Analgesia and sedation in paediatric intensive care

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Introduction

Infants and children who are admitted to the intensive care unit (ICU) require treatment for their primary disease and maintenance of their bodily functions (fluid balance, energy intake and temperature control) to optimise recovery. Additional treatments provide analgesia, reduction of the level of consciousness, and when indicated, muscle relaxation. While this triad forms the basis of classical anaesthesia, in paediatric intensive care it is used for longer periods, often below the levels required for surgery and with different goals. This brings to the fore specific problems that relate to the drugs. These include differing pharmacokinetics and drug responses because of age and individual pathophysiology, tolerance and withdrawal, toxicity associated with long-term use and the need to effectively monitor drug effect against delivery. Regrettably, administration of sedative drugs in the paediatric ICU (PICU) is often approached in a generic way and as an afterthought. Instead, more attention is paid to the primary disease. This can lead to morbidity that could have been avoided.

Undersedation and oversedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child who may be unable to move or communicate distress because of the use of muscle relaxants, while the unparalysed child may fight against the ventilator, leading to ineffective ventilation, accidental extubation or the loss of invasive access or monitors. In intensive care, agitation and inadequate sedation have been correlated with adverse short- and longer-term outcomes. Recent data have highlighted that intensive care and surgery are associated with long-term dysregulation of nociceptive mechanisms, which may change behaviour and responses to future sensory and pain stimuli. By contrast, oversedation delays recovery, promotes tolerance to the drugs and leads to distressing symptoms on withdrawal (agitation, seizures, hallucinations, psychosis, fever and tachycardia). Opioids, in particular, are associated with dose-dependant immunosuppression of both humoral and cell-mediated immunity, which acts to promote infection and sepsis during a longer PICU stay.

Maintaining ideal analgesia, while simultaneously promoting earlier extubation and PICU discharge, can be difficult to achieve. Infants have an almost binary state of consciousness. A normally active three-year-old child cannot easily be persuaded to remain quiescent for long periods in the ICU environment using nonpharmacological comforting measures alone. Furthermore, in the current healthcare environment, there are considerable consumer and parental pressures. This makes it necessary to ensure that all discomforts, whether real or perceived, are avoided. However, recent advances in drug choices, patient monitoring and other therapeutic options offer new prospects for the future.

Simplistically, analgesic drugs should be given for pain relief and sedative drugs to reduce the level of consciousness, while muscle relaxants should only be used for specific situations when paralysis is essential, e.g. low cardiac output states, when it may be necessary to anaesthetise, paralyse and cool a child. However, there is some crossover in these roles. Morphine has sedative properties, ketamine provides analgesia and anaesthesia, and even muscle relaxants may have an additive effect on the reduction of the conscious state through deafferentation. Individual

drugs have secondary properties which may be exploited therapeutically in specific situations, for example the use of high-dose opioids in the management of pulmonary hypertension. Sedation and analgesia strategies need to be viewed as a collaborative effort between the anaesthetist and intensivist in order to optimise the postoperative recovery gradient for the individual. For example, the perioperative strategy for an infant with ventricular septal defects may include on-table or early extubation within four hours, with continued sedation and analgesia to ensure that the infant can cope with the constraints of intensive care management. By contrast, the complex, postoperative neonate with a low cardiac output state may have an ongoing requirement for high-dose opioids, sedation and paralysis in PICU.

Analgesia in the PICU

Analgesic drugs comprise opioids, local anaesthetic agents, prostaglandin synthetase inhibitors [nonsteroidal anti-inflammatory drugs (NSAIDs)], acetaminophen, ketamine and the alpha-2 agonists, clonidine and dexmedetomidine. Following cardiac surgery, opioids remain the primary analgesic agents, because of their high efficacy. Co-analgesia with NSAIDs and acetaminophen plays a key role in reducing opioid requirements and side-effects. This is particularly useful in the case of PICU stay after surgery. The use of local anaesthesia with topical, regional or even neuraxial block is often underexploited in PICU.

Opioids have properties other than analgesia that can be exploited in the care of the critically ill child. Potent opioids, such as fentanyl, sufentanil and remifentanil, delivered at doses higher than that required simply for analgesia, can obtund haemodynamic and adverse hormonal and metabolic responses in the critically ill. Studies by Anand et al have demonstrated that high-dose opioids used during surgery were associated with reduced stress response, nitrogen loss, postoperative complications and mortality. This led to a view that high-dose opioid analgesia, which aims to obtund measured responses to surgery, is key to good outcome in the high-risk surgical infant. However, less is known about the benefits of high-dose opioids in the context of general paediatric intensive care. Certainly, high-dose opioid administration has been shown to be beneficial in the prevention and treatment of specific situations, such as a pulmonary hypertensive crisis in the at-risk infant. It may benefit patients with a low cardiac output state or those with a critically balanced pulmonary to systemic shunt. However, data are limited outside these specific areas.

Control of the stress response can be achieved at much lower doses than those used in the earlier studies, and exposure to high-dose opioids such as fentanyl (50 µg/kg or higher) is associated with hypotension. The issue of benefits vs. side-effects of opioids in the critical care setting have been highlighted by the results of the Neurological Outcomes and Pre-emptive Analgesia in Neonates (NEOPAIN) study in preterm neonates. The findings have been subject to considerable debate, but suggest that observed comfort was improved at the expense of systemic hypotension in preterm neonates who were given morphine in a more liberal fashion than controls. This was associated with increased risk of significant short- and long-term neurological injury and adverse outcomes. While management of the newborn baby is a special case, the inference in PICU is clear: the provision of opioids mandates careful management to avoid haemodynamic instability, whatever dose is provided. Children with severe cardiovascular compromise need careful hemodynamic monitoring and the availability of supportive therapy when first exposed to intense analgesia.

All opioids are associated with tolerance and result in increasing requirements to maintain adequate analgesia and sedation. This is accelerated by high-dose opioid techniques during anaesthesia that can cause “acute tolerance”, an effect which has been shown to be more pronounced in shorter-acting, higher-potency opioids, such as fentanyl and remifentanil. Neonates who undergo extracorporeal membrane oxygenation require five times the initial fentanyl infusion rate by day six to achieve an equivalent level of sedation because of a combination of enhanced elimination and pharmacodynamic tolerance.

Sedation in the PICU

Sedation is a broad term when used in the context of PICU. It may facilitate several goals, including:

- Unconsciousness (virtual anaesthesia) or a reduction in the level of consciousness.
- Reduced awareness.
- Loss of explicit and implicit memory.
- Compliance with the need to lie in a confined space, attached to monitors and invasive lines.
- Prevention of distress during procedures such as physiotherapy, radiological scanning or minor surgical intervention. Enhanced levels of sedation may be required.

Different drugs fulfil these roles to varying extents. Benzodiazepines, for example, provide anterograde amnaesia, with reduced or complete unconsciousness at different doses, while phenothiazines and butyrophenones (chlorpromazine and haloperidol), when used as major tranquillising drugs in schizophrenia, have psychotropic properties that render the patient disinterested in activity. Some analgesic drugs reduce both pain and consciousness.

Ketamine provides analgesia and dissociative anaesthesia or sedation, clonidine produces analgesia and a calmed relaxed state, and morphine has additional sedative properties. Therefore, choice of a sedative regimen needs to be tailored to the individual, rather than be generic.

Neonates are a special group in that morphine alone can often provide sufficient analgesia and sedation. However, outside this period, an analgesic and a sedative drug are almost always necessary. A sedative drug given at an adequate dose becomes mandatory to prevent awareness when neuromuscular blockade is required.

In the past, patients in adult ICU were given an opioid in combination with a low dose of anaesthetic agent to ensure pain relief, haemodynamic stability and tolerance to the constraints of the ICU. The potentially lethal side-effects of anaesthetic drugs that have been used for several days have only emerged after reviews of death rates and analysis of recurring adverse events. These have included immunomodulation by barbiturates, adrenocortical suppression by etomidate, and more recently, mitochondrial dysfunction with propofol in adults and children.

Sedation and analgesia in the long-stay patient

As the management of the cardiac surgical patient continues to improve, the need to ventilate infants for days and weeks has diminished. However, those with residual problems whose improvement cannot be achieved immediately by further intervention, or who remain marginal for cardiac or noncardiac reasons, may enter a phase of chronic sedation and ventilation as their issues resolve. Examples include those with cardiac failure, pulmonary hypertension, lung or airway disease or ongoing sepsis. These patients are at the most risk of experiencing drug tolerance and subsequent withdrawal. Some agents are considered to be more problematic than others. The incidence of withdrawal with midazolam has been reported as frequently as 35%. Limiting the midazolam infusion to 100 μg/kg/hour reduces the likelihood of withdrawal, but stopping the drug slowly does not reduce the risk.

Techniques that can be used in PICU to limit problems that are associated with long-term sedation include:

- Drug cycling: Change pharmacological drug groups routinely to reduce the emergence of tolerance.
- Sedation holidays: Sedative drugs should be ceased temporarily to evaluate emergence.
- Nonpharmacological techniques: Provide oral sucrose, reduce environmental stress (noise, light and interruption of the day-night cycle), and swaddle the infant.
- Transfer to oral sedation where possible.

In adult intensive care, percutaneous tracheostomy is often performed at an early stage. This allows the patient to be ventilated while awake with minimal sedation. This lets the patient breath with support ventilator modes, be able to cough and clear his or her own secretions more effectively, while reducing the risk of nosocomial chest infections. Unfortunately, this technique cannot be applied in children because of the technical issues that are associated with smaller airways and the continuing need for sedation. However, surgical tracheostomy and insertion of a long-term indwelling central venous catheter can allow a patient who requires longer-term ventilator support to be managed with little or no sedation.

Neuromuscular blockade can be useful in patients who are difficult to ventilate, i.e. in the event of inverse ventilatory ratios, high-frequency oscillation, or when there is a need to deliberately hyperventilate or hypoventilate them, depending on their underlying pathology. It continues to be used in children who require hypothermia because of dysrhythmia, or to reduce metabolic rate and oxygen demand. Neuromuscular blockade is used more commonly than in adult ICU, but as a specialty it is now being used less frequently. Recent reports have estimated use of long-term neuromuscular blockade in 14-16% of ventilated days in PICU. Avoidance of prolonged use is preferable because of the risks of critical care polyneuropathy and drug accumulation. These may result in delayed extubation.

Withdrawal phenomena remain a major concern in patients who have received sedation for several days. Symptoms can include sweating, tachycardia, hypertension, agitation, posturing, withdrawal, vomiting and diarrhoea. Occasionally, this prompts concerns about the possibility of and investigation into cardiac, neurological or gastrointestinal disease. The alpha-2 agonist, clonidine, as well as chlorpromazine and haloperidol, can be used effectively to moderate these effects and in patients who are discharged to wards on a weaning oral regimen over a period of 7-14 days. Concerns remain about abrupt cessation of clonidine and the risk of rebound hypertension.

Assessment of pain and sedation

Sedation is administered to critically ill children according to predicted requirements. However, this may not reflect actual requirements. There can be significant individual variation. Assessment of depth of sedation, with the titration of analgesic and sedative drugs, is important to ensure comfort and avoid adverse outcomes that are associated with undersedation or oversedation.

Several scales that assess behavioural or physiological measures have been developed and validated for this

purpose. These include the Comfort Scale, which is an objective measure of distress in ventilated paediatric patients, validated in all age groups. It comprises eight variables, each rated from 1-5: alertness, calmness or agitation, respiratory response, physical movement, heart rate, blood pressure, muscle tone and facial tension. The scale ranges from 0-40, with a target range of 17-26. As with other scoring systems, it is limited by interobserver variability, provides only intermittent data and cannot be used in the context of neuromuscular junction (NMJ) blockade.

Neurophysiological methods and auditory-evoked potentials have been evaluated in the research domain. Bispectral index (BIS) monitoring utilises data from electroencephalogram (EEG) to measure depth of anaesthesia. This technique assumes that changes in frequency are related and searches for phase coupling among frequency bands (biocoherance). There is minimal synchronisation in individuals who are awake because of multiple signal generators within the brain, whereas during sleep, there is less activity and the EEG reflects coupling between signal generators. A dimensionless value, the BIS number, is calculated, which ranges from 0-100. Zero indicates an isoelectric state, while 100 signifies a fully awake individual. Values of 40-60 are seen in general anaesthesia. While it may provide an accurate assessment of depth of sedation for single agents such as midazolam, propofol and volatile agents, this is not the case for opiates or ketamine. Furthermore, Messner et al demonstrated that the BIS index declines with NMJ blockade in awake volunteers. This suggests that it may not identify patients who are inadequately sedated with a muscle relaxant. The BIS monitor is age-dependent. Currently, there is insufficient evidence to support the routine use of the BIS monitor or any other neurophysiological sedation scoring technique in PICU.

Bibliography

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