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Analgesia and Sedation After Pediatric Cardiac Surgery

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Summary

In recent years, the importance of appropriate intra-operative anesthesia and analgesia during cardiac surgery, has become recognised as a factor in postoperative recovery. This includes the early perioperative management of the neonate undergoing radical surgery and more recently the care surrounding fast track and ultra fast track surgery. However, outside these areas, relatively little attention has focused on postoperative sedation and analgesia within the pediatric intensive care unit (PICU). This reflects perceived priorities of the primary disease process over the supporting structure of PICU, with a generic approach to sedation and analgesia that can result in additional morbidities and delayed recovery. Management of the marginal patient requires optimisation of not only cardiac and other attendant pathophysiology, but also to every aspect of supportive care. Individualised sedation and analgesia strategies, starting in the operating theatre and continuing through to hospital discharge, need to be regarded as an important aspect of perioperative care, to speed the process of recovery.

Keywords: Sedation; analgesia; pediatric; intensive care; cardiac; withdrawal

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General Principles

Infants and children admitted to the intensive care unit (ICU) require treatment for their primary disease and maintenance of bodily functions (fluid balance, energy intake, temperature control) to optimise recovery. Additional treatments provide analgesia, reduction of conscious level and when indicated, muscle relaxation. While this triad form the basis of classical anesthesia, in paediatric intensive care they are used for longer periods, often below the levels required for surgery and with different goals. This brings to the fore specific problems related to the drugs. These include differing pharmacokinetics and drug responses due to 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 pediatric intensive care unit (PICU) is often approached in a generic way and as an afterthought, with more attention paid to the primary disease, which can lead to avoidable morbidity.

Undersedation and oversedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child who may be unable to move or communicate distress due to use of muscle relaxants, while the unparalysed child may “fight” the ventilator leading to ineffective ventilation, accidental extubation or the loss of invasive access or monitors. In intensive care, agitation and inadequate sedation has been correlated with adverse short and longer-term outcome (1-2). Recent data has highlighted that intensive care and surgery is associated with long-term dysregulation of nociceptive mechanisms, which may change behaviour and responses to future sensory and pain stimuli (3). By contrast, oversedation delays recovery, promotes tolerance to the drugs and leads to distressing symptoms on their withdrawal (agitation, seizures, hallucinations, psychosis, fever and tachycardia) (4). Maintaining ideal analgesia whilst at the same time promoting earlier extubation and PICU discharge can be difficult to achieve. Infants have an almost binary state of consciousness, (5) and a normally active three year old cannot easily be persuaded to remain quiescent for long periods in the ICU environment using non-pharmacological comforting measures alone. Furthermore, in the current healthcare environment, there are considerable consumer/parental pressures to ensure that all discomforts whether real or perceived are avoided. Recent advances in drug choices, patient monitoring and other therapeutic options, however, offer new prospects for the future.

Simplistically, analgesic drugs should be given for pain relief, sedative drugs for reduction of conscious level, and muscle relaxants used only 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 anesthesia and even muscle relaxants may have an additive effect on reduction of conscious state through deafferentation (6). 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 anaesthetist and intensivist in order to optimise the “postoperative recovery gradient” for the individual. For example, the perioperative strategy for an infant VSD 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 (Table 1 and 2)

Table 1 and 2 near here

Analgesic drugs comprise opioids, local anesthetic agents, prostaglandin synthetase inhibitors (NSAID's), acetaminophen, ketamine and alpha-2 agonists (clonidine and dexmedetomidine). Opioids remain the primary analgesic agents after cardiac surgery because of their high efficacy. Co-analgesia with NSAID's and acetaminophen plays a key role in reducing opioid requirements and side effects (7), which is particularly useful for fast track surgery.

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 remifentanyl delivered at doses higher than that required simply for analgesia can obtund hemodynamic and adverse hormonal and metabolic responses in the critically ill. Studies by Anand and others demonstrated that high-dose opioids used during surgery were associated with reduced stress response, nitrogen loss, postoperative complications and mortality (8-10) This led to a view that high-dose opioid analgesia, which aims to obtund measured responses to surgery are key to good outcome in the high-risk surgical infant. Less is known, however, about the benefits of high dose opioids

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in the context of general pediatric 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 (11), and may benefit patients with a low cardiac output state, or those with a critically balanced pulmonary to systemic shunt. Data is limited, however, outside these specific areas.

Control of stress responses can be achieved at much lower doses than those used in the earlier studies and exposure to high dose opioids such as fentanyl ($50\text{mcg}\cdot\text{kg}^{-1}$ or higher) is associated with hypotension (12). The issue of benefits versus side effects of opioids in the critical care setting have been highlighted by the results of the “NEOPAIN” study (13) in the preterm neonate. The findings have been subject to considerable debate but suggest that in preterm neonates given morphine in a more liberal fashion than controls, observed comfort was improved at the expense of systemic hypotension. This was associated with increased risk of significant short and long-term neurological injury and adverse outcomes. Whilst management of the newborn is a special case, the inference in PICU is clear: provision of opioids mandates careful management to avoid hemodynamic 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.

Neonates have both pharmacodynamic and pharmacokinetic susceptibility to sedatives and opioids, which may deter the clinician from providing effective dosing. However, unless effective plasma concentrations of the drug have already been achieved during surgery, initial loading doses may be required in the ICU. By contrast, in older infants and young children it can be difficult to maintain comfort and a relatively quiescent state without large drug doses, often in combination with multiple sedative agents. This reflects increased volume of distribution, with high clearance, that may equal or exceed that of adults, and a relative pharmacodynamic drug resistance. It is not until adolescence that responses and handling of the drugs approaches that of the adult.

Pharmacokinetics of the opioids are not only age-dependant but also affected by cardiac failure and cardiopulmonary bypass (CPB) surgery. Studies with morphine and remifentanyl have shown that after cardiac surgery (14-15) there is a combination of an increase in volume of distribution and fall in drug clearance. Care therefore must be taken to provide adequate drug loading early on, whilst individualising continuous infusions over time to reflect

reduced drug clearance, particularly in the setting of low cardiac output, and hepatic or renal impairment. Accumulation of the active metabolite of morphine, morphine-6-glucuronide, in renal failure, can lead to excessive and long-lasting sedation that delays extubation.

All opioids are associated with tolerance, resulting in increasing requirements to maintain adequate analgesia/sedation. This is accelerated by high-dose opioid techniques during anesthesia, which can cause “acute tolerance”, an effect which has been shown to be more pronounced in shorter acting, higher potency opioids, such as fentanyl and remifentanyl (16). Neonates undergoing ECMO require five times the initial fentanyl infusion rate by day six to achieve an equivalent level of sedation, due to a combination of enhanced elimination (17) and pharmacodynamic tolerance (18).

Morphine is more water soluble than fentanyl, with slow onset and offset, and pronounced sedative effects, which facilitates effective analgesia following anesthesia. Loading doses of $100\text{--}200\text{ }\mu\text{g}\cdot\text{kg}^{-1}$, followed by infusions of $10\text{--}60\text{ }\mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$, provide reliable analgesia. Excessive sedation, respiratory depression, nausea and vomiting can be problematic. Patient-controlled analgesia, using a low background can be highly effective in older children, with nurse-controlled analgesia an option for the younger child.

Fentanyl is a potent opioid, with rapid onset and offset after short-term infusion (hours) due to its lipid solubility and extensive peripheral uptake. After lengthy infusions (days), recovery can be prolonged due to its relatively long elimination half-life. Whilst analgesia can be achieved with doses of $1\text{--}5\text{ }\mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$, infusion rates of $10\text{--}20\text{ }\mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$, may be beneficial in infants with low cardiac output states, critically balanced pulmonary and systemic circulations, or pulmonary hypertension, to reduce metabolic demands and obtund hemodynamic responses to stimuli. $5\text{--}10\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ boluses may be required for procedures such as endotracheal suctioning and physiotherapy. High doses may provide complete anesthesia and sedation for neonates, whilst older infants and children also require an hypnotic agent.

Alfentanil is highly protein bound, resulting in a small volume of distribution. It undergoes rapid hepatic metabolism to inactive compounds (19). Although less potent than fentanyl, its rapid onset and offset lend it to short-term anesthesia and analgesia.

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Remifentanyl is a synthetic opiate, offering potent analgesia, with rapid, predictable offset, making it potentially attractive for perioperative analgesia in the pediatric cardiac patient. Its short elimination half-life, of three to ten minutes, after single injection, is relatively age-independent and not affected by renal and hepatic function, as it is metabolised by plasma and tissue cholinesterases (20). Peripheral accumulation does not occur, hence the half-life remains independent of infusion duration, allowing rapid offset, which remains predictable, despite reduction in clearance associated with CPB (21). Effective plasma concentrations can be rapidly achieved by continuous infusion at doses of $0.05\text{--}0.4\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1}$, with higher doses of $1\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1}$, required to obtund stress responses (22). It has limited sedative effects, necessitating use with an hypnotic.

Despite its desirable properties, its role in postoperative pain management remains to be established, with cost and drug tolerance (23), restricting its utility to relatively short-term analgesia. Furthermore, its potency and effects on ventilation, limit its use in spontaneously breathing children and sick neonates, who can develop bradycardia and hypotension on initial exposure (22). In a study of ‘fast track’ pediatric cardiac surgery, it lacked superiority over fentanyl in terms of recovery and was associated with a significant reduction in heart rate (24). It has potential utility for procedural analgesia, in ventilated patients in PICU. Given as a single intranasal dose it provides an excellent pharmacokinetic profile providing analgesia for 15 minutes. This approach avoids fluctuant levels and the attendant side effects of single intravenous dose or infusion of remifentanyl. Verghese *et al.* have reported this technique for intubation during inhalational anaesthesia with 5% sevoflurane after a single dose of $4\mu\text{g}\cdot\text{kg}^{-1}$ of remifentanyl (25). This exiting new approach would allow modulation of analgesia for procedures such as physiotherapy and endotracheal tube change, without having to modify existing infusions or break into the intravenous circuit to give additional bolus doses.

Once the alimentary route is effective, there is some evidence that oral opioid administration results in reduced longer-term tolerance (26-28). Certainly, the use of enteral drug administration reduces the infection-risk associated with long-term intravenous access and line manipulations (29) and should be used wherever possible. Morphine undergoes considerable first pass metabolism by the liver, if absorbed through the alimentary system, resulting in considerably greater dose-requirements than by intravenous routes, with total

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3 daily doses needing to be increased by a factor of five to ten in order to achieve the same
4 level of analgesia.
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8 9 **Local Analgesia Techniques**

10 Afferent pain conduction can be eliminated with effective local anesthesia, with minimal side
11 effects. Simple local anesthetic techniques can provide an important adjunct to any analgesia
12 or sedation regimen, by reducing the background drug requirement and that for procedural
13 analgesia. Local anesthesia can be given by a wide variety of routes which include topical,
14 infiltration, peripheral nerve block or central continuous block (epidural or spinal). Topical
15 anesthesia is used regularly on the general paediatric wards and in the emergency department
16 (ED). The use of these agents in PICU is often ignored except in non-intubated patients. The
17 pain associated with venous cannulation is sufficiently distressing, even in a moderately
18 sedated child, to necessitate additional sedation. If agents such as Ametop and EMLA are
19 routinely applied in advance of an anticipated procedure, the use of intravenous analgesia and
20 sedation can be minimised. Newer, faster acting agents are now available, including
21 lidocaine-adrenaline-tetracaine gel (LAT gel), which is effective in as little as 10 minutes
22 (30-31). This agent is finding increasing favor in the ED for wound suturing, with good
23 effect. It has been suggested that its use should be extended to other areas, such as PICU, due
24 to its rapid onset of action and excellent analgesic effects. Care does need to be given,
25 however, to site of use, due to the adrenaline component.
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40 Regional anesthesia for cardiac surgery remains in the domain of a few enthusiasts rather
41 than as a mainstream technique. A variety of retrospective publications using caudal, epidural
42 or spinal techniques have suggested value in the management of children after cardiac
43 surgery, but the data remains limited and largely uncontrolled (32-34). A prospective
44 randomised trial of spinal anesthesia with an indwelling catheter, demonstrated reduced stress
45 responses and lower blood lactate concentrations compared to a high dose conventional
46 opioid technique in children under three years undergoing major cardiac surgery (35). A
47 similar technique to that described is currently being used by our group to provide stress
48 reduction in the operating theatre, facilitate early extubation and minimise the requirement
49 for systemic analgesia.
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Sedation (Table 3)

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

- 1. Unconsciousness (virtual anesthesia) or reduction in conscious level
- 2. Reduced awareness
- 3. Loss of explicit and implicit memory
- 4. Compliance with the need to lie in a confined space, attached to monitors and invasive lines
- 5. Prevention of distress during procedures such as physiotherapy, radiological scanning or minor surgical intervention, which may require enhanced levels

Table 3 near here

Different drugs fulfil these roles to varying extents. Benzodiazepines, for example, provide anterograde amnesia, with reduced or complete unconsciousness at different doses, whilst phenothiazines and butyrophenones (chlorpromazine and haloperidol), 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 a dissociative anesthesia/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 generic.

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

In the past, patients in adult ICU have been given an opioid in combination with a low dose of anesthetic agent to ensure pain relief, hemodynamic stability and tolerance to the constraints of ITU. The potentially lethal side effects of anesthetic drugs used over days have only emerged after reviews of death rates and analysis of recurring adverse events. These

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3 have included immunomodulation by barbiturates (36-37), adrenocortical suppression by
4 etomidate (38) and more recently, mitochondrial dysfunction with propofol, in both adults
5 and children (39).
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10 As with opioids, delivery via the enteral route may avoid complications associated with
11 intravenous delivery, provided enteric function is intact. Many of the sedative agents are well
12 absorbed and tolerated enterally, including benzodiazepines, clonidine and chloral hydrate.
13 An additional advantage to oral sedation is it can be weaned gradually and continued
14 following discharge from ICU if necessary.
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20 21 **Early Extubation**

22 Early extubation, with good analgesia that allows rapid mobilisation and recovery, is likely to
23 be beneficial in terms of reducing postoperative complications, although the results of more
24 general outcome studies remain inconclusive (2, 40). It should be added that a precondition of
25 early extubation, is that the postoperative repair and cardiovascular function are adequate to
26 support an awake, mobilising infant. Accelerated convalescence confers benefits in both
27 medical and economic terms, in that earlier discharge from the ICU improves throughput.
28 The last 10 years has seen a widespread acceptance of fast track pediatric surgery, with rapid
29 extubation not only for simple cases but also more complex procedures (41-42). There may
30 be specific advantages in immediate extubation for some cardiac conditions. For example
31 those with single ventricle physiology (following Glenn shunt/ Fontan repair), and Fallot's
32 Tetralogy, when reduced intrathoracic pressure, associated with spontaneous breathing,
33 improves pulmonary blood flow and oxygenation (43).
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46 A variety of techniques have been described, including the use of regional analgesia, however
47 the difficulties lie not with on table extubation but with managing pain and sedation in ICU.
48 Children need to remain sufficiently sedated after surgery to prevent restlessness with
49 attempts to remove vital monitoring or invasive catheters. In the authors' experience, this
50 usually necessitates a combination of both analgesia (opioids, acetaminophen and NSAIDs)
51 and sedation (a benzodiazepine or alpha-2 agonist). Excessive use of potent opioids during
52 surgery promotes acute tolerance, leading to a requirement for increased analgesia after
53 surgery (16). The debate on whether "pharmacological restraint" is always preferable to
54 limited physical restraint, such as bandages around the hands, arm splints or even true
55 restraint, remains unresolved, and provokes strong views.
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Continuing anesthesia for a short time after surgery in PICU allows time to assess the surgical repair, and ensure that the patient has been optimised prior to extubation. Several techniques have been described, including infusions of propofol, (5) and remifentanyl with midazolam, (15) that allow a controlled emergence. The use of propofol in PICU remains contentious due to the issues surrounding ‘Propofol Infusion Syndrome’ (39, 44). Despite these concerns, and its contraindications for use by regulatory authorities in the USA and UK, it continues to be used short-term, at low dose ($<4\text{mg}\cdot\text{kg}\cdot\text{hr}^{-1}$) for specific cases. Patients on a propofol infusion should be closely monitored for rising lactate, acidosis, reduced urine output or dysrhythmias.

Remifentanyl combined with low dose midazolam provides very reliable analgesia and sedation for early extubation. Recent studies have shown that there is a good correlation with drug infusion rate, plasma level and COMFORT score (15). Before withdrawal of remifentanyl, a loading dose of opioid is needed to maintain analgesia.

Sedation and Analgesia in the Long-stay Patient

As the management of the cardiac surgical patient continues to improve, the need to ventilate infants over days and weeks has diminished. However, those with residual problems, that cannot be improved immediately by further intervention or who remain marginal for cardiac or non-cardiac 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 the most at risk from drug tolerance and subsequent withdrawal. Some agents are considered more problematic than others: the incidence of withdrawal with midazolam has been reported as frequently as 35%. Limiting midazolam infusion to $100\text{mcg}\cdot\text{kg}\cdot\text{hr}^{-1}$ reduces the likelihood of withdrawal but stopping the drug slowly does not reduce the risk. (45).

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

- 1. Drug cycling: changing pharmacological drug groups routinely to reduce the emergence of tolerance
- 2. Sedation holidays: temporary cessation of sedative drugs to evaluate emergence.

3. Non-pharmacological techniques: oral sucrose, reducing environmental stress (noise, light, interruption of day-night cycle), swaddling etc
4. 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 whilst awake with minimal sedation, allowing the patient to breathe with support ventilator modes, cough and clear their own secretions more effectively, reducing the risks of nosocomial chest infections. Unfortunately, this technique cannot be applied in children because of the technical issues associated with smaller airways and the continuing need for sedation. Surgical tracheostomy and insertion of a long-term indwelling central venous catheter can, however, allow the patient who requires longer term ventilator support to be managed with little or no sedation

Neuromuscular blockade can be useful in patients that are difficult to ventilate, such as for inverse ventilatory ratios, high frequency oscillation, or to deliberately hyper or hypoventilate them depending on their underlying pathology (46). It continues to be used in children that require hypothermia due to dysrhythmia or to reduce metabolic rate and oxygen demand. Neuromuscular blockade is used more commonly than in adult ICU, but as a specialty we are now using it less frequently (47), with recent reports estimating the use of long-term neuromuscular blockade in 14-16% of ventilated days in PICU (48). Avoidance of prolonged use is preferable due to the risks of critical care polyneuropathy (49) and drug accumulation, which may result in delayed extubation.

Withdrawal phenomena remain a major concern in those patients who have received sedation over many days. Symptoms can include sweating, tachycardia, hypertension, agitation, posturing, withdrawal, vomiting and diarrhoea. Occasionally this prompts concerns of, and investigation for, cardiac, neurological or gastrointestinal disease. The alpha-2 agonist clonidine, chlorpromazine, and haloperidol can be used effectively to moderate these effects and the patients 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 requirement. This may not, however, reflect actual requirements, with significant individual variation.

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Assessment of depth of sedation, with titration of analgesic and sedative drugs, is important to ensure comfort and avoid adverse outcomes, associated with under or over-sedation. Several scales, assessing behavioral and/ or physiological measures have been developed and validated for this purpose. These include ‘The COMFORT Scale’, an objective measure of distress in ventilated pediatric patients, validated in all age groups (50-51). It comprises 8 variables, each rated 1-5: alertness, calmness/agitation, respiratory response, physical movement, heart rate, blood pressure, muscle tone and facial tension, the scale ranging from 0-40, with a target range of 17-26. As with other scoring systems it is limited by inter-observer variability, provides only intermittent data and cannot be used in the context of neuromuscular (NMJ) blockade. Cardiovascular responses are also difficult to assess in patients who are paced.

Neurophysiological methods and auditory evoked potentials have been evaluated in the research domain. Bispectral Index (BIS) monitoring utilizes data from electroencephalogram (EEG) to measure depth of anesthesia. This technique assumes changes in frequency are related and looks for phase coupling among frequency bands (biocoherence) (52-53). In awake individuals, there is minimal synchronisation due to multiple signal generators within the brain, whereas during sleep, there is less activity and the EEG reflects coupling between signal generators (52-53). A dimensionless value, ‘the BIS number’, is calculated, which ranges from 0-100, 0 indicating an isoelectric state, with 100 correlating with a fully awake individual. Values of 40-60 are seen with general anesthesia (54). 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 (55-56). Furthermore, Messner *et al.*, demonstrated BIS Index to decline, with NMJ blockade in awake volunteers, suggesting it may not identify those inadequately sedated under muscle relaxant (57). The BIS monitor is age-dependant (58) and currently there is insufficient evidence to support routine use of the BIS monitor, or any other neurophysiological sedation scoring technique, in PICU (59).

Future prospects

The concept of using the volatile agents for longer-term sedation on ICU’s is not a new one. Barriers in the past have been ways to safely deliver the drug (vaporisers) as well as protecting the staff and environment (scavenging systems). A few ICU ventilators in the past such as the servo 900c were able to provide a plug on vaporiser to deliver isoflurane to the critically ill patient, but these are now generally obsolete. Adult data has shown that

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3 isoflurane can be an effective and practical sedative drug in the intensive care unit when
4 combined with opioids with few side effects (60-61). More recently, Meiser and others have
5 shown the rapidly eliminated inhalational agent desflurane to have characteristics that make it
6 superior to other more conventional agents (62). The data in PICU is very limited. The early
7 10 patient study by Arnold *et al.* (63) used relatively high doses of isoflurane as a single
8 agent in patients who had already become tolerant to opioids. Their results showed that while
9 the drug was effective, there was a high incidence (50%) of tolerance agitation and dystonia
10 on withdrawal of the drug. More recent reports, particularly for treatment of status
11 asthmaticus, as part of a more balanced sedative regimen, have been more encouraging (64-
12 65). However there is major lack of good prospective data to evaluate the potential of these
13 drugs in PICU.
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25 The renewed interest in gaseous sedative agents is likely to continue with developments of
26 new delivery systems within ICU. Early studies with xenon show great potential in the
27 clinical areas of the developing neonate and neurological injury (66-67). Unlike many PICU
28 sedative agents, including midazolam, ketamine and other volatile anesthetic agents, xenon
29 has been shown in animal models to provide anesthesia and sedation without producing
30 apoptosis (68). Further studies have found that xenon can offer protection from hypoxic
31 injury. Hobbs *et al.* demonstrated that rat pups exposed to hypoxic injury had a significantly
32 better outcome with the combination of cooling to 32°C and xenon. The functional
33 improvement with this regimen was almost complete, sustained long-term, and accompanied
34 by greatly improved histopathology (69). Chakkrapani and colleagues demonstrated similar
35 neuroprotective benefits of xenon, with synergistic effects seen with hypothermia in
36 asphyxiated newborn piglets (70). Issues still remain if this drug is to become viable in PICU.
37 It is rare, expensive and requires a closed system of delivery, which necessitates the
38 developmet of new ventilatory systems.
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Drug	Indications	Dose	Elimination	Comments
Fentanyl Infusion	Analgesia	$1-5\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$	Hepatic metabolism	Large bolus doses can cause hypotension
	Intense analgesia/anesthesia in ventilated patients	$1-15\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$		Ventilatory depression
Bolus Fentanyl	Pulmonary hypertension	$10-50\mu\text{g}\cdot\text{kg}^{-1}$		Neonates may have long elimination half-lives, with delayed recovery
Morphine	Analgesia with sedation	Loading dose $50-200\mu\text{g}\cdot\text{kg}^{-1}$	Hepatic followed by renal excretion of active metabolite (morphine-6-glucuronide)	Delayed recovery in neonates
	Controlled analgesia in the extubated patient	Infusion $5-80\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ Neonates: lower infusion rates $5-20\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$		Nausea and vomiting can be problematic in older children Reduced doses may be needed with renal impairment due to accumulation of morphine-6-glucuronide
Oral morphine	Longer-term analgesia once absorption has recovered	$200-500\mu\text{g}\cdot\text{kg}^{-1}$ 4- hourly		Oral doses need to be larger than IV doses due to reduced bioavailability and first pass metabolism
Alfentanil Infusion	Rapid offset, useful for fast track surgery	Loading dose: $50-100\mu\text{g}\cdot\text{kg}^{-1}$ Infusion: $0.5-2\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	Hepatic metabolism Highly protein bound with a small volume of distribution.	Small volume of distribution and short elimination half-life make its offset very rapid
Remifentanil	Infusion in ventilated patients	Analgesia: $0.1-0.3\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	Metabolised rapidly by plasma and tissue cholinesterases.	Alternative analgesia is required before the infusion is stopped
	Intense, rapid onset/offset (largely independent of age or infusion duration)	Anaesthesia: $0.5-1.5\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$		Unsuitable for the extubated, spontaneously breathing patient
Codeine Phosphate	Oral medication	Neonate: $0.5-1\mu\text{g}\cdot\text{kg}^{-1}$ Child up to 12yrs: $0.5-1\text{mg}\cdot\text{kg}^{-1}$ Max daily: 240 mg >12 years: 30-60mg	Hepatic and renal clearance	Also used for treatment of diarrhoea due to constipating effects
Tramadol	Oral medication	>12 years: $50-100\text{mg}$ 4-6 hourly Max daily: 400 mg	Hepatic and renal clearance	Only patients >12 years Nausea, vomiting, constipation Respiratory depression in large doses

Table 1: Opioid Analgesia

Drug	Indications	Dose	Comments
Paracetamol	Hyperthermia Co-analgesia with opioids	0-3months loading dose: oral 20mg·kg ⁻¹ , rectal 30mg·kg ⁻¹ Max daily 90 mg·kg ⁻¹ (max adult 4g daily) for 48hrs reduce thereafter to 60mg·kg ⁻¹	Significant but low analgesic potency Reduced doses may be needed in the critically ill fluid restricted child to avoid hepatic dysfunction and toxicity
Diclofenac *	Opioid sparing analgesia Not used under 1 year or with significant asthma	Oral or rectal: 1mg·kg ⁻¹ Max daily: 3mg·kg ⁻¹	Has effects on gastric mucosa and platelet function Can be nephrotoxic
Ibuprofen *	As above	Oral or rectal:10mg·kg ⁻¹ Max daily: 40mg·kg ⁻¹	As above
Ketamine	Alternative intravenous analgesia to opioids (NMDA receptor antagonist)	IV infusion: 10-45µg·kg ⁻¹ ·min ⁻¹	Can be used in spontaneously breathing children Associated with dysphoria when used as a sole agent May provide useful bronchodilation
Clonidine	Less analgesic potency than morphine but can be used as co-analgesia (orally), for longer-term sedation, or for withdrawal from opioids (α-2-agonist)	Intravenous infusion: 0.5-3.0 µg·kg ⁻¹ ·min ⁻¹ Oral: 2-5µg·kg ⁻¹ 4-hourly	Can cause hypotension and bradycardia Rebound hypertension has been described in adults

Table 2: Non-Opioid Analgesia

*These drugs are used extensively outside their product licence but within recommended guidelines from the Royal College of Paediatrics and Child Health. Prevention and Control of Pain in Children 1997: BMJ Publishing Group, London

Drug	Benefits	Dose	Comments
Benzodiazepines Midazolam	Amnesic benefit in addition to sedation	Intravenous infusion: max $200\mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$ Intranasal: $0.1\text{mg}\cdot\text{kg}^{-1}$ each nostril	High risk of withdrawal with prolonged use or high doses ($>100\mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$). Helps control seizures
Lorazepam	Oral drug useful in midazolam withdrawal		Risk of respiratory depression – particularly with repeated doses
Diazepam	Status epilepticus (rectal)	Rectal: Neonate: max 2.5mg 1 month-2years: 5mg 2-12 years: 5-10mg 12-18 years: 10mg	
Propofol	Short term action – rapid wake up	Intravenous infusion: max $4\text{mg}\cdot\text{kg}\cdot\text{hr}^{-1}$ Titrate to effect Check for rising lactate or acidosis, limit infusion duration	Hypotension Risk of propofol infusion syndrome. Lipid load with infusion. Contraindicated by FDA
Phenothiazines (Chlorpromazine hydrochloride)	Dissociated sedation	Oral or IV: $500\mu\text{g}\cdot\text{kg}^{-1}$	Risk of extrapyramidal side effects
Butyrophenones (Haloperidol)	Dissociated sedation	Intravenous infusion: 1 month-12 years: $25-85\mu\text{g}\cdot\text{kg}^{-1}$ over 24 hours 12-18 years: 1.5-5mg over 24 hours	Risk of extrapyramidal side effects
Clonidine	Withdrawal Analgesic properties with opiate-sparing effect	Intravenous infusion: $0.5-3.0\mu\text{g}/\text{kg}/\text{min}$ Oral: $2-5\mu\text{g}\cdot\text{kg}^{-1}$ 4-hourly	Can cause hypotension and bradycardia Rebound hypertension described in adults
Volatile agents	Rapid clearance for quick wake up	Dose titrated to effect Depends on delivery system and gas flows	Can be useful for bronchospasm and seizures Requires vapouriser and scavenger systems
Chloral hydrate	Well tolerated	Oral or rectal: $25-50\text{mg}\cdot\text{kg}^{-1}$	Delayed clearance in neonates – be wary with regular dosing

Table 3: Sedative Drugs