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Analgesia in intensive care: part 1

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Key points

- Despite evidence of adverse impacts because of suboptimal pain management, pain still remains poorly assessed and treated in intensive care.
- In choosing the ideal analgesic drug in the critically ill, the interplay between altered drug pharmacokinetics and pharmacodynamics, organ dysfunction, and side-effect profile must be considered.
- Sedation protocols in intensive care should focus on analgesia first. The aim should also be to avoid prolonged continuous infusions and encourage targeted titration to specific individualized goals.
- Opioids remain the mainstay of analgesia management but wherever possible, multimodal approach should be considered.
- The synergistic action of the analgesic adjunct drugs has the potential to minimize the side-effects, while maintaining effectiveness.

Patients in intensive care experience distress because of a multitude of factors and a significant proportion is attributable to pain.[1] A vast majority of patients report moderate to severe pain at some point during their intensive care stay. Pain can be caused or provoked by many pre-existing conditions: acute medical, surgical, or routine aspects of intensive care (Table 1).

Pain is widely regarded as the fifth vital sign, and it induces a myriad of deleterious physiological changes in most organ systems. Severe pain induces a stress response and sympatho-adrenergic stimulation causing tachycardia, hypertension, increased myocardial oxygen consumption, and can induce myocardial ischaemia in susceptible patients. Poorly managed pain from abdominal incisions reduces diaphragmatic function, causes hyperventilation and atelectasis. Pain especially in sedated patients can present as agitation, delirium and when badly managed can have psychological sequelae like post-traumatic stress disorder,[2] depression, and anxiety or it can progress to chronic pain. Systemic deleterious effects of pain include systemic inflammatory response syndrome, hyperglycaemia, immunosuppression, impaired wound healing, hypercoagulability, and increased catabolism. All these detrimental effects can lead to an increased length of intensive care and hospital stay, and mortality.

Despite overwhelming evidence of adverse clinical impact, pain still remains infrequently assessed and poorly managed in the intensive care unit (ICU).[3] Patients who had regular assessments for pain are more likely to have lighter levels of sedation, an increase in the use of non-opioid multimodal analgesic therapies and pre-emptive analgesia before painful procedures. This in effect has been shown to decrease the duration of mechanical ventilation and ICU stay.[3]

There are numerous barriers to pain management in the ICU and surveys have revealed wide national and international variations in assessment, monitoring, drugs, protocols and algorithms used for sedation, and analgesia. The objective of this article is to discuss the key principles of pain management in ICU and the commonly used systemic analgesics and adjuvants; the role of regional analgesia in ICU is covered in a subsequent article.

Recognition of pain in ICU

Recognition of pain in ICU patients is the important first step in its management. However, verbal reporting is not always

Table 1 Causes of pain in intensive care. SCI, spinal cord injuries; GBS, Guillain–Barre syndrome; MS, multiple sclerosis

Constant background pain (requiring infusion of opioids/adjuncts)	Postoperative: surgical incision, abdominal/chest drains Pre-existing: exacerbation of chronic pain, arthritis Neurological conditions: phantom limb pain, SCI, demyelinating neuropathy-GBS, MS Trauma: amputations, fractures, soft tissue injuries, burns, pressure sores
Intermittent/periprocedural pain (requiring boluses of opioids/adjuncts)	Invasive procedures: central/arterial line placement, tracheal tubes, nasogastric tubes, catheters Routine care: position change, physiotherapy, tracheal suctioning, mobilization, wound/burn dressing changes

possible because of difficulties in communication (e.g. sedation, delirium, tracheal intubation, neuromuscular block and weakness). Physiological parameters, which are usually related to pain, can be caused or masked by various other factors in the ICU setting (e.g. arrhythmias, sepsis, inotropic therapy, beta-blockade, and other pharmacological interventions).

Pain assessment

Less than 50% of intensive care professionals assess pain, and even when done, it is only done infrequently.[3] Lack of training in the assessment is a frequently cited factor for poor pain management. The main principles of pain assessment in the critically ill are to:

(i) Understand and identify the causes of distress, most common, but not all, of which is attributable to pain.
(ii) Assess pain, sedation, and delirium using validated scales, regularly and accurately, and use all the information in conjunction.
(iii) Appreciate that vital signs should not be used alone in the assessment of pain, but may be used as a cue to begin further assessment.[4]

Pain scales

Self-reporting of pain is considered as gold standard[4, 5] and wherever possible, healthcare professionals should try and rate patient's self-reported pain using validated scales. Pain scales can be continuous or discrete, unidimensional or multidimensional, subjective or objective. Commonly used pain scales in the ICU are unidimensional and are quite useful in the assessment of pain and measuring the response to treatment.

Pain scales for patients able to communicate.

(i) *Visual Analogue scale (VAS)*: Patients mark their pain on a 100 mm line, with verbal descriptors at each end (0: no pain; 100: very severe pain). The score is obtained by measuring the distance in millimetres from the left end of the line.
(ii) *Numerical Rating Scale (NRS)*: Patients rate pain on an 11-point scale (0: no pain; 10: severe pain).
(iii) *Verbal Rating Scale (VRS)*: 4-point scale, in which the pain can be rated as 1: absent, 2: mild, 3: moderate, and 4: severe.

Pain scales for patients unable to communicate.

(i) *Behavioural Pain Scale (BPS)*: this scale uses clinical observations of facial expression, upper limb movements, and synchrony with mechanical ventilation. BPS ranges from 3 to 12, scores >6 require pain management (Table 2).[6]
(ii) *Critical Care Pain Observation Tool (CPOT)*: the scale uses a four-component clinical observation of: facial expression, body movements, muscle tension, and compliance with the ventilator for intubated patients or vocalization for extubated patients. Each component has a score of 0–2, and total score ranges from 0 to 8. A score of >2 has a high sensitivity and specificity for predicting significant pain in post-operative ICU patients exposed to a painful procedure.[4,5]

Table 2 The behavioural pain scale.[6] Reproduced with kind permission from Wolters Kluwer Health

Clinical observation	Score
Facial expression	
Relaxed	1
Partially tense	2
Totally tense	3
Grimace	4
Movement of upper limbs	
Relaxed	1
Partially flexed	2
Totally flexed	3
Totally contracted	4
Mechanical ventilation	
Tolerating movements	1
Coughing but tolerating most of the time	2
Fighting the ventilator	3
Impossible to control ventilation	4

Principles of pain management in the ICU

The basic principles in management of pain in the ICU are very similar to the perioperative setting:

(i) Ensuring a holistic approach to pain management by using a combination of non-pharmacological and pharmacological interventions (systemic analgesia and loco-regional techniques).
(ii) Using multimodal approach to management of pain so as to improve the quality of analgesia and reduce side-effects.

The important modifications are:

(i) Emphasis on analgesia before sedation ('analgesia first: A1') and daily planned interruption of sedation. Consider distress because of anxiety and delirium after pain has been adequately managed (Appendix).
(ii) Titration of analgesia to specific individualized goals with reassessments and avoidance of continuous prolonged infusions.[4,7]
(iii) Understanding that drugs can cause organ dysfunction and also organ dysfunction can influence the choice of drugs and dosages: needing an individually adapted analgesic regimen.

Greater use of sedatives (Sedo-analgesia) is associated with cardiovascular depression, increased duration of mechanical

ventilation and intensive care stay, delirium, and cognitive dysfunction. Algorithms emphasizing adequate analgesia before sedation [Analgo-Sedation or analgesia first (A1)] reduces the requirements for sedatives, duration of mechanical ventilation without increasing the incidence of accidental extubations, or post-traumatic stress disorder. Wherever possible pain should be pre-empted and treatment initiated before potentially painful procedures.[4] Evidence shows that an algorithm-based approach to sedation and pain management improves outcomes and whatever the algorithm used, analgesia should be goal directed and titrated to effect. Hence, guidelines and protocols should be made available in every unit (e.g. Appendix).

Specific problems in intensive care patients

These patients usually have multiple physiological derangements, which influences the pharmacokinetic and pharmacodynamic profile of the drugs. It is paramount to recognize that these factors are also likely to change or develop newly in the dynamic setting of intensive care. Some of these factors are:

(i) *Ileus*: unpredictable absorption of orally administered drugs.
(ii) *Altered protein binding*: increase in free drug fractions in hypoalbuminaemia.
(iii) *Deranged acid–base balance*: affects the ionized and bound fractions of drugs.
(iv) *Altered splanchnic blood flow*: reduces phase 1- and 2-dependent metabolism (i.e. in patients with shock, inotropes, or both).
(v) *Organ dysfunction*: hepatic and renal dysfunction reduces metabolism and excretion of drugs and their active metabolites.
(vi) *Drug induced worsening of organ dysfunction*: NSAIDs may worsen renal function.
(vii) *Drug interactions*: influences both metabolism and effectiveness (synergism or antagonism) of concomitantly administered drugs.
(viii) *Pharmacodynamic effects*: alterations in the blood brain barrier can result in increased sensitivity to the effects of drugs (opioids and respiratory depression; CNS toxicity to local anaesthetics).

Modalities of management

The modalities available for pain management include both systemic and regional analgesia.

Systemic analgesia

There is no evidence to support the superiority of one analgesic over another in ICU. Intravenous (I.V.) administration of medication is preferred to enteral and other parenteral routes of administration because of potentially decreased or erratic absorption that can occur in low perfusion states. Additionally, the i.v. route also has the benefits of faster onset of action, higher bioavailability and is easily titratable to effect.

Ideal analgesic

The ideal analgesic agent must have:

(i) Rapid onset, offset, and be titratable.
(ii) Predictable dose response.
(iii) High therapeutic index.
(iv) Short context sensitive half-time.
(v) Less accumulation in organ dysfunction.
(vi) No interactions.
(vii) Minimal adverse effects.
(viii) Cost-effectiveness.

Multimodal analgesia and synergism

Pain pathways are numerous and complex, and involves various receptors. Simultaneous use of different classes or modes of drugs to modulate the different pathways and receptors to provide best benefit is called the multimodal approach. The actions of analgesics can be additive or synergistic; hence, multimodal approach reduces dose requirements, side-effects, and complications.

Analgesics classification

The variety of drugs available to treat pain reflects the varied and complex nature of pain that is seen in critically ill patients. The drugs available can be classified into:

(i) Opioid analgesics.
(ii) Non-opioid analgesics.
(iii) Analgesic adjuncts: neuropathic drugs.

Opioid analgesics

Opioids are considered to be the mainstay for treatment of acute pain in critically ill patients. Opioids act by stimulating μ-, κ-, and δ-opioid receptors, which are widely distributed within the central nervous system and throughout the peripheral tissues. All opioids are considered to have equivalent analgesic efficacy when titrated to same pain intensity endpoints without any difference in clinical outcomes. The dosages, routes of administration, interactions, and considerations in organ dysfunction are summarized in Tables 3 and 4.

Management of background pain is best achieved by an initial bolus followed by an infusion (Tables 3 and 4). For infusion regimes, generally a step-up approach is recommended, where the opioid is started at a lower dose and increased by 15–20% of the initial dose until adequate pain control is achieved. This minimizes the incidence of side-effects because of inter-individual variability. Continuous infusions of conventional opioids can lead to drug accumulation and prolonged duration of action. Hence, emphasis must be placed on regular assessment of pain and titrating down the infusion rates if the pain goals are achieved; the infusion rates can be decreased in a stepwise fashion by 25%.

The prolonged use of opioids has been associated with high incidence of side-effects like tolerance and withdrawal. This does not differ between the different opioids, the route, or the regimen used. The adverse effects of opioids include hypotension, bradycardia, ileus, nausea/vomiting, urinary retention, constipation, delirium, hallucinations, and hyperalgesia. Rare side-effects include immunosuppression, seizures, and muscle rigidity.

Non-opioid analgesics

The simple analgesics like paracetamol and the non-steroidal anti-inflammatory drugs (NSAIDs) are both effective for treating mild nociceptive pain.

Paracetamol. The mechanism of action of paracetamol is not well understood. Paracetamol can be given through many routes, including oral, i.v., and rectal. Paracetamol reduces opioid requirements, and so unless contraindicated should be considered as a first line drug in management of mild to moderate pain and should be included as part of the multimodal regimen in treatment of severe pain. Dosing of paracetamol in patients with low body weight, reduced glutathione stores (i.e. malnutrition or comorbidity) should be done cautiously as paracetamol may potentially cause liver injury even within normal recommended doses.

Table 3 Pharmacokinetics of commonly used opioids. Doses below are guides and vary widely for individual patients. B, bolus; I, infusion; PCA, patient-controlled analgesia; ESRF, end stage renal failure; IBW, ideal body weight; M3G, morphine-3-glucouronide; M6G, morphine-6-glucouronide. *Bolus doses are titrated in aliquots for achieving pain relief

Opioid	Onset after iv bolus	Half-life ($t_{1/2}$)	Dosage*	Important considerations
Fentanyl	1–2 min	2–4 h	B: 1–2 μg kg^{-1} I: 1–10 μg kg^{-1} h^{-1} PCA: 10–25 μg bolus, lock out: 5–15 min, 4 h limit 400–800 μg Patches: 25–100 μg h^{-1}	Metabolized in the liver with no active metabolites. Accumulation in hepatic impairment. Less likely to accumulate in ESRF. Less hypotension than with morphine. Highly lipid soluble, duration of action is significantly increased when continuous infusions are used for prolonged periods. Transdermal patches used in palliative care and opioid rotation
Morphine	5–10 min	3–4 h	B: 0.1–0.2 mg kg^{-1} I: 0.05–0.1 mg kg^{-1} h^{-1} PCA: 1–3 mg bolus, lock out: 5–15 min, 4 h limit: 30–70 mg Enteral: 5–20 mg fourth hourly	Metabolized by glucouronidation, active metabolites: M6G and M3G. Oral bioavailability poor 15–65%. M6G is more potent than morphine and accumulates in renal impairment and M3G can cause delirium. Caution in both hepatic and renal impairment. Morphine causes histamine release
Alfentanil	1–2 min	1.6 h	B: 10–30 μg kg^{-1} I: 20–60 μg kg^{-1} h^{-1}	Less lipid soluble, quick onset and offset. Dose related, short duration respiratory depression, elderly patients particularly sensitive. Clearance prolonged in hepatic impairment (cirrhosis) but unaffected in renal impairment
Remifentanil	1–3 min	3–10 min	B: 1 μg kg^{-1} I: 0.05–2 μg kg^{-1} min^{-1}	Hydrolysis by plasma esterases. No active metabolites. No accumulation in hepatic/renal failure. Use IBW in obese individuals. Used more often in the neuro-intensive care for early neurological assessment

Table 4 Pharmacokinetics of less common opioids used under special circumstances. *Bolus doses are titrated in aliquots for achieving pain relief

Opioid	$t_{1/2}$	Dosage*	Important considerations
Oxycodone	4–6 h	s.c. 2.5–5 mg fourth hourly Enteral: 5–10 mg fourth hourly	Predictable and higher oral bioavailability 60–87%, caution in hepatic and renal impairment. Used both in acute pain and in cancer/palliative pain
Diamorphine	3–4 h	I.V. bolus: 0.05–0.1 mg kg^{-1} s.c: 5–10 mg fourth hourly Enteral: 5–10 mg fourth hourly	Metabolized to active components monoacetyl morphine and morphine by esterases. Highly lipid soluble, less likely to cause respiratory depression when administered intrathecally. Mainly used for cancer pain and palliative care as subcutaneous infusions
Tramadol	4–6 h	I.V.: 50–100 mg fourth to sixth hourly Enteral: 50–100 mg fourth to sixth hourly	High oral bioavailability, only partial antagonism by naloxone, causes less respiratory depression. Accumulates in renal and hepatic impairment. Caution in patients with epilepsy. Contraindicated with concomitant use of mono amino oxidase inhibitors
Codeine	4–6 h	Enteral: 30–60 mg fourth hourly	50% oral bioavailability, 10% undergoes O-demethylation to morphine, less effective against severe pain. CYP 2D6 polymorphisms produce unpredictable effects. Poor metabolizers have inadequate pain relief; ultra-rapid metabolizers may have respiratory depression

Non-steroidal anti-inflammatory drugs. NSAIDs work by inhibition of the cyclooxygenase (COX) enzymes COX-1 and COX-2. They regulate production of prostaglandins and thromboxane from arachidonic acid with varying ratio of COX-1 *vs* COX-2 inhibition. NSAIDs have analgesic, anti-pyretic, and anti-inflammatory properties. The analgesic property of NSAIDs has not been well studied in critically ill patients, so it is unclear whether the potential benefits (e.g. reduced time of mechanical ventilation or decreased duration of ileus) outweigh potential risks (i.e. renal dysfunction, gastrointestinal bleeding). In a retrospective cohort study on patients admitted to ICU after rib fractures, ketorolac use was associated with decreased pneumonia, increased ventilator, and ICU-free days. The rates of acute kidney injury, gastrointestinal haemorrhage, and fracture non-union were not different.[8]

NSAIDs should be avoided in patients at risk of renal dysfunction (hypovolaemia and inotrope dependent shock), GI bleeding (mechanical ventilation, burns, and alcoholic liver disease) and in patients with platelet abnormalities, coagulopathy, concomitant angiotensin-converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, or aspirin sensitive asthma. Even selective COX-2 inhibitors have a similar effect to non-selective NSAIDs on reducing renal blood flow. Apart from the stable postoperative patient, NSAIDs find limited usage in ICU and are in general avoided. However, NSAIDs do have a place in critical care due their inhibition of prostaglandin synthesis (e.g. closure of patent ductus arteriosus in preterm neonates; hypothermic sepsis).

Analgesic adjuncts

There is abundant evidence to support the perioperative use of adjunctive drugs in reducing postoperative pain intensity and opioid consumption but there is paucity of evidence to support their routine use in critical care, except under specific circumstances. In general, pre-existing adjuvant drugs like gabapentinoids and tricyclic antidepressants (TCA) should be continued in ICU as cessation can precipitate withdrawal states.

Neuropathic pain is poorly treated with opioids and is best treated with analgesic adjuncts like the gabapentinoids, TCAs, or both.[4] Established neuropathic pain is very refractory to treatment, hence patients who are at a high risk of developing neuropathic pain should be started on the adjuvant medications early.

Adjuvant drugs (Table 5) lower opioid consumption and in addition to improving the quality of analgesia they also lower sedative requirements. They aid pain management in opioid tolerant individuals, facilitate opioid rotation and are useful in opioid and alcohol withdrawal.

Gabapentinoids. Gabapentin and pregabalin work by binding to the $\alpha_2\delta$ subunits of voltage dependent calcium ion channels. They reduce the development of hyperalgesia and central sensitization and are useful adjuncts in the treatment of neuropathic pain. Up to 89% of patients experience pain after demyelinating immune polyradiculoneuropathies like Guillain–Barre syndrome (GBS); the pain can be severe during the acute phase and up to a third may progress to develop chronic pain.[9]

Pain management in patients with conditions like GBS, multiple sclerosis (MS) or spinal cord injuries (SCIs) can be complicated and refractory. Gabapentin compared with carbamazepine or placebo reduces pain intensity in patients with GBS without increasing adverse side-effects. In a recent meta-analysis, both gabapentin and pregabalin have a moderate to large effect in reducing pain after SCI in the short and long term. In addition, they improve secondary measures like sleep, anxiety and depression and are now the first line drugs for post-SCI neuropathic pain.[10] Gabapentin has been used for pain management in the post-burn period and after surgical debridement.

The gabapentinoids are only available in the enteral formulation. Bioavailability of gabapentin is inversely related to the dose. Gabapentin is absorbed in a relatively small part of the duodenum and has a lower bioavailability compared with pregabalin, which is absorbed throughout the small intestine. Hence, gabapentin will be ineffective in patients on jejunal feeding. Side-effects of gabapentinoids include somnolence, dizziness, confusion, convulsions, and ataxia.

Tricyclic antidepressants. Amitriptyline is not licensed in the UK for treatment of acute pain but is useful for management of chronic and neuropathic pain. Specific circumstances relevant to intensive care where TCAs should be considered are neuropathic pain secondary to malignancy, diabetes, HIV, porphyrias, SCI, GBS, and MS. Side-effects of TCA include dry mouth, sedation, blurred vision, arrhythmias, and postural hypotension. TCAs must be avoided in patients with QT_c prolongation.

α_2-Agonists. Clonidine and dexmedetomidine are α_2-adrenoceptor agonists, which provide both analgesia and sedation. Dexmedetomidine has eight times more affinity for α_2-receptors compared with clonidine. Despite the well-known synergistic property of α_2-agonists and opioids, there is limited evidence to support their routine use for their opioid sparing properties in intensive care.

In contrast to clonidine, which has found a place as a perioperative analgesic adjunct, dexmedetomidine is more commonly used as an analgo-sedative in the intensive care setting. Dexmedetomidine infusion has been shown to reduce the prevalence and duration of confusion and delirium when compared with the use of morphine and midazolam.[11]

Both clonidine and dexmedetomidine have been used to treat opioid, benzodiazepine and alcohol withdrawal. Iatrogenic opioid withdrawal syndrome is a well-recognized entity both in the adult and paediatric intensive care (PICU) and occurs in up to 57% of PICU patients for which α_2-agonists are useful second line agents.[12] α_2-Agonists are used to improve quality of analgesia and aid opioid rotation in opioid tolerant individuals (e.g. burns, substance abuse). The side-effect profile of both α_2-agonists includes bradycardia and hypotension, which may limit the dose that can be safely administered. Abrupt cessation of α_2-agonists can cause rebound hypertension and can rarely cause a withdrawal syndrome.

Ketamine. Ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist that is effective both as an analgesic and also a sedative agent. It improves the quality of analgesia with a tolerable neuropsychiatry side-effect profile. Ketamine is used more commonly as an analgo-sedative in PICU but it is reserved for special situations in the adult ICUs. In a study of patients admitted to the surgical intensive care after major abdominal surgery, low-dose ketamine infusion ($\leq$0.12 mg kg^{-1} h^{-1}) reduced cumulative PCA morphine requirements by up to 25% despite having similar VAS scores at rest and mobilization.[13] Low-dose infusions of ketamine ($\leq$0.25 mg kg^{-1} h^{-1}) with midazolam (0.5–1 mg h^{-1}) have been found to be effective in the management of pain in sickle cell crisis with improved pain scores and reduced morphine

Table 5 Adjuvant drugs. B, bolus; I, infusion

Drug	$t_{1/2}$	Dosage	Important considerations
Ketamine	2.5–3.5 h	B: 0.1–1 mg kg^{-1}; I: 0.125–0.5 mg kg^{-1} h^{-1}	Metabolite nor-ketamine is less potent and has hypnotic effect. Oral bioavailability 20%. Caution in patients with raised ICP, ischaemic heart disease, significant hypertension and psychotic states
α_2-Agonists			
clonidine		B: 2–5 μg kg^{-1}; I: 0.3 μg kg^{-1} h^{-1} Enteral: 50–150 μg	Reduced myocardial ischaemia, sedation, and hypotension at higher doses
dexmedetomidine		B: 1 μg kg^{-1}; I: 0.2–1 μg kg^{-1} h^{-1}	Not available orally
Gabapentinoids			
gabapentin	4.8–8.7 h	Enteral: 900–3600 mg day^{-1} in 3 divided doses	Bioavailability of gabapentin inversely related to dose. Both gabapentinoids have no hepatic metabolism and are excreted largely unchanged in the urine. Dose adjustment in renal impairment
pregabalin	5.5–6.7 h	Enteral: 50–300 mg day^{-1} in 2–3 divided doses	
Amitriptyline		Enteral: 10–100 mg	Useful in neuropathic pain. Caution in elderly, start at night-time at low dosage. Avoid in heart blocks and QT_c prolongation
Magnesium		B: 40 mg kg^{-1} I: 10 mg kg^{-1} h^{-1}	Delayed tendon reflexes in high doses/prolonged infusions. Prolongs duration of action of neuromuscular blockers

use. Addition of ketamine provides an opioid sparing effect in burns and opioid dependent/tolerant patients.

Pain and stress response because of tracheal suctioning (TS) causes increases in mean arterial pressure (MAP), intracranial pressure (ICP), mean cerebral blood flow velocity (mCBV), and cerebral perfusion pressure (CPP); acute rises of these parameters can be deleterious in head injured and neurosurgical patients. In a small observational study in patients sedated with propofol and remifentanil, addition of an infusion of ketamine at 0.1 mg kg^{-1} min^{-1} for 10 min before TS reduced cough scores and inhibited the increase in MAP, CPP, and mCBV but not ICP. Similarly in neurosurgical patients, infusions of S(+) ketamine compared with fentanyl for analgesia showed no differences in pain scores, cerebral haemodynamics or rates of developing ileus but patients who had S(+) ketamine showed a trend of decreasing norepinephrine requirements.[14] Ketamine is used as a useful adjunct in analgesic drug rotation and facilitating weaning from long-term opioid therapy in ICU. Ketamine's sedative and bronchodilatory properties have been used in refractory status epilepticus and status asthmaticus respectively. Side-effects of ketamine include delirium, hallucinations, nausea, and vomiting.

Magnesium. Magnesium causes blockade of NMDA receptors and acts as a useful perioperative adjunct by reducing analgesic requirements without major haemodynamic complications. In ICU, there is no evidence to support its use for analgesia or opioid sparing effect but its use is limited to management of atrial fibrillation, prevention of vasospasm after aneurysmal subarachnoid haemorrhage and for management of blood pressure in pre-eclampsia or eclampsia.

Alternative therapy

Other modalities of pain management like transcutaneous electrical nerve stimulation, acupuncture, and aromatherapy have a very weak evidence base in acute pain management and in intensive care, but should be considered as their side-effect profile is low.

Renal and hepatic dysfunction

The incidence of renal dysfunction in the mixed intensive care population is ~20%[15] and the incidence of liver dysfunction remains unknown as there is no universal definition for liver dysfunction. Most analgesic drugs depend on hepatic and renal clearance of either the parent drug, its metabolites (toxic or active), or both. Moreover, some drugs may aggravate pre-existing or cause new liver (e.g. amitriptyline, carbamazepine, and valproate) or renal dysfunction (e.g. NSAIDs). In general, short-acting drugs with very rapid clearance and no/minimal active metabolites (fentanyl, alfentanil, sufentanil, remifentanil, buprenorphine, paracetamol, and ketamine) can be used safely in renal failure. Drugs like morphine, oxycodone, tramadol, amitriptyline, clonidine, and gabapentin have been used in renal dysfunction, but require dosage adjustment based on the estimated glomerular filtration rate. In liver dysfunction, most drugs have significantly impaired clearance and higher oral bioavailability because of the reduced first pass metabolism. Drugs with short half-life and independent of hepatic clearance (e.g. remifentanil) must be considered.

Conclusion

Pain is a common problem in intensive care and remains poorly assessed and managed. Pain adversely affects multiple organ systems and inadequately managed pain has a direct impact on outcomes. When managing pain, emphasis must be placed on regular assessment and using a protocol-based multimodal analgesic regimen. The decision on the choice of the analgesic drugs must take into the account the varied physiological derangements that can also occur in ICU and also the potential for these drugs to cause organ damage.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

References

1. Puntillo KA. Pain experiences of intensive care unit patients. *Heart Lung* 1990; **19**: 526–33
2. Schelling G, Stoll C, Haller M *et al*. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med* 1998; **26**: 651–9
3. Payen JF, Chanques G, Mantz J *et al*. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology* 2007; **106**: 687–95
4. Barr J, Fraser GL, Puntillo K, Ely EW *et al*. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**: 263–306
5. Sessler CN, Grap MJ, Ramsay MA. Evaluating and monitoring analgesia and sedation in the intensive care unit. *Crit Care* 2008; **12**(Suppl. 3): S2
6. Payen J, Bru O, Bosson J *et al*. Assessing pain in critically ill sedated patients by using a behavioural pain scale. *Crit Care Med* 2001; **29**: 2258–63
7. Jacobi J, Fraser GL, Coursin DB, Riker R *et al*. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; **30**: 119–41
8. Yang Y, Young JB, Schermer CR, Utter GH. Use of ketorolac is associated with decreased pneumonia following rib fractures. *Am J Surg* 2014; **207**: 566–72
9. Moulin DE, Hagen N, Feasby TE, Amireh R, Hahn A. Pain in Guillain-Barré syndrome. *Neurology* 1997; **48**: 328–31
10. Mehta S, McIntyre A, Dijkers M *et al*. Gabapentinoids are effective in decreasing neuropathic pain and other secondary outcomes after spinal cord injury: a meta-analysis. *Arch Phys Med Rehabil* 2014; **95**: 2180–6
11. Riker RR, Shehabi Y, Bokesch PM *et al*. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301**: 489–99
12. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med* 1994; **22**: 763–7
13. Guillou N, Tanguy M, Seguin P *et al*. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. *Anesth Analg* 2003; **97**: 843–7
14. Schmittner MD, Vajkoczy SL, Horn P *et al*. Effects of fentanyl and S(+)-ketamine on cerebral hemodynamics, gastrointestinal motility, and need of vasopressors in patients with intracranial pathologies: a pilot study. *J Neurosurg Anesthesiol* 2007; **19**: 257–62
15. Wang HE, Muntner P, Chertow GM *et al*. Acute kidney injury and mortality in hospitalized patients. *Am J Nephrol* 2012; **35**: 349–55

Appendix

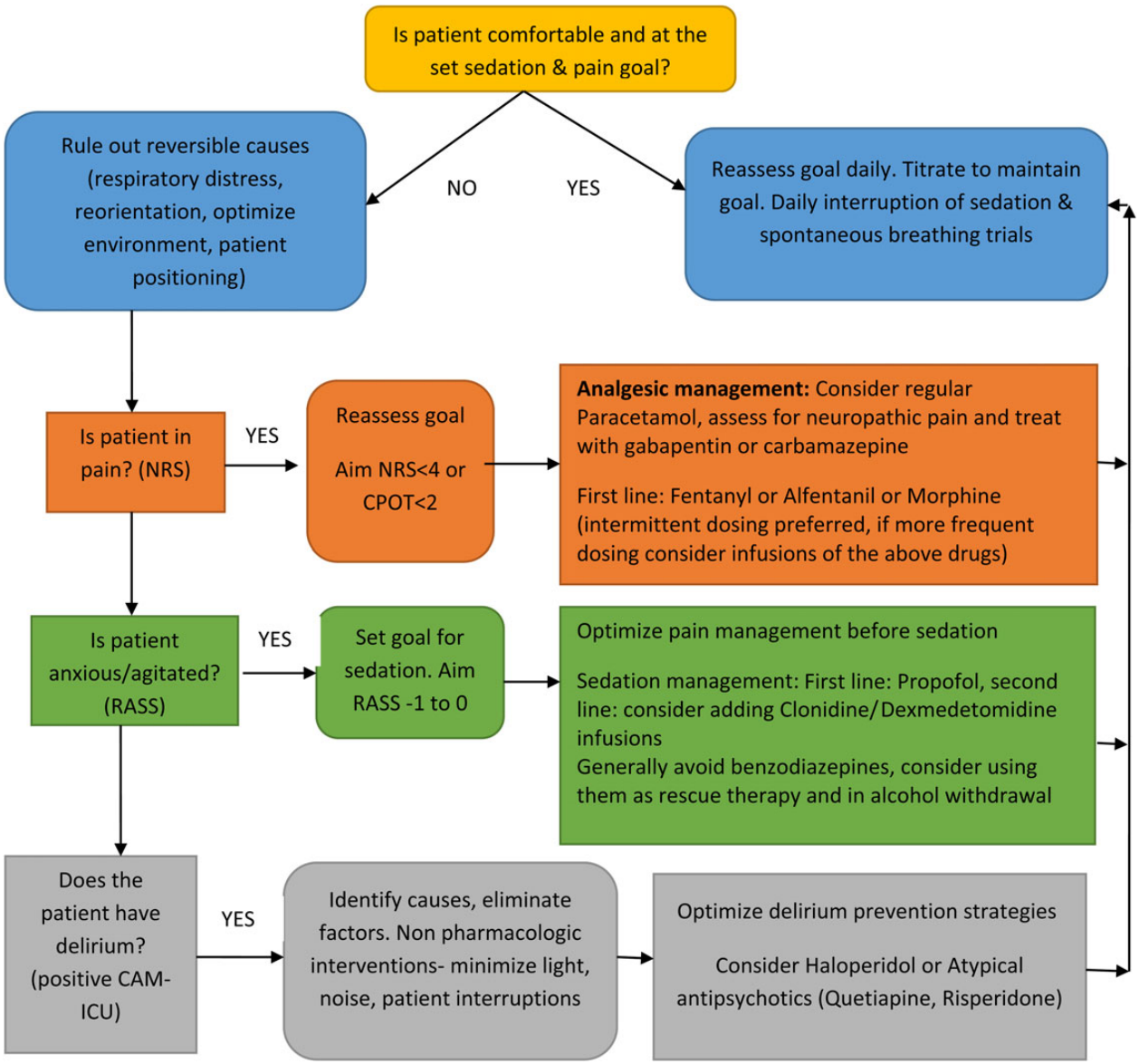

Fig A1 Composite pain, agitation and delirium management guideline in mechanically ventilated adult ICU patients. NRS, numerical rating scale; CPOT, critical care pain observation tool; RASS, Richmond agitation and sedation scale; CAM-ICU, confusion assessment method for ICU. Adapted from Barr and colleagues.[4]