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Sedation in Critically Ill Children

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Abstract

Sedation and analgesia are crucial elements in managing discomfort and facilitating critical care interventions in children. Our choice of sedative agents has a significant impact on the physiological and psychological outcomes of our patients. Oversedation and undersedation are associated with adverse events, including increased risk of PICU readmission, mortality, and longer duration of mechanical ventilation. Studies have shown significant variation in sedation and analgesia practices across different regions and specialties. Consensus clinical guidelines have been developed to standardize sedation and analgesia practices; commonly used intravenous agents include opioids (fentanyl, morphine and remifentanil), α-2 agonists (clonidine and dexmedetomidine), benzodiazepines (particularly midazolam), ketamine and volatile anesthetic agents (isoflurane and sevoflurane). Our goal should be to administer the smallest possible number of sedative and analgesic agents, in the lowest possible doses, for the shortest amount of time, whilst adequately controlling the pain and agitation of our patients. Aside from drug management, non-pharmacological interventions, such as family presence, music, and virtual reality, can also play a significant role in maintaining comfort in critically ill children. Validated clinical tools are available to measure sedation and to assess iatrogenic withdrawal syndrome and delirium. Daily interruption of sedatives and protocolized sedation management have been shown to reduce the duration of mechanical ventilation and PICU stay in some studies, but their effectiveness is still debated. Further research is needed to optimize sedation and analgesia practices in critically ill children. By adopting evidence-based guidelines and incorporating non-pharmacological interventions, healthcare providers can improve patient outcomes and reduce the risk of adverse events.

Keywords: pediatric intensive care (PICU); sedation; analgesia; tolerance; withdrawal; delirium

1. Introduction

Sedation and analgesia are some of the most common treatments administered to critically ill children worldwide to manage their discomfort and to facilitate critical care interventions. These agents are often considered as inconsequential treatments, administered to enable life-saving management. It is increasingly clear, however, that the choice of sedative agents has a significant impact on the physiological and psychological outcomes of our patients with both oversedation and undersedation being associated with significant adverse events. Ding and colleagues have demonstrated that the administration of any sedative agents during Pediatric Intensive Care Unit (PICU) admission is a significant risk factor for PICU readmission within 1 year of discharge (62.14% Vs 48.05%, p=0.047) [1]. In adult patients, deeper levels of sedation have been associated with higher mortality rates (interquartile odds ratio (OR) = 5.42, 4.23-6.95; $p < 0.001$) and a significant decrease in ventilator-free days (− 7.27; $p < 0.001$), ICU-free days (− 4.38; $p < 0.001$), and hospital-free days (− 7.00; $p < 0.001$) [2]. In a propensity-matched retrospective cohort study, Wu and colleagues demonstrated that early deep sedation was associated with post-hospital one-year mortality in critically ill adult surgical patients [3]. In 2013, Shehabi and colleagues demonstrated that deep sedation in critically ill adults was independently associated with longer time to extubation (hazard ratio (HR) 0.93, 95%,

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confidence interval (CI) 0.89–0.97, P = 0.003), hospital death (HR 1.11, 95 % CI 1.05–1.18, P<0.001) and 180-day mortality (HR 1.09, 95 % CI 1.04–1.15, P = 0.002) [4]. Conversely, Treggiari and colleagues have demonstrated that a strategy of light sedation in critically ill adult patients is associated with benefits in terms of a reduction of intensive care unit stay and duration of mechanical ventilation without negatively affecting subsequent patient mental health or patient safety [5]. Throughout this review, for clarity, references to sedation will generally refer to the administration of combinations of sedative and analgesic agents as 'sedation' rather than the more technically correct term 'analgo-sedation'.

Patel and colleagues published a paper in 2020 evaluating sedation, analgesia, and neuromuscular blockade practices in 66,443 critically ill children between 2009 and 2016 in 161 US PICUs [6]. The authors documented that 63.3% of children (42,070) received analgesics, sedatives, and/or neuromuscular blocking agents which, remarkably, included 83 different agents. Analgesic agents were administered to 58.4% of children (38,776), of which non-opioid analgesics were prescribed to 67.4% of children (26,149). The median duration for opioid analgesic administration was found to be 32 hours (interquartile range; 7-92 hours). Sedatives were administered to 39.8% of children (26,441) with a median duration of 23 hours (interquartile range; 3-84 hours), of which benzodiazepines were the most commonly administered agents (73.4%; 19,426 children). Similar variation in clinical practice was demonstrated by Jenkins and colleagues in 2007, who conducted a prospective observational study of 338 critically ill children in 20 UK PICUs. The authors found total of 24 different sedative and analgesic agents were used during the study with the most commonly used sedative and analgesic agents being midazolam and morphine [7].

When Playfor and colleagues reviewed UK practice in 2003, the most commonly used sedative agent was midazolam in combination with morphine and written clinical guidelines for the sedation of critically ill children were available in 45% of units [8].

In a survey of 215 PICUs in 27 European countries, carried out by Daverio and colleagues in 2022, 71% of PICUs stated that they used clinical guidelines for sedation and analgesia. These guidelines were more frequently used in lower-volume PICUs with 450 admissions per year or less (77% Vs 63%, p=0.028). The most popular drug combination was found to be fentanyl (51%) and midazolam (71%). Alpha-2 agonists were only used in 18% of the PICUs as a first line agent, with dexmedetomidine being used more frequently than clonidine. Ketamine was more often used in the higher volume PICUs (16% vs 2%, p = 0.000). A daily assessment of pain (81%) and sedation (87%) was reported by the majority of units, most commonly using the FLACC scale (54%) and the COMFORT Behavioural scale (48%) [9].

It has been demonstrated that sedation and analgesia clinical practice varies considerably by geography [10] and by specialty; infants who may be cared for in either Neonatal Intensive Care Units or PICUs have been shown to be likely to receive very different management [11].

Most critically ill children who need mechanically ventilated require a combination of multiple sedative and analgesic agents to maintain their comfort; Tillman and colleagues demonstrated that a mean of 2.58 ± 1.18 agents are required per patient during their PICU admission [12]. In this retrospective, single-center study of 130 critically ill children, only 17% of patients were managed with a single medication, 36% of children received 2 medications, 29% of children received 3 medications, 12% of children received 4 medications, and 6% of children required 5 or 6 medications during their PICU stay. The dosing ranges of medications received by children in this study were extremely variable, with patient weight, age and hospital length of stay all being significantly associated with sedation requirements. The older and heavier patients required more medication (on a per kg basis) to achieve the desired level of comfort. Mean overall infusion rates for fentanyl were 1.67 ± 0.81 μg/kg/hour, for morphine 0.12 ± 0.08 mg/kg/hour, and for hydromorphone 17.84 ± 13.4 μg/kg/hour. The mean infusion rate of dexmedetomidine was 0.59 ± 0.28 μg/kg/hour, and for midazolam was 0.14 ± 0.1 mg/kg/hour.

As such ubiquitous agents, sedative and analgesic drugs are common contributors to adverse drug events in the pediatric critical care environment; Silva and colleagues have identified that

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sedative and analgesic agents are associated with 15.5% of adverse drug events in PICUs, with each event being associated with an increased length of stay [13].

It must be remembered that non-pharmacological interventions can play a significant role in maintaining the comfort of critically ill children. Such environmental factors can include family presence, reducing ambient noise, provision of music, sleep hygiene, early mobilization and the use of virtual and augmented reality technology. Facilitation of parental or caregiver presence in the PICU during routine care and interventional procedures can provide comfort to the child, decrease parental levels of stress and increase the quality of patient experience. Several studies have demonstrated that personalized music intervention is feasible and helpful; in 2020, Liu and colleagues published a feasibility study of a personalized music intervention with mechanically ventilated patients in the PICU [14]. Children in the intervention arm of the study listened to their favorite music for 60 minutes, 3 times a day; Children exposed to music had lower COMFORT Behavior scores (15.7 vs 17.6; $p = 0.011$), better physiological outcomes; heart rate (140 vs 144; $p = 0.039$), respiration rate (40 vs 43; $p = 0.036$), systolic blood pressure (93 vs 95 mmHg; $p = 0.031$), oxygen saturations (96% vs 95%; $p < 0.001$), diastolic blood pressure was not significantly (52 vs 53 mm Hg; $p = 0.11$). Children in the music group also had a shorter ventilation time (148.7 vs 187.6; $p = 0.044$) and a shorter length of stay, but not significantly so (11.2 vs 13.8; $p = 0.071$). Children in the control arm required a higher total amount of midazolam. Similarly, exposure to live music has been shown to be beneficial within the critical care environment [15,16]. In addition, extended reality (XR) technology such as, is being increasingly used in pediatric critical care medicine with reported positive impacts on outcomes including relief of pain, anxiety, and improving sleep and physiological parameters such as integer heart rate variability [17,18].

2. Clinical Guidelines

In response to concerns regarding the considerable variation in clinical practice, the first consensus clinical guidelines for the provision of sedation and analgesia in critically ill children were developed and published by Playfor and colleagues in 2006 using a modified Delphi technique [19]. Twenty key recommendations were produced, with 10 relating to the provision of analgesia and 10 relating to the sedation of critically ill children. Particular emphasis was placed on non-pharmacological interventions including environmental factors, relaxation, distraction, promotion of sleep and day-night orientation.

In more recent years, two significant consensus-based clinical guidelines for the provision of sedation and analgesia in critically ill children have been produced; in 2022 the Italian Society of Neonatal and Pediatric Anesthesia and Intensive Care (SARNePI) published their 'Recommendations for analgesia and sedation in critically ill children admitted to intensive care unit' [20], and also in 2022, Smith and colleagues published the '2022 Society of Critical Care Medicine Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients With Consideration of the ICU Environment and Early Mobility' [21]. The Italian group recommended as a first-line strategy, optimizing analgesia using opiates and adopting alpha-2 agonists as sedative agents, considering benzodiazepines as second-line agents, with the administration of ketamine in cases of difficult analgesia/sedation. The SCCM guidelines included 44 recommendations (14 strong and 30 conditional) and 5 good practice statements. They recommend that intravenous opioids are used as the primary analgesic for treating moderate to severe pain in critically ill pediatric patients, and that alpha-2 agonists are administered as the primary sedative class in critically ill pediatric patients requiring mechanical ventilation.

3. Measuring Sedation

While there are many clinical scoring scales reported in the literature, relatively few have been rigorously assessed for suitability in the PICU population. The COMFORT score has been widely used in pediatric sedation research literature [22] and was recommended by the European Society of

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Pediatric and Neonatal Intensive Care (ESPNIC) for sedation monitoring in 2016 [23]. It was developed in 1992 and consists of an eight-domain scale based on observations of spontaneous movement, calmness, facial tension, alertness, respiratory activity, muscle tone, heart rate, and blood pressure. Subsequent studies showed that the physiological variables of heart rate and blood pressure, were not required and as a result, an abbreviated version, the 'behavioral' COMFORT-B scale, using the six remaining domains, has been widely validated and adopted in routine practice.

The use of processed electroencephalography for monitoring the depth of sedation is increasing in critical care with many devices being available; however, the utility and optimal deployment of this type of monitoring remains unclear [24].

4. Daily Interruption of Sedation

In 2000, Kress and colleagues published the results of a randomized, controlled trial involving 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs [25]. Patients who underwent a daily interruption of sedative agents required mechanical ventilation for a median duration of 4.9 days compared with 7.3 days in the control group (P=0.004), and a median length of stay in the intensive care unit of 6.4 days as compared with 9.9 days in the control group (P=0.02). However, concerns about daily interruption of sedation including patient discomfort, treatment interference and increased clinician workload, led to further work in this area; the results of a randomized, controlled trial facilitated by the SLEAP Investigators subsequently demonstrated that a daily interruption of sedative agents in 65 adult patients in 14 Canadian and 2 US intensive care units led to no difference in median time to successful extubation, no difference in critical care or hospital stay, but increased nursing workload [26]. A similar study of interrupted versus continuous sedative infusions in 102 mechanically ventilated children, published by Gupta and colleagues in 2012, suggested the mean length of mechanical ventilation in the interrupted sedation group was significantly less than that in the continuous sedation group (7.0 ± 4.8 days vs. 10.3 ± 8.4 days; p = 0.021). Similarly, the difference in the median duration of PICU stay was significantly less in the interrupted sedation group as compared to the continuous sedation group (10.7 days vs. 14.0 days; p = 0.048) [27]. In 2015, Curley and colleagues published the results of the RESTORE study, a cluster-randomized trial of 2449 children conducted in 31 US PICUs to investigate the impact of a nurse-implemented, goal-directed sedation protocol compared with usual care [28]. The duration of mechanical ventilation was not statistically significantly different between the two groups (median; interquartile range: intervention: 6.5 days; 4.1-11.2 vs. control: 6.5; 3.7-12.1). Sedation-related adverse events including inadequate pain and sedation management, clinically significant iatrogenic withdrawal, and treatment interference were not statistically significantly different between the two groups. Blackwood and colleagues published the results of a pragmatic multicenter, stepped-wedge, cluster randomized clinical trial that was conducted in 18 PICUs in the UK [29]. A total of 4688 children were managed according to a sedation and ventilator liberation protocol intervention that consisted of assessment of sedation level, daily screening for readiness to undertake a spontaneous breathing trial, a spontaneous breathing trial to test ventilator liberation potential, and daily rounds to review sedation and readiness screening and set patient-relevant targets. There was a significantly shorter median time to successful extubation for the protocol intervention compared with usual care (64.8 hours vs 66.2 hours, respectively; adjusted median difference, −6.1 hours (interquartile range, −8.2 to −5.3 hours); adjusted hazard ratio, 1.11 (95%CI, 1.02 to 1.20), P = 0.02): Whilst statistically significant, a 6 hour reduction in the duration of mechanical ventilation is of uncertain clinical significance.

It is for this reason that the latest SCCM guidelines state that the practice of daily sedation interruption to sedation protocolization is not recommended due to lack of demonstrated improvement in outcomes.

Intensive Care Unit Liberation is a philosophy that encourages critically ill patients to be awake, interactive, and as physically mobile as possible to reduce the burden of critical care-acquired morbidity. Survivors of pediatric critical illness have been demonstrated to suffer significant

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physical, cognitive, and psychosocial morbidities, which can lead to delayed recovery, increased utilization of healthcare resources, functional impairment, and overall reduced quality of life.

The ABCDEF bundle (Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of analgesia and sedation; Delirium assess, prevent and manage; Early mobility and exercise; and Family engagement and empowerment) is at the heart of the Society of Critical Care Medicine's ICU Liberation collaborative. This evidence-based multifaceted, 6-step programme was developed to liberate adult patients from interventions initiated during critical illness. Carrying forward this approach into the PICU environment is challenging given the lack of definitions around early mobilization, age-related variations, developmental status, comorbidities, and diagnostic variation. The PICU Up! initiative undertaken at the Johns Hopkins Hospital in the US was the first structured, multi-disciplinary, early mobilization programme demonstrated to improve the activity levels of children in a tertiary PICU [30]. The initial quality improvement programme focused on a bundled approach to improving sleep hygiene and delirium prevention, while the subsequent PICU Up! trial was a multicenter stepped-wedge, cluster-randomized trial to assess the effectiveness of the intervention. The trial recruited 1196 patients in the pre-intervention phase and 1076 in the post-intervention phase; this led to a significant increase in compliance with the bundle. In a review of 161 participating PICUs, Ista and colleagues demonstrated that only 15 (9%) managed to incorporate all of the six ABCDEF bundle components into daily practice [31]. The widespread adoption of PICU liberation programs has been hindered by mixed evidence of efficacy in PICU, the resource-intensive nature of facilitating mobilization, the heterogeneity of the PICU population, and lack of confidence amongst clinical staff in mobilizing critically ill children [32]. In a 2019 survey of UK PICUs, Thompson and colleagues identified that limited resources and the lack of local and national clinical guidelines were significant barriers to adoption [33].

In an international study of 380 PICUs in 47 countries, Loberger and colleagues demonstrated considerable variation in international pediatric ventilation liberation practice, and poor protocol implementation [34]. Similar difficulties have been encountered in promoting organizational compliance with delirium screening tools [35] and considerable educational initiatives are required to embed these developments into routine clinical practice [36,37]. It is agreed, however, that optimal administration of sedative agents and timely weaning of mechanical ventilation are key factors in improving the outcomes of PICU survivors [38]. PICU-STARS will be a single center, before-and-after trial and implementation study, designed to evaluate if a multidimensional, nurse-led PICU liberation model of care can be applied to the PICU and be successful in reducing PICU-related problems in a mixed quaternary center [39].

5. Withdrawal

The likelihood of withdrawal (which is quoted as around 35% for all ventilated, sedated PICU patients) is directly related to the overall quantity of the sedative agents administered to the patient. Symptoms of withdrawal include central nervous system irritability (poor sleep pattern, tremor, irritability, hallucinations or convulsions), gastrointestinal disturbance (vomiting, diarrhoea, abdominal pain) and autonomic disturbance (sweating, fever, yawning, hiccups, chills, increased airway secretions, tachycardia, tachypnoea and hypertension). Withdrawal has long been associated with the use of opioids and over more recent years it has become clear that other agents used in the field of sedation and analgesia are also capable of inducing tolerance and withdrawal, including propofol, midazolam, isoflurane, clonidine and dexmedetomidine.

Opioid tolerance appears to occur earlier in younger patients and may be exacerbated by background neurological insults and associated with the shorter acting opioids which have a high affinity for opioid receptors.

Two validated scoring tools are available for PICU practice: the Withdrawal Assessment Tool-1 (WAT-1) [40] and the Sophia Observation Score (SOS) [41]. The WAT-1 consists of 11 domains and takes around 7 minutes for completion. The SOS was constructed from a multidimensional analysis of co-occurrences between children who were divided into two groups by an experienced group of

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nurses and doctors depending on whether they were considered to have problems of withdrawal or not on weaning sedation. SOS scores appear to be very reliable in predicting those children that will not develop overt features of withdrawal but, like other scales, may be less sensitive in predicting those that will develop withdrawal. It is recognized that other factors such as pain, distress, and delirium may be confounding factors.

6. Delirium

Delirium is acute neurologic dysfunction in the setting of serious illness and is characterized by a fluctuating disturbance in cognition and awareness. Delirium can be identified in around 40% of children admitted to the PICU for more than 6 days. Risk factors for delirium include mechanical ventilation, benzodiazepine administration, narcotic administration, use of physical restraint, and exposure to vasopressors and anti-epileptic agents. Children with developmental delay have been shown to have a 3.5 times greater likelihood of having a diagnosis of delirium in PICU. Delirium can lead to longer periods of mechanical ventilation, prolonged PICU admission and is a strong and independent predictor of mortality. It is associated with a significant financial burden on healthcare systems and has been associated with an 85% increase in PICU costs.

Administration of sedative and neuromuscular blocking agents, and the occurrence of withdrawal symptoms and delirium are also significant risk factors for the development of the so-called post-intensive care syndrome and also for significant neuromuscular weakness due to polyneuropathy or myopathy known as 'ICU-acquired weakness'. Pediatric delirium has been associated with a clinically important decline in health-related quality of life.

Validated assessment tools are available, specifically for critically ill children. The pCAM-ICU is an interactive, cognitively-oriented tool designed for use with children over 5 years of age. In contrast, the Cornell Assessment of Pediatric Delirium (CAPD) is a validated observational tool and designed for children of all ages including those with varied developmental abilities [42]. More recently the Preschool Confusion Assessment Method tool (psCAM-ICU) has been developed for pediatric delirium monitoring and has been validated for use in children between 6 months and 5 years of age [43]. The development of the CAPD and psCAM-ICU tools represent significant advances allowing PICU clinical teams to screen for, and monitor, delirium in young children, including those receiving invasive mechanical ventilation.

7. Commonly Used Sedative Agents

7.1. Opioids

Morphine has played a pivotal role in medicine since its discovery by Friedrich Wilhelm Adam Sertürner in 1805 and has been a cornerstone of analgesia for children since the development of organized PICUs in the 1950s and 1960s.

It has long been recognized that prolonged administration of opioids induces tolerance with the need to administer increased doses to produce the same desired clinical effect [44]. This effect may be due to either 'tolerance' where the μ-opioid receptor complex becomes desensitized through repeated stimulation, or 'tachyphylaxis' where compensatory physiological changes, such as activation of antagonist signaling systems like the N-methyl-d-aspartate (NMDA) pathway. Both of these mechanisms mean that if the opioid is suddenly removed, withdrawal symptoms can develop.

Morphine is the only poorly lipid soluble opioid in common use, it produces active metabolites that are dependent on adequate renal elimination; it is converted in the liver to morphine-6-glucuronide, which is very active at opioid receptors, and morphine-3-glucuronide. Maturation of the renal clearance of morphine in preterm infants does not normalize at term, but over a longer trajectory; thus, the administration of morphine to preterm infants should reflect this pharmacokinetic difference.

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Morphine administration may result in the release of significant amounts of histamine and inhibit compensatory sympathetic responses; the vasodilation produced by morphine can therefore result in significant hypotension particularly after bolus administration.

Fentanyl, first synthesized in 1960 by Paul Janssen, is a synthetic opioid with 100 times the analgesic potency of morphine. It is a highly lipid soluble agent, which accounts for its rapid onset of action. Fentanyl administration generally causes less histamine release than morphine and therefore is associated with less hypotension. However, fentanyl may lead to a reduction in cardiac output by decreasing the heart rate. When given intravenously, fentanyl has a relatively short half-time owing to rapid redistribution into peripheral compartments. With prolonged administration, fentanyl accumulates within these peripheral compartments leading to an increase in the context sensitive half-time and tolerance can rapidly develop. Fentanyl metabolism occurs almost exclusively in the liver and clearance is dependent upon hepatic blood flow. Fentanyl has no active metabolites, meaning that there is no cross-reactivity in patients allergic to morphine.

Remifentanil is a newer synthetic opioid, a phenylpiperidine derivative, which acts as a pure μ-receptor agonist. It is as potent as fentanyl, with similar cardiorespiratory effects to other opioids but with unique properties. Remifentanil has an exceptionally short half-time of only 3 minutes in all age groups as is metabolized by plasma and tissue esterases with a very small volume of distribution. The effects of remifentanil reliably wear off rapidly, even after prolonged infusion, giving it a very short context sensitive half-time. Remifentanil infusions are increasingly being used to provide analgesia in PICU, although prolonged use of this agent is associated with the rapid development of tolerance and relatively high cost.

Benefits: Morphine improves ventilator synchrony, blunts catecholamine surges, and when used in an analgesia-first paradigm can reduce the requirement for other hypnotic agents. Fentanyl confers rapid procedural analgesia, minimal histamine release and cardiovascular stability. Remifentanil can enable fast, predictable wake up times to facilitate neurological examinations or when extubation needs to occur at specific times.

Risks: All opioids carry the risk of respiratory depression, constipation and tolerance. The risks of oversedation can be mitigated with the use of regular sedation scoring systems with nurse-driven titration of analgesic agents. Opioid stewardship programs employing multimodal adjuvants (such as paracetamol, non-steroidal anti-inflammatory agents, and low dose ketamine) to significantly reduce cumulative doses of administered opioids. Structured tapering of opioid doses by 10-20% increments of the original dose daily or rotation to enteral opioids may help prevent iatrogenic withdrawal syndrome when infusions are administered for longer than five days.

7.2. Benzodiazepines

Benzodiazepines have specific activity at gamma-aminobutyric acid (GABA) receptors, which are part of the dominant inhibitory system of the central nervous system. The most commonly used benzodiazepines in PICU are midazolam, lorazepam, and diazepam.

Midazolam was initially synthesized in the mid-1970s and was rapidly adopted into ICUs as a potent, short-acting, relatively water-soluble benzodiazepine which at plasma pH converts into an unionized form that crosses the blood brain barrier rapidly and has the shortest elimination half-time of the benzodiazepines. It produces antegrade amnesia without impairing the retrieval of previously learned information. Following a single bolus injection, the time to peak sedation is 5-10 minutes with a duration of action of 30-120 minutes. When given by continuous infusion, the duration of action is significantly longer and with prolonged administration, sedation effects may persist for 48 hours after discontinuation of the agent.

Midazolam is metabolized to 1-hydroxymidazolam and 1,4-dihydroxymidazolam through cytochrome P450 isoenzyme 3A4 hydroxylation (CYP3A4 is the most abundant cytochrome P450 enzyme in the liver and intestine, which metabolizes more than 50% of medications), and then undergoes glucuronidation. Glucuronidation of 1-hydroxymidazolam by UDP-glucuronosyltransferases generates inactive metabolites which are excreted in the urine. The

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accumulation of active metabolites can produce prolonged sedative effects in patients with renal insufficiency, while substrate competition for CYP3A4 after the co-administration of certain drugs, such as erythromycin, can also lead to prolonged sedation. A similar effect can be seen through inflammation-induced suppression of CYP3A4, driven by inflammatory cytokines like interleukin-6.

Midazolam has been the most commonly administered sedative agent for prolonged intravenous administration in PICUs over the last 30-40 years. The main adverse events associated with midazolam are the development of tolerance, dependence, and withdrawal after subsequent discontinuation. Hypotension may occur, particularly after bolus administration in the setting of hypovolemia. There is also evidence of reduced sedative efficacy when midazolam is administered to younger children.

Benefits: Provides anxiolysis, antegrade amnesia and muscle relaxation. Intranasal midazolam can facilitate procedures and diagnostic imaging without intravenous access.

Risks: Observational studies have linked benzodiazepines to prolonged mechanical ventilation and the development of delirium. Consequently, modern guidelines advocate benzodiazepine-sparing bundles and the preferential use of α-2 agonists as first line agents for ongoing sedation [20-21].

7.3. Ketamine

Ketamine was introduced into clinical practice in the 1960s, it is a fast-acting general anesthetic with both sedative and analgesic properties that offers value as an adjunct for sedation in mechanically ventilated PICU patients. Ketamine blocks glutamate by antagonizing N-methyl-D-aspartate (NMDA) receptors but also affects a variety of other cellular signaling pathways. It induces a dissociative state, provides effective anesthesia, and also has antidepressant effects. Ketamine maintains pulmonary compliance while reducing airway resistance, meaning it has demonstrated benefits in children with severe bronchospasm. Unlike other sedative agents, ketamine has mostly beneficial effects on the cardiovascular system; it tends to increase catecholamine concentrations through a combination of release and reuptake blockade, leading to modest increases in heart rate, blood pressure, and cardiac output. There are concerns that in catecholamine-depleted states, ketamine administration may lead to hypotension when given as a bolus dose. Ketamine has been associated with emergence phenomena, with vivid dreams and hallucinations being reported. Sub-anesthetic infusions of ketamine have been shown to reduce opioid requirements by 30-50% and mitigate opioid-induced hyperalgesia [45].

Benefits: Analgesia and sedation while preserving the respiratory drive, hemodynamic stability, potent bronchodilation, during controlled ventilation ketamine can reduce intracranial pressure while raising central perfusion pressure. NMDA blockade can terminate seizures resistant to GABAergic drugs without respiratory compromise. Continuous ketamine has been integrated into burns unit sedation protocols allowing reductions in benzodiazepine and opioid exposure by up to 40% [46].

Risks: Sympathomimetic surges, sialorrhoea (drooling or hypersalivation) which can be mitigated with glycopyrrolate. Laryngospasm risk is negligible at sub-dissociative doses. Emergence agitation, vivid dreams, hallucinations in school-age children and adolescents. Mild, reversible transaminase elevation with prolonged use for over 5 days. Can potentiate hypotension when administered in combination with propofol or high dose dexmedetomidine. Apnea can occur in children, particularly in neonates, after rapid intravenous bolus dosing of ketamine but is a rare phenomenon, occurring in 0.3% of cases [47,48]; slower intravenous bolus administration over 60 seconds eliminates this problem (https://rcem.ac.uk/wp-content/uploads/2022/02/Ketamine_Procedural_Sedation_-for_Children_in_EDs_Feb_2020.pdf).

7.4. Alpha-2 Agonists

Clonidine was introduced into clinical practice in 1966 as a centrally acting anti-hypertensive agent. It has since become popular as a low-cost intravenous sedative agent that preserves respiratory

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drive. The α-2 agonists work at several sites where α-2 receptors exist; presynaptically at sympathetic nerve endings, mediating sympatholysis, within the substantia gelatinosa, modulating substance P release for analgesia, and more centrally on the locus coeruleus, facilitating sedation and analgesia. These agents also potentially act at the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve mediating parasympathetic stimulation.

In children, clonidine clearance is dependent on renal function, with around 50% being excreted unchanged by the kidney and 50% undergoing hepatic transformation. Clearance is therefore dependent upon renal function and, for smaller infants, by renal maturity. The context-sensitive half-time of clonidine may double with prolonged infusions, as a function of its high lipid solubility and sequestration in peripheral compartments.

The use of clonidine accelerated after the 2014 SLEEPS randomized clinical trial [49] which showed that clonidine infusions were as effective as midazolam in critically ill children yet was cheaper and associated with fewer iatrogenic withdrawal symptoms. This led many units to adopt intravenous and enteral clonidine as first-line sedative and weaning agents.

Dexmedetomidine has eight times the affinity of clonidine for the α-2 receptor, while having a half-time of only 2–3 hours compared to 12–24 hours for clonidine. The metabolic breakdown product of dexmedetomidine, 3-hydroxy-dexmedetomidine, is believed to have only 0.5% of the pharmacodynamic activity of the parent compound, which adds to its safety profile. It has demonstrated sedative, analgesic and anxiolytic effects and is well tolerated in critically ill children [50]; the Baby SPICE study confirmed that a dexmedetomidine first, benzodiazepine-sparing sedation pathway was feasible, safe and effective [51].

Modern sedation guidelines advocate benzodiazepine-sparing bundles and the preferential use of α-2 agonists as first line agents for ongoing sedation [20,21].

Benefits: Minimal to little effect on respiratory drive, facilitates early spontaneous breathing tests, opioid and benzodiazepine reduction, patient can remain rousable, fewer days of agitation, reduced iatrogenic withdrawal syndrome.

Risks: Bradycardia (2-10%) and hypotension require low starting rates and atropine readiness. Rebound hypertension can be avoided by infusion tapering or oral clonidine bridging.

7.5. Volatile Anesthetics

Volatile anesthetic agents have been used sporadically to provide sedation to critically ill patients in critical care units since the 1980s. Early experience demonstrated the consistent finding of sedation quality that was at least as good as standard intravenous agents, but with much more rapid wake-up and extubation times [52].

Early use of volatile agents was hampered the practical complexity of delivery and scavenging; this meant that less capable anesthetic ventilators needed to used, or ad-hoc scavenging systems had to be put together. Case series published in the 1990s demonstrated that prolonged administration of volatile agents to critically ill children was practical and feasible and delivered the same benefits of high quality sedation and rapid wake-up times following discontinuation [53]. A significant breakthrough was the development of inline vaporizer the anesthetic conservation device, AnaConDa™. Proposed in the mid-1990s by Louis Gibeck, the original developer of the disposable HME (humidified-moisture exchanger) device, the AnaConDa™ is a single-use, disposable, inline vaporizing device designed to deliver volatile anesthetics (isoflurane or sevoflurane) to patients on mechanical ventilation, using existing critical care ventilators and standard syringe pumps. During the 2000s, use of the AnaConDa™ was described in anesthesia, adult critical care and PICUs. The AnaConDa-S™, with only a 50ml dead space, was released in 2017, this allowed the device to be used in its standard configuration on smaller children.

In 2021, Meiser and colleagues demonstrated that isoflurane was non-inferior to propofol sedation in critically ill adults, finding that use of inhaled isoflurane was associated with reduced opioid requirements, facilitated spontaneous breathing, and led to faster, more predictable

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emergence from sedation [54]. The results of a similar international, multi-center trial, the IsoCOMFORT study, conducted in critically ill children, are currently in press.

Benefits: Dependable route of drug administration and elimination. Little metabolism. Rapid onset and offset; shorter wake-up times. Less variability in dose-response effect. Easily titratable depth of sedation. Bronchodilation, volatile agents have been shown to be life-saving in cases of acute severe asthma. Potential organ protective properties; isoflurane and sevoflurane have been demonstrated to have cytoprotective effects in several organ systems through various mechanisms, including the activation of protective signaling pathways by modulating inflammation.

Risks: Rare cases of malignant hyperthermia (1:62,000). Hypotension. Rapid wakening during device disconnection, such as for physiotherapy. Reversable neurological phenomenon including pupillary changes and clonus.

7.6. Propofol

Propofol, 2,6 Di-isopropylphenol, was first synthesized in 1973 by Imperial Chemical Industries from the chemical solvent 1,3 Di-isopropylbenzene by replacing hydrogen with hydroxy groups. In 1986, propofol was introduced for therapeutic use as a lipid emulsion in the United Kingdom and New Zealand. Propofol (Diprivan) received FDA approval in October 1989. Propofol's favourable pharmacokinetic properties, very short onset and offset time, and relatively modest hemodynamic impact have made it the world's most frequently used intravenous hypnotic agent and it is currently used in hundreds of millions of surgeries every year.

The first case of death attributed to the now so-called propofol infusion syndrome (PRIS) occurred in Denmark in 1990, and the Danish Side-effects Committee issued a warning about the use of propofol infusions in children. In 1992, a report by Parke and colleagues generated significant, widespread concern about the safety of continuous propofol infusions in children. The authors reported on the deaths of five children aged from 4 weeks to 6 years who were admitted to the PICU for the management of severe respiratory tract infections. The children, who were mechanically ventilated and sedated with high dose propofol infusions, developed metabolic acidosis, hyperlipidemia, hepatomegaly, bradyarrhythmias and, ultimately, progressive cardiac failure [55]. It is believed that the development of PRIS is related to the inhibition of intracellular energy production within mitochondria by propofol.

Propofol is not recommended for long-term sedation of critically ill children in any recognized clinical guideline. An explicit recommendation in the first UK national consensus guidelines on sedation and analgesia in critically ill children, published by Playfor and colleagues in 2006 was that 'Propofol should not be used to provide continuous sedation in critically ill children' [19].

In the 2022 US SCCM Clinical Practice Guidelines it is suggested that that continuous propofol sedation at low doses and administered for less than 48 hours may be a safe and that short term administration, for less than 48 hours, may be a useful adjunct during the peri-extubation period to facilitate weaning of other analgosedative agents prior to extubation [21].

8. Future Innovation

Volatile anesthetic agents are likely to be used increasingly frequently in this context as evidence of their benefits continue to be illustrated. Xenon is a noble gas that has been used sporadically as a sedative agent in critical care settings due to its unique properties with rapid onset and offset of action, minimal cardiovascular effects, and potential neuroprotective benefits. Currently, xenon is prohibitively expensive but advances in closed-circuit ventilation systems with agent recycling will make its use more feasible. Ciprofol is a recently developed, short-acting γ-aminobutyric acid receptor agonist sedative which is more potent than propofol; it was approved for use in critically ill patients requiring sedation during mechanical ventilation in July 2022 [56]. Remimazolam is a novel ultra-short-acting benzodiazepine, showing promise for sedation in critical care due to its rapid onset, organ-independent metabolism, and quick recovery time [57]. Sufentanil is a synthetic opioid which is 5-10 times more potent than fentanyl with rapid onset and a long duration of action. FDA approved

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in 1984, sufentanil has been used to provide long term sedation in the intensive care unit. Its rapid distribution and elimination profile suggest that the rapid reversibility of sedation with sufentanil is maintained after long duration of infusion [58]. Alfaxalone (3α-hydroxy-5α-pregnane-11,20-dione) is a synthetic neuroactive steroid which has been used as a fast-acting intravenous anesthetic with a high therapeutic index in veterinary practice since the 1970s [59]. Alfaxalone is believed to be neuroprotective and free from neurotoxic activity. Brexanolone is a GABA-A modulator, a proprietary, aqueous formulation of the neuroactive steroid, allopregnanolone [60]. It has been used in post-partum depression, as a treatment for super-refractory status epilepticus, and shows promise as a sedative for critically ill patients.

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