Sedation and analgesia for critically ill children

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Abstract

Effective sedation and analgesia in the critically ill child ensures physical comfort and minimises psychological distress. In the UK the most commonly used sedative and analgesic agents for critically ill children are midazolam and either morphine or fentanyl. Consensus clinical practice guidelines for the provision of sedation and analgesia in critically ill children were published in 2006 by the UK Paediatric Intensive Care Society, but considerable variation in practice persists.

It is important to treat pain, and in addition to the obvious immediate effects of untreated pain there is increasing evidence that pain experienced early in life may result in long-term changes in neurosensory function. There are however also concerns that sedative and analgesic agents may themselves be associated with developmental neurotoxicity, particularly amongst neonates, and adverse psychological outcomes in survivors of critical care.

Withdrawal syndrome and delirium remain poorly understood, although we have emerging tools such as the Sophia Observation withdrawal Symptoms-scale (SOS) and the paediatric Confusion Assessment Method for the ICU (pCAM-ICU). The most important single factor in reducing avoidable psychological morbidity in survivors of PICU is to minimise the administered doses of sedative and analgesic agents.

Keywords analgesia; critical care; delirium; midazolam; morphine; sedation; withdrawal

Sedation and analgesia for critically ill children

Providing effective analgesia and sedation for critically ill children in the Paediatric Intensive Care Unit (PICU) involves caring for both the physical comfort and the psychological well-being of the child. Correctable environmental and physical factors causing discomfort should be addressed before the commencement of pharmacological agents. Once an adequate level of analgesia has been achieved, additional sedative agents may be required. The aims of sedation are to reduce anxiety and distress in the child, to facilitate uncomfortable therapeutic and diagnostic procedures, and to reduce the risk of inadvertent self-extubation and other forms of so-called 'treatment interference'. Analgesia and sedation strategies must account for the background discomfort of ongoing interventions such as the presence of a tracheal tube, and allow for the provision of temporary deeper levels of sedation, with appropriate analgesia, to facilitate intermittent painful procedures.

Tachyphylaxis, tolerance and dependency are well-known adverse effects of sedative and analgesic agents. More recently associations have been made between the administration of these agents and the incidence of cerebral apoptosis and impaired psychological well-being in survivors of critical care.

Current practice

Considerable variation in the use of pharmacological agents for analgesia and sedation for critically ill children has been demonstrated. In a prospective observational study of critically ill children in 20 PICUs throughout the UK, a total of 24 different sedative and analgesic agents were reported to be used. Surveys have shown that the most commonly used sedative and analgesic agents for critically ill children within the UK are midazolam and morphine, whereas in the USA midazolam and fentanyl are more commonly administered. In critically ill adults, the administration of continuous infusions of sedative agents has been associated with prolonged periods of mechanical ventilation and a routine daily interruption of intravenous sedative agents is now recommended practice. This practice has led to a reduction in duration of mechanical ventilation and reduced duration of intensive care admission, without any apparent adverse psychological effects. Whilst it has been proven that increased sedative use in the first 24 hours of weaning from mechanical ventilation is associated with subsequent failure of extubation in infants and children, a routine daily interruption of intravenous sedative agents has yet to be thoroughly evaluated in critically ill children where the potential adverse effects of discontinuing sedative agents include inadvertent self-extubation, adverse cardiovascular effects and possible negative psychological outcomes.

The introduction of clinical guidelines has been associated with a significant reduction in sedative costs per bed day in adult critical care units. Consensus clinical practice guidelines for the provision of sedation and analgesia in critically ill children were published in 2006 by the UK Paediatric Intensive Care Society.

When Long surveyed PICUs across Australia and New Zealand in 2005 it was found that only half of the units had sedation guidelines, and that sedation and pain assessments were not carried out using validated paediatric scales. Amigoni reported similar deficiencies in the provision of sedation and withdrawal monitoring in Italy in 2012. In a recent online international survey of PICU sedation management by Kudchadkar only 27% of units had written sedation protocols, 70% used sedation scoring systems and only 42% utilised goal directed sedation management. The State Behavioral Scale was the most common scale used in North America and the COMFORT score used in all other countries; in this study 72% of units used a combination of an opiate and a benzodiazepine.

Analgesia

Regional analgesia

Subcutaneous or topically administered local anaesthetics such as tetracaine, prilocaine and lignocaine are used in critically ill children for the short-term relief of painful procedures. Regional techniques such as epidural analgesia may be particularly

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effective in the post-operative patient, whilst peripheral nerve blocks are used less frequently in PICU.

NSAIDs and paracetamol

NSAIDs provide analgesia through the non-selective, competitive inhibition of cyclo-oxygenase, a critical enzyme in the inflammatory cascade. Although the administration of NSAIDs has been shown to significantly reduce opioid requirements in adult and paediatric pain after surgery by approximately 15—30%, the analgesic benefits of NSAIDs have yet to be systematically studied in critically ill children. Paracetamol is an analgesic used to treat mild to moderate pain. When used in combination with opioid agents, paracetamol produces a greater analgesic effect than higher doses of opioid alone, and has also been shown to have an opioid-sparing effect in adults.

Opioids

Opioids produce analgesia via a variety of central and peripheral opioid receptors, particularly the mu and kappa receptors. It is believed that interaction at other receptors may be responsible for the adverse effects associated with these agents. The pharmacokinetics and pharmacodynamics of systemic analgesic agents vary with age. Neonates frequently demonstrate reduced clearance of agents because of hepatic enzyme system immaturity, whilst older children may demonstrate higher weight-indexed clearance than adults because of their relatively large liver mass.

Morphine

Morphine is the only poorly lipid soluble opioid in common use. When administered in a single dose of 0.1 mg/kg intravenously, its peak analgesic effect occurs after 20 minutes and its duration of action is approximately 4 hours. Morphine undergoes extensive hepatic and extra-hepatic glucuronidation and metabolites are excreted primarily in the urine. The elimination of morphine from the body is slow and quantitatively different in newborns, but increases towards adult values within the first 6 months of life. Morphine may stimulate the release of significant amounts of histamine and inhibits compensatory sympathetic responses; hence the vasodilation produced by morphine may result in significant hypotension particularly after bolus administration. Discontinuation of morphine infusions has been associated with withdrawal phenomena, which may include pupillary dilatation, lacrimation, sweating, goose pimples on the skin, hypertension, pyrexia, vomiting, abdominal pain, diarrhoea, muscle and joint pains, and characteristic behavioural changes.

Fentanyl

Fentanyl is a synthetic opioid with approximately 100 times the analgesic potency of morphine. It is highly lipid soluble, and this accounts for its rapid onset of action. Fentanyl administration causes less histamine release than morphine, and therefore is less associated with the onset of hypotension. When given intravenously, fentanyl has a relatively short half-time of 30—60 minutes owing to rapid redistribution into peripheral compartments. With prolonged administration, there is accumulation within these peripheral compartments causing an increase in the context sensitive half-time and tolerance may rapidly develop. Metabolism occurs almost exclusively in the liver and clearance is markedly affected by hepatic blood flow. Fentanyl has no active metabolites and does not cross-react in patients with morphine allergy.

Remifentanil

Remifentanil is an ultra-short acting synthetic opioid, which acts as a pure mu-receptor agonist. The cardiorespiratory effects of remifentanil are similar to those of the other opioids. This drug has an exceptionally short half-time of 3 minutes in all age groups as it is metabolised by plasma and tissue esterases with a very small volume of distribution. The effects of remifentanil dissipate rapidly, even after prolonged infusion, giving it a very short context sensitive half-time. Remifentanil has been used to provide ongoing analgesia in PICU although prolonged use of this agent is associated with the rapid development of tolerance and relatively high cost. This agent may have more potential for procedural analgesia in the critical care setting given its rapid onset and offset times and effective blunting of airway reflexes, although respiratory and cardiovascular depressant effects should be anticipated in this setting.

When used in 17 children for sedation during painful procedures, Bauman and colleagues found an unacceptably high incidence of life-threatening respiratory depression at subtherapeutic levels of the drug. This feature may makes remifentanil more suitable for facilitating painful procedures in situations where the airway is already protected, either in the mechanically ventilated PICU patient or during procedures such as bronchoscopy.

Long term effects of early pain

In addition to the obvious immediate physiological effects of untreated pain there is increasing evidence that pain experienced early in life can result in long-term changes in neurosensory function. The likely reason for this is that the nervous system is sensitive to changes levels of neuronal activity. Similarly, increased levels of neuronal activity due to pain or injury may lead to changes in the subsequent pattern of neural connectivity and sensitivity.

Any long-term changes in neurosensory function produced as a result of exposure to pain in early life depend on multiple factors and mechanisms including the following:

- The type, duration and severity of the pain experienced in early life. It has been demonstrated that ex-preterm infants who have undergone surgery in addition to medical neonatal intensive care have a greater degree of subsequent sensory change. Similarly, it has been demonstrated that the severity of a burn injury experienced in infancy can influence sensitivity to mechanical and thermal stimulation in later life.
- Timing of the pain. Pain pathways undergo significant structural and functional changes during postnatal development; therefore the age at which pain is experienced influences later effects. These changes include alterations in the expression and distribution of neurotransmitters and receptors, changes in the distribution of sensory fibres throughout the spinal cord, and changes in the balance of excitatory and inhibitory modulation. Hence, surgical incisions occurring in the first week of life have been associated with long-term changes in sensory processing, but not if they occur later in life.