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Pain management in critically ill patients

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Abstract

Pain is a common and distressing symptom in intensive care unit (ICU) patients and despite of pain research, guideline development, numerous awareness campaigns and intense educational efforts, it remains currently under evaluated and undertreated. The pain relief in critically ill patients may be difficult to achieve due to complex interplay between mechanisms of critical illness, drug interactions, organ dysfunctions and factors involved in influencing pain perception. A different medications have been proposed for pain control and they have unique considerations when contemplated for use in the critically ill patient.

The purpose of this article is to provide an overview of most important pharmacologic pain treatment in the critically ill patient.

INTRODUCTION

Pain is a common and distressing symptom in intensive care unit (ICU) patients and represents a major clinical, social, and economic problem. It has been reported that almost 80% of patients experience different intensities of pain during their intensive care unit stay and identify it as one of the greatest sources of stress *(1, 2)*.

Such pain is problematic because produces adverse psychological and physiological response that includes increased heart rate, blood pressure, respiratory rate, neuroendocrine secretion and psychological distress. Failure to relieve pain produces a prolonged stress state, which can result in harmful multisystem effects and can therefore impair a patients recovery and discharge *(3)*. The primary goal of acute pain management in ICU patients are pain control and attenuation of the negative physiologic and psychological consequences of unrelieved pain. Although, a number of recent surveys, reported that enhanced pain management was associated with improved patient outcome in the ICU *(4, 5)* and despite of pain research, guideline development, numerous awareness campaigns and intense educational efforts, pain remains currently under evaluated and undertreated in patients who are critically ill *(6)*. Therefore, the importance of quality pain management in the ICU is inherently compelling and highly challenging.

Etiology and pain assessment in ICU patients

Although, adequate pain control is a basic human right *(6)*, a number of factors complicate the management of pain in the critically ill patient. In particular, critically ill patients may experience pain due to their underlying disease or surgery, but also it may be result of various and painful medical procedures (procedural pain) such as inserting urinary catheter, nasogastric tube, chest tubes, tracheal suctioning, invasive

lines, (arterial and central venous catheter) suture removal and routine nursing care. Nursing care procedures such as bathing, massage of back and pressure points, sheets change and repositioning are the most common painful procedures in ICU patients *(7)* Vazquez M *et al. (8)* analyzing pain intensity during 330 turnings in 96 medical-surgical patients and reported significantly increased pain score between rest and turning. The bolus of analgesic was used in less than 15% of the turnings. Further, although some ICU patients may be able to communicate, many critically ill patient with cognitive or communication problems due to stroke or brain injury, dementia, confusion, mechanical ventilation and concomitant use of sedatives, may have difficulty in reporting pain. Presence of the some causes mentioned above increases the likelihood for poor pain management, and worsens a patient's experience of pain. The first step in providing adequate pain relief for ICU patients is appropriate assessment. Pain should be assessed by self-reporting scales in patients able to communicate, or by behavioral pain scores in patients unable to communicate. Even though various self-report pain scales and behavioral pain scales specifically developed for use in critically ill adults are available, these are not always routinely used in the ICU. Patients'self-reporting of their pain is the gold standard of pain assessment and provides the most valid measurement of pain *(9).* The most widely used pain intensity scales are the Numeric Rating Scale (NRS) and Visual Analogue Scale (VAS) while Behavioral Pain Scale (BPS) is considered to be an alternative tool for assessing pain in critically ill, sedated, and mechanically ventilated patients. The BPS assesses pain through evaluation of facial expression, upper limb movements, and compliance with mechanical ventilation. A similar behavioral scale called the Critical-Care Pain Observation Tool (CPOT) may also be used.

Route of administration

The route of medication administration is an important consideration for the pharmacologic management of pain in the ICU setting. Intravenous administration is more commonly the route of choice in critically ill patients because of altered GI tract function that could lead to unpredictable absorption of medication.

The choice of intermittent vs. continuous infusion IV administration depends on factors such as the frequency and severity of pain, and the pharmacokinetics of the pain medication. The administration in bolus is associated with the variation in the peak plasma concentration, since the infusion maintains a more stable concentration, but can lead to accumulation of medication especially in patients with renal or liver failure.

Patient-controlled analgesia (PCA) is an effective method for administering analgesic medication and gives patients a sense of control over their pain, expecialiy in postoperative settings. Patients can determine when and how much medication they receive, regardless of analgesic technique. However, this technique requires fully conscious and orientated patients which make use of PCA limited in ICU patients.

Intravenous administration is generally preferred over subcutaneous or intramuscular routes given potentially inadequate absorption due to regional hypoperfusion (e.g., shock, subcutaneous edema). Regional or neuraxial (spinal or epidural) modalities may also be used in ICU following selected patients and selected surgical procedures. Epidural analgesia (EA) is probably the most often used regional anaesthetic technique in the ICU. EA should be proposed in critically ill patients, such as post-operative after thoracic, abdominal surgery, major vascular surgery and orthopedic surgery or trauma patients, typically.

The major disadvantages of epidural analgesia are the rare but catastrophic complications such as infection, epidural hematoma formation and nerve damage, which can occurred in ICU patients who have a high risk of developing these complications *(10).*

Pharmacotherapy

In January 2013, The Society of Critical Care Medicine (SCCM) published the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit *(11).* Table 1. shows the commonly used pain management drugs and recommended doses. There are no data to support the preference of analgesic over the other.

Opioids

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. Recommended opioids include fentanyl, remifentanil, morphine, and hydromorphone. The choice of opioid and the dosing regimen should be individualized based on drug's potency, pharmacokinetics and pharmacodynamic profiles, side effect profile, patient comorbidities, and function of specific organ systems, in particular the liver and kidneys.

Morphine sulfate is the most frequently used opioid in the ICU and has been traditionally a first-line opioid for the treatment of severe pain. Morphine has a half-life of 1.5 to 2h after intravenous administration in normal subjects, but in ICU patient, distribution volume and protein binding may be abnormal. Therefore, the patients can respond very differently to morphine doses in terms of the analgesic effect but also in terms of the side effects. Although, morphine, such as all opioids, may lead to respiratory depression, it is noteworthy to point out that the morphine-6-glucuronide metabolite is more potent than morphine itself, and that accumulation can occur, espe-

cially in patients with renal impairment. Therefore, morphine use should be avoided for patients with known renal insufficiency or failure. Side effects include histamine release, sedation, nausea, ileus, constipation, and spasm of the sphincter of Oddi. Morphine sulfate should be administered intravenously and titrated to effect. The loading dose of 0.05 mg/kg (2–5 mg) should be given over 5 to 15 min. In most patients, the average maintenance dose is 4 to 6 mg/h and should be administered at the dosing interval of 1–2 hrs. Continuous IV morphine can be administered with an initial 2–5 mg bolus dose followed by 1 mg/h.

Fentanyl is synthetic opioid roughly 100 times the potency of morphine, which does not cause histamine release and was preferred analgesic agent for critically ill patients with hemodynamic instability. It efficacy is due to its lipid solubility (600 times more lipid soluble than morphine), so if used > 4 hrs fentanyl must be used in the lowest tolerated dose to prevent prolonged effects. With prolonged infusion, the half-life increases dramatically from 30 – 60 minutes to 9–16 h and care must be taken to adjust infusion rate with time.

Fentanyl causes only minor hemodynamic changes and does not affect cardiac inotropy. The dose range for fentanyl infusions is variable and some patients may require higher doses. Bolus dose of 25–100 μg, with subsequent doses of 0.25–0.5 μg/kg every 15–30 minutes might be a good first alternative to morphine in treating acute painful conditions. Alternatively, a bolus dose of 1–2 mcg/kg (25–100 mcg) may be administered followed by initiation of the continuous infusion. Most patients will be adequately treated with 1 to 2 μg/kg/hr (25–200 μg/h infusion).

Remifentanil is a fast-acting drug and presents an equally fast recovery *(11)*. It is 150 –200 times more potent than morphine. Its metabolism does not depend on the liver. Analgesia-based sedation with remifentanil is a useful option for mechanically ventilated patients and it can be used in patients that need frequent neurological assessment. Studies have shown a shorter duration of mechanical ventilation and quicker ICU discharge with remifentanil compared with other opioids *(12, 13)*. It offers precise control of analgesia for painful procedures in ICU patients and has a highly predictable onset and offset, with a stable context sensitive half-time (3–10 min). No need for initial dose adjustment is required for patients with impaired renal and hepatic function. Therefore, analgesia-based sedation with remifentanil has been introduced as an option in ICU patients. Remifentanil can be administrated in higher doses than are normally used with other opioids without concerns about accumulation and the possibility of unpredictable and/or delayed recovery. Most ICU patients can be managed without bolus doses; if required, a bolus of 0.5–1 μg/kg is usually sufficient. It is recommended that remifentanil infusions should be started at 6–9 μg/kg/h and than titrated in the range dose 0.5–15 μg/kg/h. Some authors recommended dose to 60 μg/kg/h *(14)*. Even under these controlled conditions, this practice has not found widespread use because of the associated incidence of hypotension and bradycardia.

Hydromorphone is a semisynthetic opioid agonist that, like fentanyl, has a more rapid onset of analgesia (within 30 minutes) and a short half-life (2–4 hours). While the duration of action is similar to morphine, it does not stimulate histamine release. Hydromorphone is primarily metabolized in the liver to an active metabolite – hidromorphone-3-glucuronide, but it is not clinically significant. Hydromorphone is potent respiratory depressant and may accumulate in patients with renal failure, resulting in neuroexcitation and cognitive impairment. Dosing begins at 0.2 to 0.6 mg and titrated by 0.5 mg increments. Most patients requiring 1 to 2 mg every 1 to 2 hrs. In addition, if given as an intravenous continuous infusion the dose should be 0,5 –3 mg/h.

Tramadol is a centrally acting opioid-like drug, and acts by binding to the μ opiate receptor where it is a pure agonist like morphine and inhibits adrenaline and serotonin re–uptake. It is used to treat moderate to severe pain. 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.

Recommended dosage of 100 mg can be administered as an initial bolus. During the 90 minutes following the initial bolus further doses of 50 mg may be given every 30 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 mg or 100 mg 4 to 6 hourly up to a total daily dose of 400 mg.

Non-opioid analgesics

Non-opioid analgesics are indicated for use in management of mild to moderate pain and moderate to severe pain with adjunctive opioid analgesics. Potential advantages of multimodal analgesia, that involves combination of analgesics with different mechanisms of action, include improved analgesia, effective analgesia with lower opioid doses, and decreased risk of opioid-related adverse effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have opioid sparing effect but this has not been sufficiently investigated in ICU patients. Although the use of NSAIDs is still contraversial, they may be used as adjuncts to opioid therapy. The most common side effect include gastrointestinal bleeding, renal dysfunction and inhibition of platelet function.

All parenteral NSAIDs should be avoided in patients with preexisting renal insufficiency, asthma, hypoperfu-

TABLE 1
Commonly used pain management drugs and recommended doses.

Drug	Elimination Half-Life	Peak Effect (IV)	Suggested Dosage	Comments
Morphine	2-4 h	30 min	2-5 mg bolus 1-10 mg/h infusion	Avoid in hemodynamically unstable patients. Active metabolite accumulates in renal dysfunction. May cause itching due to histamine release.
Fentanyl	2-5 h	4 min	25-100 µg bolus 25-200 µg/h infusion	Fastest onset and shortest duration. Accumulation with hepatic impairment. Muscle rigidity.
Remifentanil	3-10 min	1-3 min	0.5-1 mcg/kg IV bolus 0.5-15 µg/kg/h infusion	No accumulation in hepatic/renal failure. Use IBW if body weight >130% IBW
Hydro-morphone	2-4 h	20 min	0.5-2 mg bolus and 0.2 to 0.6 mg every 1-2 h intermittent 0.5-3 mg/h infusion	Therapeutic option in patients tolerant to morphine/ fentanyl. Accumulation with hepatic/renal impairment 5-10x more potent than morphine.
Tramadol	5-6 h	45 min	100 mg bolus and 50 mg every 30 min up to 250 mg including the initial bolus. total daily dose of 400 mg.	The elimination of tramadol may be prolonged in hepatic/renal impairment Contraindicated in patients on MAOI or epilepsy.
Acetamino-phen	2-3 h	15 min	1 g every 6 h	May cause hypotension when given by infusion and may cause liver and kidney damage, when taken at higher than recommended doses (overdose).
Lidocaine	1,5-2 h	45-90 s	100 mg or 1.5–2 mg/kg at least half an hour before surgical incision, followed by an infusion of 1.33–3 mg/kg/h intraoperatively	Avoid in patients with arrhythmias, heart failure, coronary artery disease, Adams-Stokes, or heart blocks. Caution should be taken in patients with hepatic or renal failure, sinus bradycardia and incomplete branch block.

sion, advanced age, concomitant use of steroids and anticoagulants, situations that are frequently observed in ICU patients *(15)*. Treatment should be limited to the minimum dosage for the shortest possible time, not to exceed five days.

Acetaminophen (paracetamol) was approved for intravenous use in 2010 and is commonly administered for the short-term treatment of mild to moderate pain and febrile critically ill patients with infection. It differs from the available opioids and NSAIDs, since paracetamol does not increase incidence of nausea, vomiting, and respiratory depression that can occur with opioids, or the platelet dysfunction, gastritis, and renal toxicity that are associated with NSAIDs. Although, represents a relatively good safety profile, there is limited information regarding IV use in critically ill patients. Research to date has described that paracetamol can cause transient abnormalities of liver function and may cause hypotension in critically ill patients *(16)*. Acute liver failure is the most serious potential complication of the use of paracetamol. The key criteria for assessing potential hepatotoxicity with conventional doses of paracetamol may include hypoxic injury, altered pharmacokinetics, relative over-dosage, muscle glutathione depletion, malnutrition, dehydration, older age and alcoholism which is often seen in critically ill patients. The British National Formulary (BNF) suggests to administer a maximum daily infusion dose of 3 g in adults in these patient groups *(17)*.

Randomised, placebo-controlled trial that investigating the safety and efficacy of paracetamol in febrile ICU patients with known or suspected infection is currently underway study (the HEAT -Permissive HyperthErmiA Through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit) *(18)*. The results of this trial are expected to publish in early 2015 and should provide essential information on efficacy and safety of paracetamol in febrile critically ill patients. The recommended dose for IV acetaminophen is 1 g every 6 h with a maximum allowable dose of 4 g/daily.

Lidocaine is commonly used for regional anesthesia and nerve blocks, however, recent clinical studies demonstrated that intravenous perioperative administration of lidocaine can lead to better postoperative analgesia, reduced opioid consumption, improved intestinal motility and decrease hospital length of stay *(19, 20)*. Although, the analgesic effect depend on dose, there is considerable individual variability in pharmacokinetic response to lidocaine infusions. Serum steady state is achieved following a bolus of 1.5–2.0 mg/kg of lidocaine and infusion rates of 0.9–3.6 mg/kg/h. These doses generally result in plasma levels of 1.3–3.7 µg/ml, which provide a small

marigin of safety. Large doses have better analgesic effect but induce systemic lidocaine's toxicity. Lidocaine induces analgesia when serum ranges are kept at 1–5 μg/m. Although the half-life of the drug is only 120 minutes, the analgesia provided by systemic lidocaine is prolonged, over days or even weeks. With regard to analgesia, it has been reported that intravenous lidocaine produces three different pain relief stages: the first is during infusion and 30 to 60 minutes after its end; the second is a transient stage approximately 6h after infusion; and the third stage appears 24 to 48h after infusion and continues for 21 to 47 days *(21).* Intravenous lidocaine should not be used in patients with arrhythmias, heart failure, coronary artery disease, Adams-Stokes, or heart blocks. Caution should be taken also when using lidocaine in patients with hepatic or renal failure, sinus bradycardia, and incomplete branch block since possible accumulation of lidocaine or its metabolites may lead to toxic phenomena.

Although there is no clear consensus on the dosage regimen, many studies have used a bolus dose of 100 mg or 1.5 mg/kg at least half an hour before surgical incision, followed by an infusion of 1.33–3 mg/kg/h intraoperatively and continued after operation variably up to 24 h. The application of continuous lidocaine has not been documented in the ICU in controlled studies and more study is needed to confirm beneficial effects of lidocaine in critically ill patients.

Regional anesthesia and analgesia

Regional anesthesia and analgesia although, not commonly used as a primary modality for analgesia in critically ill patients, can help to improve respiratory and bowel function, mental status and patient comfort secondary to its opioid-sparing effects. It minimizes patient discomfort and reduces the physiological and psychological stress, as in non-critical patients. Limitations for the use of regional anesthetic techniques are mainly associated with bleeding risks, coagulation disorders, hemodynamic disturbances and difficulties in neurologic assessment. The use of regional analgesia in the ICU settings should evaluate the risk and benefits due to limited cooperation of the patient, and the indication for it use should be carefully assessed regarding to patients clinical condition.

As mentioned above, epidural analgesia is probably the regional anaesthetic technique most often used in the ICU, but nerve blocks and other sophisticated techniques started in the operating room may also be used for pain relief in critically ill patients and should not be discontinued when the patient is transferred to ICU.

CONCLUSION

Pain management is an essential component of quality care delivery for the critically ill patient. The patients in ICU often suffer from undertreated and unrecognized pain, with potentially serious physical and psychological effects. The availability of a wide range of treatment options together with the recognized importance of adequate management enables better understand, evaluate and manage pain in the critically ill patient. It's therefore important for clinicians to recognize a patient's pain profile and rational choice of pain medication should be based upon individual needs and desired effect of analgesic. Effective pain management is a moral imperative and professional responsibility for both doctors and nurses.

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