive neuron in the medulla (spinal-thalamic neuron).
- The second sensitive neuron transmits the painful sensation to the thalamus (spinal-thalamic tract).
- The thalamic-cortical tract transmits the painful feeling to the cortex, where pain becomes consciously perceived and a response is eventually elaborated.

When the thalamus is activated, a modulating, descending response is also built that starts in the periaqueductal grey matter and acts at spinal levels, inhibiting the activation of spinal-thalamic tract by the pseudo-unipolar neuron [2]. This mandates a "multimodal approach" to analgesia, i.e. many different analgesic techniques or drugs can be simultaneously employed to block pain at different levels (see Sect. 3.3). As an example, opioids or paracetamol blocks the transmitting of pain from periphery; nonsteroidal anti-inflammatory drugs (NSAIDs) reduce local release of mediators; local anaesthetics inhibit the action potential travelling along pain tracts, peripherally or centrally [8, 9]. Clinically, multimodal analgesia has been suggested as a tool to implement the synergistic effect of analgesics reducing their doses and side effects [10].

3.3 General Principles

3.3.1 Assessment of Pain in ICU

Being a subjective feeling, pain can be very difficult to assess in ICUs, particularly in semiconscious or intubated patients, whose communication skills can be variably impaired. Thus, routine assessment of pain and need for analgesics is recommended by many guidelines [11–13].

In patients who can speak and/or communicate, visual analogue scales (VASs) may be used, which include continuous or discrete numeric scales. VASs have the advantage of being easy to apply and not expensive and are globally validated and accepted as a tool to assess pain and pain control [14].

In semiconscious or intubated patients, pain is suspected when facial expressions like grimacing or signs of sympathetic activation such as tachycardia, hypertension or tachypnoea are seen [15]. The Behavioral Pain Scale and the Critical Care Pain Observation Tool (CPOT) are tools that include behaviours and sympathetic activation as part of a global evaluation of discomfort in ICU patients [16–18].

All these tools can be used not only to assess pain but also to drive therapy. As for sedation, pain control should be patient-centred and goal-directed. Even though the goal of analgesia should always be the complete abatement of pain, side effects of analgesics must be taken into account too (e.g. respiratory depression or ileus); thus, a minimum level of pain, which could be acceptable for the single patient, needs sometimes to be targeted and tolerated to avoid these effects. Pain assessment tools may help to attain and maintain this level.

3.3.2 Multimodal Analgesia

Most of the evidence about analgesia in ICUs involve surgical patients admitted postoperatively. The general principles of acute pain management in these patients applies to ICU patients too. As stated above, a combination of techniques, drugs and routes of administration is generally recommended to optimise analgesia and reduce the side effects of single agents, particularly opioids. Opioid-driven respiratory depression and ileus can contribute to a substantially increased ICU-LOS; tolerance and opioid-induced hyperalgesia can ensue, making pain control difficult to attain [19]. However theoretically advantageous, multimodal analgesia is considered a standard of care only for postoperative, ICU patients, while many medical patients can be safely managed with single, low-dose analgesics [13, 20].

Even though intravenous infusion is generally preferred in ICU patients, oral administration can be considered in those whose gastrointestinal tract is normal, i.e. when oral or enteral feeding is well tolerated [21]. Sublingual administration can be considered as well, particularly for postoperative patients needing morphine or sufentanil [22]. Subcutaneous or intramuscular administration should be avoided because of potentially inadequate absorption due to hypoperfusion or tissue oedema; additional pain and risk of hematoma/local infection counter-indicate this route.

Intravenous administration can be done in boluses or as continuous infusions. Boluses can be administered "as needed", possibly using an assessment tool like the VAS as a target; or they can be given as a "pre-emptive" analgesia, i.e. analgesics are given just before the painful stimulation. This last approach is preferred in otherwise "pain-free" patients who will face a single painful stimulation, like the insertion of a chest drain [23].

If patients can cooperate, patient-controlled analgesia (PCA) is the gold standard of pain control. In this case, the patient is instructed to self-administer a bolus of analgesic when she or he feels is necessary to achieve pain control. A safe interval lock-time can be chosen to avoid overdosing; if needed, a background, continuous infusion can be added to optimise pain control. In postoperative patients, PCA has been shown to be the most effective and safe modality of analgesic administration [23].

In a multimodal approach, these modalities of infusion (boluses as needed, pre-emptive boluses or PCA) can be applied also to epidural infusion. Epidural PCA (PCEA) is the gold standard of pain control in thoracic and major abdominal surgery. In this setting, PCEA may contribute to a reduced rate of respiratory complications and better outcome [23].

Table 3.1 Equipotential doses of opioid agents

Analgesic	Strength (relative)	Parenteral dose (mg)
Codeine	0.1	100
Tramadol	0.1	50–100
Piritramide	0.7	7.5–15
Morphine	1	5–10
Oxycodone	1.5–2	4.5–6
Buprenorphine	40–50	0.15–0.3
Alfentanil	10–50	0.5–1
Fentanyl	70–100	0.05–0.1
Sufentanil	500	0.025

3.3.2.1 Opioids

Intravenous opioids (Table 3.1) are the treatment of choice for most ICU patients with acute pain, due to their potency and safety profile. Opioids can be used in association to sedatives as part of a strategy to manage agitation in ICU [24].

If a deep level of sedation is needed, as in mechanically ventilated, postoperative patients, *sedo-analgesia* is chosen, i.e. a continuous co-administration of sedative and analgesic agents. If a light level of sedation is indicated, *analgo-sedation* is the preferred technique, i.e. an analgesic driven continuous infusion during which sedatives are given only as low doses of short-acting agents in case of "breakthrough" agitation.

The pharmacologic bases of this approach are linked to the pleiotropic effects of opioids on several receptors. All opioids (agonists, antagonists, and mixed agonist–antagonists) act primarily through the binding to the μ-opioid receptor. Other receptors include k-opioid receptor and δ-opioid receptor [19]. All three receptors (μ, δ, κ) mediate analgesia but have differing side effects. M-receptors mediate respiratory depression, sedation, euphoria, nausea, urinary retention, biliary spasm, and constipation. K-receptors mediate dysphoric, sedative and diuretic effects. Δ-receptors mediate euphoria, respiratory depression and constipation [25].

Morphine is the most commonly used opioid both in and outside ICU [26, 27]. Equipotential doses of opioids are comparative in respect to morphine (Table 3.1). Onset of analgesia for i.v. administration is 5–10 min, with peak effect occurring in 1–2 h. Sublingual administration can be used in postoperative patients; there are some data suggesting that pre-emptive use can reduce postoperative opioid consumption. Morphine doses are titrated to the desired effect, and its efficacy monitored with a consistent pain assessment tool (see above). Morphine has an elimination half-life of 4–5 h. Hepatic conjugation leads to formation of glucuronide metabolites, whose renal elimination occurs in 24 h [28]. In ICU patients with reduced creatinine clearance (particularly below 30 mL/min), the morphine-6-glucuronide can accumulate and account for prolonged analgesia and side effects, particularly over-sedation and respiratory depression [29].

Fentanyl is a synthetic derivative of morphine. It is approximately 100 times more potent than morphine, exhibiting a faster onset due to higher lipid solubility and penetration into the blood–brain barrier [26, 30]. Side effects too are more pronounced, including sedation and respiratory depression. Fentanyl can be administered as pre-emptive/rescue boluses or as continuous i.v. infusion. However, its

potential for accumulation in fat tissues and muscles counter-indicates prolonged infusions, which are linked to prolonged sedation [31]. In case of renal dysfunction, the use of single boluses of fentanyl may be preferred to morphine continuous infusion [32].

Remifentanil is an ultrashort-acting fentanyl derivative with fast onset/offset of action (<3 to 5–10 min). Analgesic potency of remifentanil is similar to that of fentanyl. Its favourable pharmacokinetics is linked to its organ-free, extensive inactivation by circulating esterases; this makes remifentanil a good option in cases of renal or hepatic dysfunctions [10]. Due to its potency and sedative effects, remifentanil may be used as the main drug during ICU analgo-sedation (see above): a continuous infusion of remifentanil can be supplemented as needed with single boluses of short-acting sedatives, i.e. propofol or midazolam. This strategy has been suggested to reduce duration of mechanical ventilation and ICU-LOS, even though evidence is not definitive in this sense [24, 33]. Major drawbacks of its potency include a major degree of respiratory depression at relatively low doses (>0.05 μg/kg/min) and fast onset of opioid-induced hyperalgesia; its cost may be of concern too [34, 35]. Finally, since the drug is licenced only for a short lasting continuous infusion, longer infusions may be considered off-label.

Sufentanil is a synthetic, potent opioid with highly selective binding to μ-opioid receptors. Analgesia induced by sufentanil has a potency seven- to tenfold higher than fentanyl and 500- to 1000-fold higher than morphine (per oral dose). The high lipophilicity of sufentanil allows it to be administered sublingually and achieve a rapid onset of analgesic effect [22, 36]. Data on sublingual use of sufentanil in ICU patients are scarce, and its use cannot be routinely recommended in all patients.

Tramadol is a centrally acting opioid-like drug and acts by binding to the μ-opiate receptor as a pure agonist; it inhibits adrenaline and serotonin reuptake. It is used to treat moderate to severe pain [37]. The most common adverse effect is typical to other opioids and includes nausea, vomiting, dizziness drowsiness, dry mouth and headache. However, tramadol produces less respiratory and cardiovascular depression than morphine, and euphoria and constipation are also less common [38].

Non-analgesic Effects of Opioids

- Opioids exert sedative properties that are proportional to their analgesic potency. In mechanically ventilated ICU patients, this effect may be advantageous and may be part of a “sedative-sparing” regimen (analgo-sedation). However, in spontaneously breathing patients who are being weaned from ICU supports, opioid-driven sedation may be undesired and problematic; as such, light sedation with shorter-acting sedatives such as midazolam and dexmedetomidine may be preferable [39].
- Respiratory depression is proportional to analgesic potency; chest wall rigidity may be of concern with fentanyl and remifentanil. Respiratory depression is usually seen as an undesired side effect, particularly in ICU patients who are spontaneously breathing [40, 41]. However, in selected cases, a carefully titrated

infusion of an opioid may reduce respiratory workload and oxygen consumption and increase compliance to non-invasive mechanical ventilation (NIV). The elderly, the obese and those patients with hepatic/renal dysfunction are particularly prone to undesired and prolonged respiratory depression. In these cases, naloxone can be used as the antagonist to reverse opioid-induced respiratory depression. This reversal may be associated with sudden reappearance of pain, tachycardia, hypertension and pulmonary oedema. Attention must be paid to these effects in cardiopathic patients.

- Delirium, which can be due to uncontrolled pain, may be related to appropriately prescribed opioids as well. In general, as per all undesired effects of drugs, opioids should be discontinued and an alternative strategy for pain control should be adopted [24]. In case of persistent delirium, other organic causes need to be ruled out and a specific treatment is indicated.
- Opioid-driven hypotension may be linked to histamine release, particularly by morphine; or it can be the direct vasodilatory effect of these drugs [19, 42]. As such, in hemodynamically unstable patients, single boluses should be administered slowly, and a cautious infusion of the less potent morphine could be preferred. Bradycardia may ensue, particularly with remifentanil and sufentanil, and it may be of concern for patients with rate-dependant cardiac output; however, in tachycardic and normo-/hypertensive patients, bradycardia can reduce myocardial oxygen consumption and left ventricular wall stress.
- Gastrointestinal effects: nausea, vomiting and ileus are commonly observed during opioid administration and are linked to activation of brain's chemoreceptor trigger zone or intestinal receptors [40]. Ondansetron, alizapride or metoclopramide may help reduce the rate of opioid-associated nausea and vomiting. Ileus better responds to cessation of administration [43]. If this is not possible, i.v. instrastigmine can be administered, if not contraindicated. Alternative strategies for pain control should be considered in these cases.
- Tolerance, i.e. a reduced clinical effect of opioids over the time, ensues typically during prolonged or chronic administration; with more potent agents like remifentanil, it can ensue even after very short infusions. Mechanism of tolerance includes lower density of receptors on cell surface and receptor accommodation. Thus, to overcome it, it is advisable to bridge to other, non-opioids agents to control pain. However, an abrupt discontinuation may be linked to symptoms of withdrawal, which include abrupt breakthrough of pain, tachycardia/hypertension, profuse sweating and malaise; delirium may ensue as well. Clonidine or dexmedetomidine are typically used to control those symptoms. In complicated cases and in case of chronic opioid abuse and/or methadone treatment, a clinical toxicologist should be consulted.

Opioids can paradoxically induce hyperalgesia, through a sensitisation to painful stimuli [44]. This is more commonly observed with remifentanil infusion. The exact mechanism is not well understood, even though the combination of extreme potency and ultrashort duration can play a role. Timely shifting from remifentanil to morphine infusion is widely advised to minimise the risk of exacerbation of acute pain.

3.3.2.2 Non-opioid Analgesics

Non-opioid analgesic drugs can be employed as main therapy for pain control or associated with opioids as part of a multimodal strategy (see above). In this case, synergic effects of those agents allow a spare of opioids, reducing their doses and side effects. Due to their heterogeneous pharmacology, they can be employed in many different clinical settings. They are not devoid of potentially severe side effects, particularly cumbersome in ICU patients. Patients with renal dysfunction, gastrointestinal bleeding, recent surgical bleeding, platelet abnormality, cirrhosis or asthma are at risk of complication with nonsteroidal anti-inflammatory drugs (NSAIDs) [45]. Thus, their use must be carefully weighed against opioid side effects. Non-opioid analgesia may be used in ICU patients with mild to moderate acute pain, to reduce doses of opioids. Temperature and pain control can be achieved with paracetamol. Procedural analgesia can be performed with ketamine. All patients that develop tolerance or hyperalgesia with opioids need to be bridged to a non-opioid pain control strategy which may include NSAIDs use and clonidine/dexmedetomidine. In ICU patients with neuropathic pain, gabapentin or pregabalin can be used with or without concomitant use of opioids. For difficult cases of ICU patients chronically taking analgesics for pain syndromes, a pain medicine specialist should be consulted.

Parenteral paracetamol is an analgesic and antipyretic agent used in ICU patients to treat fever and/or mild pain. After surgery, paracetamol decreases the total needed dose of morphine [46, 47]. The individual response to analgesic effects of paracetamol is variable, with some patients being completely insensitive to its analgesic effects. In sensitive patients, pre-emptive paracetamol associated with a tramadol rescue dose may be a good strategy to control mild to moderate postoperative pain. Hypotension is a well-described side effect, particularly with parenteral administration; however, evidence is that paracetamol-driven hypotension is transitory and rarely needs pharmacologic intervention [48–50]. Of note, hemodynamic unstable patients or those with progressive or severe hepatic dysfunction should be spared paracetamol infusion. Renal dysfunction, on the contrary, does not counter-indicate its use.

NSAIDs are inhibitors of cyclooxygenase (COX), an enzyme of the arachidonic metabolic pathway which facilitates the release of pain mediators like prostaglandins, prostacyclins and tromboxane. NSAIDs, particularly ketorolac and ibuprofen, may be used as adjuncts in multimodal pain control strategies to spare opioid dosing [51, 52]. As stated above, renal and gastrointestinal side effects can be cumbersome in ICU patients, limiting their use to the stable, postoperative patient without renal, hepatic or platelet dysfunction [45]. When not counter-indicated, a single bolus of NSAIDs can be used as a rescue to treat mild to moderate breakthrough pain. The use of selective COX-2 inhibitors is discouraged to avoid potentially severe myocardial effects.

Ketamine provides dissociative anaesthesia and analgesia by blocking *N*-methyl-D-aspartate (NMDA) receptors and binding to σ-receptors for opioids. It is employed as a substitute or adjunct for opioid therapy in selected patients, particularly those with opioid tolerance or hyperalgesia [53–55]. Its use is associated with hallucination, and premedication with diazepam or midazolam is advisable [56].

Lidocaine is an amide local anaesthetic that has analgesic and anti-inflammatory properties. By blocking sodium channels, G protein-coupled receptors and NMDA receptors, lidocaine has multiple mechanisms of modulating pain. Intravenous lidocaine in abdominal surgery was associated with lower pain scores and opioid usage, faster return of bowel function and shorter length of stay as compared with controls. At blood levels >5 mg/mL, serious toxic side effects are noted on the central nervous system, including focal and grand mal seizures, psychosis and rarely respiratory arrest. It is therefore crucial to check lidocaine levels on any patient in whom a lidocaine infusion is going to be administered and titrated to a level <5 mg/mL [65]. In addition, in patients with peripheral neuropathic pain syndromes such as allodynia and hyperalgesia, a transdermal application of 5% lidocaine has proven to be effective at alleviating pain [66]. A lidocaine infusion in the intensive care setting has been shown to be effective as an adjunct to an opioid analgesic in the postoperative setting for the first 24 h [67]. Although many studies have validated the effectiveness of lidocaine in the perioperative setting with bowel surgery, further study is necessary in order to validate prolonged lidocaine infusion as a safe and effective analgesic in the intensive care setting.

3.4 Adjuncts and Complementary Agents

Other drugs can be used as adjuvant analgesic therapy in the ICU: antidepressant, anticonvulsant agents and neuroleptics. Antidepressants are commonly used for various chronic pain conditions and are classified according to chemical structure and/or mechanism of action. The most common classes of antidepressants include tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors [57]. Antidepressants show efficacy in the treatment of chronic pain; multiple positive trials suggest the therapeutic potential of antidepressants for treatment of acute, or prevention of chronic, postoperative pain, which needed to be replicated [58].

Dexmedetomidine and clonidine are selective α_2-central agonists with sympatholytic, sedative, analgesic and anti-shivering effects. They can be used to provide light sedation and analgesia to ICU patients. Their analgesic effect is mild, and they need to be associated as adjuncts to other, more potent analgesics. They are devoid of respiratory depressant effects, and thus they are particularly useful to manage pain and agitation in ICU patients on NIV, such as those with acute exacerbations of chronic obstructive pulmonary disease (COPD). In those patients, α_2-central agonists have the advantage to control tachycardia and hypotension without inducing bronchospasm. Occasionally, they can be used to manage withdrawal from opioids or other drugs [59, 60].

Gabapentin and pregabalin are analogues of the gamma-aminobutyric acid (GABA) that can be used to treat neuropathic pain in the general and ICU population. They act inhibiting neurotransmission at the synaptic level of pain neurons [61]. Common dose-related adverse effects include somnolence and confusion. These agents may be used as adjuncts as part of a multimodal pain control strategy,

particularly in ICU patients already taking them at home [62, 63]. Gabapentin and pregabalin are available as oral medications; in ICU patients on mechanical ventilation, they can be administered via a nasogastric tube.

3.4.1 Regional Anaesthesia

In ICU patients, regional anaesthesia is most commonly performed through neuraxial blocks and peripheral blocks (e.g. transversus abdominis planus, TAP, or intercostal block).

Advantages of regional analgesia in ICU include [64–66]:

- A reduced need for i.v. analgesics, mostly opioids
- A faster weaning form mechanical ventilation
- A faster recovery of bowel function

Neuraxial analgesia is commonly used to treat pain in postoperative ICU patients since many high-risk patients who are managed with a programme of enhanced recovery after surgery (ERAS) will be postoperatively admitted in ICUs [67]. Other than retaining the general advantages of regional analgesia, neuraxial blockade may reduce the risk for thromboembolism and cardiorespiratory complications [64–66]. However, in ICU patients, the cardiocirculatory effects of neuraxial analgesia may be cumbersome and noradrenaline is often needed; weaning from noradrenaline may take time, thus increasing ICU-LOS. A proper, goal-directed strategy for fluid supplementation must be implemented in high-risk patients who undergo neuraxial blockade. In septic patients these techniques are better avoided for both the sepsis-related cardiocirculatory dysfunction and coagulopathy [67, 68].

The TAP block has been proposed to reduce opioid consumption in patients following abdominal surgery [69]; in ICU, the TAP block may be used in patients whose hemodynamic status counter-indicates neuraxial blocks. A TAP catheter may be left in place to provide a continuous infusion of local anaesthetics. However, pelvic and visceral pain is not covered by TAP and i.v. supplemental analgesia is often needed [70].

3.4.2 Non-pharmacologic Interventions

Physical therapy can help in increasing functional mobility and muscle strength, including respiratory muscles' strenght and resistance [71]. Epidural analgesia, early mobilisation and early oral feeding are all part of the ERAS programs which aim at improving the outcome after abdominal surgery [72, 73]. Their role in ICU patients is more difficult to ascertain. Transcutaneous electrical nerve stimulation, relaxation techniques, massage therapy and music therapy may contribute to pain control in some patients [74].

Conclusions

- Pain is common among ICU patients and can be due to either surgery, underlying conditions and ICU procedures.
- Routine assessment and management of pain are integral part of ICU good practice. The use of VAS or behavioural scales is recommended.
- In agitated patients, the need for analgesia needs to be ruled out prior of administration of sedatives.
- Medical ICU patients can be safely generally managed with a low dose, single agent infusion, such as morphine.
- Surgical ICU patients are better managed with multimodal analgesia, including PCEA, TAP block, oral or sublingual opioids and/or continuous infusion of morphine or more potent opioids.
- FANS, α_2-agonists or complementary drugs such as antidepressants can be added as needed.

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