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REVIEW ARTICLE

Analgesia and sedation in children: practical approach for the most frequent situations

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Abstract

Objectives: To review the most frequent recommendations, doses and routes of administration of sedatives, analgesics, and muscle relaxants in children, as well as the methods for monitoring the level of sedation.

Sources: Review of the literature using the MEDLINE database and review of the experience in pediatric intensive care units.

Summary of the findings: The continuous administration of analgesics and sedatives prevents the development of undersedation and is less demanding in terms of care than intermittent administration. Midazolam is the most commonly used drug for continuous sedation of critically ill children. Opioid derivatives and nonsteroidal anti-inflammatory drugs are the most widely used analgesics in critically ill children. Opioids combined with benzodiazepines, given in continuous infusion, are the drugs of choice in mechanically ventilated children, especially morphine and fentanyl. The use of protocols and monitoring through clinical scores and objective methods (e.g. bispectral index) allow adjusting medication more appropriately, preventing oversedation, undersedation, and the withdrawal syndrome. Non-pharmacological interventions, such as music therapy, noise control, adequate use of light, massage, conversation with the patient, are ancillary measures that help children to adapt to the adverse hospital environment.

Conclusions: Sedation should be tailored to each child for each specific situation. Protocols that facilitate the correct selection of drugs, their appropriate administration and careful monitoring improve the quality of sedation and analgesia and avoid their adverse effects.

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Introduction

One of the major objectives in the pediatric intensive care unit (PICU) is to treat children less invasively, thus avoiding physical and emotional suffering. Sedatives are necessary to reduce the anxiety and agitation that result from the admission to a hostile environment and from medical procedures. Analgesics are used to treat pain secondary to surgical interventions and/or invasive methods, besides the pain inflicted by the disease itself. Moreover, the combined use of analgesics and sedatives allows patients to adapt to mechanical ventilation through the hypnotic effects of these drugs, respiratory depression, and cough reflex.[1] However, the incorrect use of sedatives and analgesics may have negative effects, causing a prolonged necessity for ventilatory support, increasing mortality and morbidity, and lengthening the PICU stay.[2] The use of protocols that facilitate the selection of appropriate drugs, their adequate administration and careful monitoring can improve the quality of sedation and analgesia and prevent their adverse effects. There is a wide availability of sedative and analgesic drugs that can be used in critically ill children, and each one of them has advantages and disadvantages. Nevertheless, no analgesic or sedative meets all the criteria of an ideal drug: rapid onset action, short half-life, metabolization and elimination by organs that are less susceptible to failure (liver and kidney), minimum secondary effects without hemodynamic or respiratory involvement, no interaction with other drugs, and availability of a specific antidote. When choosing a medication, one should bear the following in mind: pharmacodynamics of the drug, its route of administration, secondary effects, patient's age, underlying disease, mechanical ventilation, nutritional status, kidney and liver functions, cost, etc. There is a paucity of reviews and practical guidelines for the use of sedatives, analgesics, and muscle relaxants in critically ill children,[3,4] and most recommendations are based on experiences with adult patients.[5,6] This review provides practical guidelines that should be adapted to each patient, based on the results from the objective and subjective monitoring analyses of sedation and analgesia.

Non-pharmacological treatment

Several non-pharmacological interventions can improve the routine of children in the PICU, reducing their anxiety, improving their sleep-wake cycles, and minimizing the necessity for sedative and analgesic drugs.[7] Music therapy has proven efficient in overcoming anxiety and increasing relaxation of critically ill patients of any age, including preterm infants.[8] Other effective measures include noise control in the PICU, control of lighting to maintain the day and night pattern and the sleep-wake cycle, massage, and communication, if patient's age and health status allow so.[9]

Sedative drugs

Sedation is necessary in many PICU children, especially in those who need ventilatory support. Sedation inhibits the neuroendocrine effects caused by stress (hypertension, tachycardia, tachypnea and hyperglycemia), which increase oxygen consumption and hinder synchronism with the ventilatory support equipment. In addition, it prevents anxiety, which is accountable for sleep deprivation and subsequent psychological disorders. Despite the fact that there are a wide variety of drugs with different indications, there is no sedative that suits all situations. Table 1 summarizes the basic characteristics of the most important drugs.[6,10] The selection of the drug depends on several factors, such as age, disease, and organ dysfunction/failure. The most commonly used drugs are: midazolam, lorazepam and propofol, which are given in continuous intravenous doses. Midazolam is the benzodiazepine of choice for continuous sedation of critically ill children. When given quickly, it may reduce systemic vascular resistance and cause hypotension in hypovolemic patients. However, its continuous intravenous infusion produces few hemodynamic effects. For sedation, it is necessary to administer a bolus dose prior to continuous infusion. Prolonged infusion produces tolerance, and hence the necessity to gradually increase the dose in order to achieve the same sedative effect. In this situation, midazolam should be combined with another sedative (opioid, propofol or other). High doses may lead to "midazolam infusion syndrome," which consists of delayed arousal hours to days after discontinuation, increasing the length of ventilatory support. In case of prolonged use for several days, it is necessary to gradually decrease midazolam infusion so as not to induce the withdrawal syndrome. Lorazepam has a similar effect to that of midazolam, but its use in critically ill children is less documented.[11] The enteral route has been used for its administration in order to minimize the need of continuous midazolam infusion and to prevent subsequent withdrawal syndrome.

The major characteristics of propofol are its rapid onset of action and its rapid elimination of adverse effects after withdrawal ("rapid arousal"). This can be particularly useful in patients who require frequent neurological assessment (e.g. traumatic brain injury or convulsive *status epilepticus*). Propofol has vasodilator properties and may cause reduced cardiac contractility and negative chronotropic effects, especially in patients with hypovolemia and/or abnormal myocardial contractility. For quick procedures (e.g.: respiratory endoscopy), we use a loading dose of 1.5 mg/kg, with small bolus doses of 0.5 mg/kg, as necessary. The maximum dose of propofol recommended for children is

4 mg/kg/hour.[12] Higher doses for prolonged periods are associated with the "propofol infusion syndrome," which consists of cardiogenic shock (reduced myocardial contractility and conduction disorders) in addition to metabolic disorders (lactic acidosis, hypertriglyceridemia) and/or rhabdomyolysis with high mortality.

Table 1 - Characteristics of sedatives most widely used in children

Drug	Dose (mg/kg)	Onset (minutes)	Indication	Comments
Midazolam	OR, IR: 0.5-0.75 IN, SL: 0.2-0.5 IV: 0.2 INF: 1-10 µg/kg/min	2-3	Short procedures Prolonged MV	Tolerance and with drawal syndrome Lower dose in renal and liver failure Hypotension in bolus dose
Lorazepam	IV: Loading dose: 0.02-0.06 INF: 0.02-0.1 mg/kg/h	5-20	Prolonged MV Withdrawal syndrome	Limited clinical experience
Propofol	IV: Loading dose: 2-3 INF: 1-4 mg/kg/h	1-2	Short procedures Short MV	Propofol infusion syndrome Hypertriglyceridemia
Ketamine	IM: 3-5IV: Loading dose: 1-3 INF: 0.7-3 mg/kg/h	0.5-1	Short procedures Intubation in acute severe asthma	Releases endogenous catecholamines Not recommended in ICH
Etomidate	IV: 0.2-0.3	Immediate	Intubation with hemodynamic findings	Suprarenal failure
Thiopental	IV: Loading dose: 3-5 INF: 1-5 mg/kg/h	Immediate	Intubation in ICH	Negative inotrope Vasodilation
Dexmedetomidine	IV: Loading dose: 1 µg/kg INF: 0.2-0.75 µg/kg/h	2-5	Short procedures Short MV	Underdocumented in children Without respiratory depression
Clonidine	OR, IV: 1-4 µg/kg/6-8 h INF: 0.1-0.2 µg/kg/h	5-20	Prolonged MV Withdrawal syndrome	Hypertension in case of sudden withdrawal Without respiratory depression
Chloral hydrate	OR, IR: 25-75 mg/kg	5-20	Short procedures	Agitation and late disinhibition
Chlorpromazine	OR, IR: 0.5-1.5 every 6-8 h IV: 0.5 mg/kg		Agitation- Delirium	Extrapiramidal reactions

ICH = Intracranial hypertension; IM = intramuscular; IN = intranasal; INF = continuous infusion; IR = intrarectal; IV = intravenous; MV = mechanical ventilation; OR = oral route; SL = sublingual.

There are numerous studies comparing both drugs.[13] Midazolam allows maintaining adequate sedation and amnesia levels at a low cost, but its use is more complex, requiring more ventilatory support and showing a greater association with the withdrawal syndrome after its discontinuation. Propofol has a more rapid action and allows earlier weaning from the ventilator, but it causes more vascular depression during induction, it is also more expensive and should be given through an independent intravenous route. Midazolam is still the drug of choice in patients who need sedation with intravenous infusion. Propofol is the drug of choice for short procedures[3] and, in our setting, it is a safe and appropriate drug if low supplemental doses are used in those patients in which adequate sedation is not obtained with midazolam.[5,14]

Etomidate is one of the intravenous anesthesia-inducing agents that causes the fewest hemodynamic alterations. For some time, it was the drug of choice for rapid and emergency intubation in critically ill patients. However, recently, it has been contraindicated as it causes suprarenal failure, even when it is used as a single dose for intubation.[15] In addition, it may cause trismus during anesthetic induction, so it must be used with a neuromuscular blocking agent (NMBA). Therefore, its single and repeated administration or infusion is contraindicated in septic patients, since it may cause suprarenal failure.

Other sedative drugs include barbiturates such as pentobarbital and thiopental. Among other indications, they are recommended in the treatment of refractory seizures and traumatic brain injury with severe intracranial hypertension. Currently, they are seldom used in critically ill patients, as they cause hemodynamic instability and accumulate in peripheral tissues after prolonged infusion, delaying the patient's arousal. Phenobarbital can also be used as supplementary treatment in patients submitted to prolonged ventilatory support in remarkable need for sedation. Chloral hydrate given orally or rectally can be used as sedative in rapid interventions (e.g.: echocardiogram), but its onset and length of action vary considerably.

Analgesic drugs

Children admitted to the PICU have pain caused either by the underlying disease or by the diagnostic or therapeutic procedures. More often than not, patients receive insufficient analgesic treatment, even for painful procedures. A recent study showed that 44% of children recalled the painful experiences they had been put through during their PICU stay. As occurs with sedation, there is not such a thing as an all-purpose analgesic, and the selection of drugs depends on numerous factors. Table 2 summarizes the characteristics of the most commonly used drugs.

Opioid derivatives and non-steroidal anti-inflammatory drugs are the most widely used analgesics in critically ill patients. Opioids are the drugs of choice for mechanically ventilated patients,[16] especially if combined with benzodiazepines, since they have shown a synergistic effect that allows reducing the dose of both medications.[1] Morphine and fentanyl are widely used in continuous infusion, but remifentanil, tramadol and meperidine have been increasingly used as well.[17,18]

Morphine has low solubility, which explains its delayed maximum effect on the central nervous system (CNS) – 15 minutes – and its longer effect – 3-6 hours. It is metabolized by the liver, originating two active metabolites that accumulate in case of renal failure. When given intravenously, it may cause hypotension by producing venodilation and by releasing histamine. Usually, its elimination half-life is longer, but its elimination is smaller in newborn (NB) infants, compared to other children and to adults. The greater difference is mostly perceived in preterm NB infants. Nonetheless, less morphine binds to the protein in NB infants, leading to a higher amount of morphine, increasing the risk for respiratory depression. The elimination half-life and clearance similar to that of an adult is obtained at 2 months of life.[19]

Fentanyl is 60-100 times more potent than morphine. Its fat-solubility is higher, which explains its rapid action and short duration, due to its fast distribution. If given for a prolonged time, there is rapid tolerance and accumulation in the adipose tissue; therefore, its half-life is longer than that of morphine. It does not produce active metabolites. It does not release histamine, allowing for greater hemodynamic stability than morphine. An infrequent adverse effect is chest wall rigidity, which is related to the dose used, rate of infusion and age < 6 months.

Remifentanil is a fentanyl derivative with similar potency and rapid onset action. Its peak effect is achieved in less than 3 minutes and it is short-acting (its effect disappears within few minutes, being metabolized by nonspecific plasma esterases), regardless of the length of its infusion and of the presence of liver and/or renal dysfunction. This profile allows earlier extubation than other opioids and the use of higher doses, in which the analgesic effects combine with sedative effects without any risk of accumulation. Only approximately 30% of patients may need another sedative at low doses in order to achieve the goals of sedation and analgesia. Disadvantages include large economic cost, quick development of tolerance, and higher frequency of

hypotension compared to fentanyl.[20] Its use as continuous infusion has been more and more frequent, also among NB and infants.[21] Due to its potency, hemodynamic stability and short action at low doses, fentanyl is ideal for short painful procedures in children, especially in the PICU.[22]

Mild to moderate pain can be effectively managed with non-opioid analgesics, such as acetaminophen (paracetamol), or with non-steroidal anti-inflammatory drugs (NSAIDs). Acetaminophen has a very good therapeutic power, with few contraindications. It may be used in any age

Table 2 - Characteristics of the drugs most commonly used in critically ill children

Drug	Dose (mg/kg)	Onset (minutes)	Indication	Comments
Morphine	IV: 0.1-0.2 mg/kg/4-6 h INF: 10-40 µg/kg/h	20	Sedation and analgesia in MV Acute or chronic pain Pulmonary edema	Lower dose in renal or liver failure Releases histamine Nausea and vomiting
Fentanyl	IV: 1-3 µg/kg INF: 1-10 µg/kg/h	1-2	Short painful procedures Same as morphine	Prolonged clearance Better hemodynamic tolerance Thoracic rigidity after quick administration
Remifentanil	IV: 1 µg/kg INF: analgesic: 0.5-6 µg/kg/h Sedation: 6-12 µg/kg/h	1	Sedation and analgesia in MV Immediate postoperative period	Immediate clearance Better hemodynamic tolerance Thoracic rigidity after quick administration
Alfentanil	IV: 15-25 µg/kg in 60 min INF: 0.4-2 µg/kg/min	1-2	Short painful procedures	High-priced Not to be used in liver failure
Methadone	IV: 0.1-0.2 mg/kg/4-6 h	45	Treatment of withdrawal syndrome Chronic pain	Nausea and vomiting
Tramadol	IV: 1-2 mg/kg/4-6 h INF: 0.2-0.4 mg/kg/h	10	Acute pain	Good hemodynamic tolerance Less respiratory depression
Paracetamol	IV: 10-15 mg/kg/6 h	30	Moderate pain Hyperthermia	Central action Hepatotoxicity
Ketorolac	OR: 2 mg/kg/day every 6-8 h IV, IM: 0.2-1 mg/kg/6 h	30	Moderate to severe pain Anti-inflammatory drug	Gastrointestinal bleeding Nephrotoxicity
Metamizole	IV: 10-40 mg/kg/4-6 h INF: 4-6.6 mg/kg/h	15-30	Moderate to severe pain Hyperthermia	Synergistic effect with opioids Hypotension in case of quick infusion

IM = intramuscular; INF = continuous infusion; IR = intrarectal; IV = intravenous; MV: = mechanical ventilation; OR = oral route.

group, even in preterm infants, and it is possible to obtain synergistic effects with other NSAIDs or opioids, due to its analgesic effect on the central nervous system.[23,24]

NSAIDs have analgesic and anti-inflammatory properties, both of which are useful in the management of postoperative and chronic pain[25] or of mild to moderate pain. The most widely used NSAIDs are ketorolac, ketoprofen and diclofenac. An advantage is that they do not cause respiratory depression or sedation. The mechanism of action occurs through the inhibition of cyclooxygenase (COX), the enzyme in charge of arachidonic acid metabolization.[26,27] In recent years, they have been increasingly used in combination with opioids in the postoperative period, as they produce a synergistic analgesic effect that allows better pain management with fewer secondary effects and lower doses.[28]

Ibuprofen and naproxen are the most common NSAIDs in pediatrics.[27] They are not indicated in the initial stages of septic shock, due to their secondary effects on the gastric mucosa, renal function and platelets. Metamizole is one of the non-opioid analgesic drugs most widely used in European, South American and African countries and can be used to treat moderate to severe pain, combined with opioids in order to enhance the analgesic effects and delay the development of tolerance. It may cause hypotension as a result of vasodilation if administered as rapid intravenous infusion. The risk of agranulocytosis and bone marrow aplasia is very low. At some centers, they are frequently used in continuous infusion in the immediate postoperative period, including heart surgeries, with excellent results.

Tramadol is an atypical opioid structurally related to codeine. Its double mechanism of action includes central inhibition of norepinephrine as serotonin reuptake inhibitor and weak agonist action on the theta receptor, due to an active metabolite. Tramadol is 10 to15 times less potent than morphine. It is known for producing fewer side effects than other opioids. The use of tramadol should be avoided in patients with seizures or traumatic brain injury or who are being treated with drugs that lower the seizure threshold. In general, tramadol is a safe and efficient analgesic in the management of mild to moderate pain in children.[29]

Analgesic and sedative drugs

Ketamine

It is a phencyclidine derivative that produces dissociative anesthesia. It has analgesic effects, even at lower doses than the sedative dose. It is a potent analgesic at subanesthetic doses and regularly used in painful procedures in children in the emergency room (e.g.: fracture reduction, burn dressings) and in the PICU.[30] Its half-life ranges from 2-3 hours, and may be extended if continuous infusion is used or in case of liver failure. Unlike other sedative drugs, it activates the sympathetic nervous system (by releasing endogenous norepinephrine), with increase in heart rate, in vascular resistance, and with bronchodilation. Although it has a negative inotropic effect, sympathetic stimulation runs counter to this effect, except in cases of catecholamine-refractory cardiogenic shock. The difference between intramuscular and intravenous administration lies only in the onset of action (1-2 minutes and 5-10 minutes). Intravenous doses provide around 10 minutes of sedation and analgesia for each mg/kg, i.e., 1 mg/kg of IV ketamine produces analgesia and sedation for 10 minutes, whereas 2 mg/kg produces approximately 20 minutes of analgesia and sedation. However, the residual effect may last for 2-3 hours. One IV dose of 1-2 mg/kg is usually well tolerated in procedures that involve a larger amount of pain, such as fracture reduction.

Ketamine in continuous infusion combined with benzodiazepines can be used in hemodynamically unstable critically ill patients, providing good sedation and analgesia and reducing the dose of catecholamines. Ketamine is mostly useful for sedation and analgesia in invasive procedures, and is often used in combination with midazolam and as an anesthesia inducing agent in emergency intubation in *status asthmaticus*.[31]

Adrenergic alpha-2-agonists

Clonidine and dexmedetomidine have a sedative and analgesic effect due to their action on alpha-2 receptors.[32] Clonidine causes minor respiratory depression. There are some contradictory reports in the literature with regard to the effects of dexmedetomidine on ventilatory function in some (human and animal) studies, suggesting mild respiratory depression, reduction of the minute ventilation and reduction of CO_2 response, whereas other reports do not show this effect.[33]

Clonidine has been used as premedication before surgery, for peripheral blockade, as an analgesic in intrathecal perfusion and for the control of tolerance and of the deprivation syndrome of other sedatives.[34,35] Its oral administration is used in several PICUs for the prevention and treatment of deprivation syndrome of other sedatives. Dexmedetomidine in intravenous infusion has sedative and analgesic effects, minimizing the need for opioids. It may be very useful in the immediate postoperative period, facilitating early extubation.[36] It is an alpha-2-agonist receptor that acts centrally, with affinity for a receptor that is eight times larger than clonidine. The use of dexmedetomi-

dine was initially considered as a sedative to be used in mechanically ventilated adults, but now its use in children is also documented. Although dexmedetomidine has been primarily investigated for its sedative effect, it apparently has analgesic effects that are appropriate for cases where opioids are needed, therefore allowing for a lower opioid use.[33]

Monitoring of sedation and analgesia

The monitoring of sedation level is key to avoiding undersedation, which causes suffering to the patient, and oversedation, which delays extubation.

Clinical scores are the most common tools for monitoring the levels of sedation. However, these scores are limited, since they are subjective, their assessment is intermittent, they sometimes interrupt patient's rest and sometimes give more importance to pain sensitivity than to the sedation level. Moreover, their usefulness is quite limited in deep levels of sedation and in patients with muscle relaxation. The Ramsay and Comfort scores are the most widely used tools for determining the level of sedation in pediatrics. The Ramsay score can be easily and quickly applied, but its use has not been validated in children, and it is not useful in relaxed patients. In addition, it uses auditory and painful stimuli to evaluate responses, which increases its subjectivity. The Comfort score was designed for mechanically ventilated children and does not require the use of any stimulus for evaluation. Nevertheless, it is more time-consuming and complex, it assesses both objective and subjective parameters, it includes variables such as heart rate and blood pressure, which change in critically ill patients as a result of several other factors, and it has not been validated in children with muscle relaxation. A recent study has described a simplified Comfort score with the same value as the original score, in which physiological variables were eliminated.[37]

In the last few years, several methods have been developed that allow objectively assessing the level of consciousness by analyzing electroencephalographic findings, such as the bispectral index (BIS), auditory evoked potentials of intermediate latency and analysis of electroencephalographic (EEG) spectra.[38-40] These instruments have been developed and validated to assess the depth of anesthesia in patients submitted to surgical interventions; however, there is a paucity of studies on their usefulness in critically ill patients. BIS is the most frequently used, as it continually assesses EEG findings and provides a numerical measurement of the sedation level, ranging from 0 (electrical silence) to 100 (awake). BIS allows improved and continuous monitoring of patients that need deep sedation and neuromuscular blockade.

The assessment of pain in the PICU is much more difficult, especially in mechanically ventilated sedated patients. Quite often, it is not possible to make a distinction between pain and anxiety, and both should be treated simultaneously. Furthermore, pain expression in newborns and infants is undifferentiated. To assess pain, different scales have to be used for each stage of childhood. At the preverbal stage (NB to 3 years), the scales use mainly facial expression and motor and physiological response, such as crying. Parents' opinions must be taken into account in order to distinguish between reactions caused by pain and others that are caused by anything else.[41] At the verbal stage (3-8 years), it is possible to use self-information through pictures and face drawings. After the age of 8 years, the verbal, numerical, graphic, and visual analog scales can be used.[42]

Neuromuscular blocking agents

In certain situations, in addition to sedative and analgesic drugs, the use of neuromuscular blocking agents (NMBAs) is necessary. They are subdivided into depolarizing and non-depolarizing agents. Table 3 shows the most widely used NMBAs.

Succinylcholine is still the most widely used muscle relaxant for emergency intubations, due to its rapid action, whereas rocuronium is the most efficient alternative with fewer secondary effects.

Muscle relaxants are also useful in some patients in which sedation and analgesia are not enough to allow adaptation to mechanical ventilation. They increase the compliance of the respiratory system, reducing the pressure that is necessary to ventilate and minimize oxygen consumption. It has been suggested that their early use in mechanically ventilated patients with acute respiratory distress syndrome (ARDS) can prevent progression of inflammation and ventilator-induced lung injury.

Vecuronium is more widely used in critically ill patients,[43] as it does not cause hemodynamic changes and does not release histamine. It has an intermediate half-life, it does not often bind to proteins, has a high distribution volume and is metabolized by the liver into active metabolites that are eliminated by the kidneys. This explains why its effects last longer in patients with renal and/or liver dysfunction.

All patients on muscle relaxants must be previously sedated to avoid anxiety of involuntary immobilization in alert patients. Neuromuscular blocking agents must be given at the least effective dose and for the shortest time. Their main risk includes residual neuromuscular blockade and accumulation due to prolonged administration, which may lead to muscle weakness and neuromyopathy, being more

frequent when combined with the use of corticosteroids in patients with sepsis, renal or liver failure.

Maintenance of a minimum depth of neuromuscular blockade can reduce the incidence of complications. The train of four (TOF) is the most commonly used method to assess the depth of neuromuscular blockade. It consists in applying four supramaximal, consecutive electrical stimuli on a peripheral nerve using a neurostimulator.[44] Under normal conditions, this stimulus produces four identical contractions in the muscle zone of the stimulated nerve. In the presence of NMBA and according to the level of blockade generated, the number of responses diminishes. In general, neuromuscular blockade is adequate if there are two or three contractions in response to the four stimuli.

Withdrawal syndrome

The withdrawal syndrome results from sudden discontinuation of sedative and analgesic drugs in patients with physical tolerance due to prolonged administration of such drugs. The signs and symptoms vary substantially in terms of presentation and severity, depending on the drug and on the patient's status. Among these signs and symptoms are CNS activation (irritability, abnormal reflexes, tremors, clonus, hypertonicity, delirium, and seizures), gastrointestinal disorders (gastrointestinal intolerance, nausea, vomiting and diarrhea) and activation of the sympathetic nervous system (tachycardia, hypertension and tachypnea). Finnegan's score can be used to assess their presentation and intensity.[45]

Table 3 - Characteristics of the neuromuscular blocking agents most frequently used in children

Drug	Action	Dose (mg/kg)	Onset (minutes)	Length (minutes)	Advantages	Comments
Succinylcholine	Depolarizing	1-2 Not recommended for INF	Immediate	3-5	Short action (intubation)	Hyperpotassemia Fasciculations
Vecuronium	Non-depolarizing	Initial bolus: 0.08-0.2 INF: 0.08-0.2 mg/k/h	2-4	20	No cardiovascular effects	Muscle weakness
Pancuronium	Non-depolarizing	Initial bolus: 0.1 INF: 0.1 mg/k/h	2-4	30-45	Longer action	Tachycardia, hypertension Increase in ICH
Atracurium	Non-depolarizing	Initial bolus: 0.3-0.6 INF: 0.3-0.6 mg/k/h	2-3	25-30	Not metabolized by the liver and kidney	Bronchospasm Bradycardia
Rocuronium	Non-depolarizing	Initial bolus: 0.6-1.2 INF: 5-15 µg/k/min	1-2	30-40	No cardiovascular effects	Tachycardia at high doses
Mivacurium	Non-depolarizing	Initial bolus: 0.1-0.2 INF: 10-14 µg/k/min	2-4	12-18	Short action	Bronchospasm Coughing
Cisatracurium	Non-depolarizing	Initial bolus: 0.15 INF: 1.5 µg/k/min	3-4	30	Not metabolized by the liver and kidney	No cardiovascular effects

ICH = intracranial hypertension; INF = continuous infusion.

Table 4 - Protocol for sedation and analgesia (PICU of Gregorio Marañón hospital, Spain)

Intubation
Atropine: 0.01-0.02 mg/kg (minimum dose 0.1 mg)
Sedation: etomidate: 0.2-0.3 mg/kg,* midazolam 0.3-0.5 mg/kg or propofol 2-3 mg/kg, except if:
TBI with increase in ICP: thiopental 3-5 mg/kg
Acute severe asthma: ketamine 2 mg/kg
Muscle relaxants
Succinylcholine: 1-2 mg/kg
Rocuronium (0.6-1.2 mg/kg) or vecuronium (0.1 mg/kg) in cholinesterase deficiencies, hyperkalemia and intracranial hypertension
Invasive procedures in patients with spontaneous breathing
IV ketamine (bolus 1-2 mg/kg) + IV midazolam (bolus 0.1-0.3 mg/kg)
IV fentanyl (bolus 1-2 µg/kg) + propofol (bolus 1-2 mg/kg and maintenance at 0.5-5 mg/kg/h)
Extubated in postoperative period or extubation within the next hours (including heart surgery)
Fentanyl (0.5-2 µg/kg/h) + metamizole (6 mg/kg/h) in continuous infusion
Combine with paracetamol 15 mg/kg/6 h if pain persists or when fentanyl is withdrawn
Remifentanil (3-12 µg/kg/h) or dexmedetomidine (0.2-0.75 µg/kg/h)
Postoperative period with extubation within the first 24 hours
Midazolam (2 µg/kg/min) + fentanyl (2 µg/kg/h) in continuous infusion
Propofol (1-4 mg/kg/h) + fentanyl (1-3 µg/kg/h) in patients with frequent need of neurological reassessment
Sedation and analgesia with mechanical ventilation longer than 24 hours
Midazolam (2-10 µg/kg/min) + fentanyl (1-10 µg/kg/h) as necessary
Combine with propofol (1-4 mg/kg/h) if the need for sedation increases
If bolus doses are necessary: midazolam 0.1-0.2 mg/kg; fentanyl 2 µg/kg; propofol 1 mg/kg
Combine with methadone (0-1-0.2 mg/kg/6 h), clorazepam (0.5-2 mg/kg/dose) and clonidine (1-4 µg/6-8 h) OR if longer than 7 days of sedation
Muscle relaxation in mechanically ventilated patients
Vecuronium (0.1-0.2 mg/kg/h). Bolus of 0.1 mg/kg if necessary
Special situations
Thiopental or pentobarbital (1-5 mg/kg/h) in intracranial hypertension and convulsive status epilepticus
Ketamine (0.5-2 mg/kg/h) in acute severe asthma

CP = intracranial pressure; IV = intravenous; OR = oral route; TBI = traumatic brain injury.
* Editor's note (JPP): Since it has been recently recommended that the use of etomidate should be avoided[49] because it causes suprarenal failure, sedation for intubation can be obtained with fentanyl (5-10 µg/kg) combined with midazolam (0.3-0.5 mg/kg) or propofol (2-2.5 mg/kg) combined with fentanyl (5 µg/kg) or ketamine (2-4 mg/kg) combined with midazolam (0.2-0.5 mg/kg).

This syndrome has been described in the administration of most sedative and analgesic drugs, such as opioids, benzodiazepines, barbiturates, and propofol. The withdrawal syndrome occurs in 50% of the cases with an overall fentanyl dose greater than 1.5 mg/kg or administration longer than 5 days, rising to 100% when the overall dose is greater than 2.5 mg/kg or with an administration longer than 9 days. The incidence of this syndrome increases significantly with an overall midazolam dose greater than 60 mg/kg, and with an overall pentobarbital dose greater than 25 mg/kg.[46]

Different methods are used to prevent the development of the withdrawal syndrome, such as gradual reduction in doses,[46] methadone administration,[47] subcutaneous use of fentanyl and midazolam and avoidance of continuous intravenous sedation. Recently, it has been proposed that administration in adults be completely discontinued for some time every day after continuous infusion of sedative and analgesic drugs. In some studies, this measure managed to reduce the length of mechanical ventilation and ICU stay.[48] This measure can certainly lead to a higher risk of acute deprivation, pain, and agitation, and because of that, it is not frequently used in pediatric patients. It is therefore recommended that the level of sedation be reduced every day for some hours without withdrawing the sedative and analgesic drugs and that the new objective methods be used to monitor the level of consciousness. The most widely used method consists of the progressive replacement of continuous intravenous drugs with long-acting enteral drugs. The most common drugs include enteral methadone and morphine, lorazepam, chlorazepate, and alpha-2-agonists (e.g.: clonidine). In our PICU, we gradually weaned our patients from continuous fentanyl and midazolam perfusion for over 7 days in order to prevent the withdrawal syndrome, and we replaced them with methadone and chlorazepate dipotassium given enterally every 6-8 hours. In case of signs of withdrawal syndrome or if the dose of intravenous sedatives could not be reduced, then we gave enteral clonidine.

Protocols in medical practice

The introduction of clinical guidelines for the management of sedation and analgesia in the ICU has been associated with better sedative and analgesic control, with reduction in the length of mechanical ventilation and in ICU stay, as well as with a reduction in expenditures on sedative and analgesic drugs.

Theoretically, the continuous administration of analgesic and sedative drugs is more appropriate. Moreover, this is less demanding in terms of care and prevents undersedation. The strict use of protocols for sedation using continuous perfusion can result in larger need for mechanical ventilation, longer ICU and hospital stay, and larger number of reintubations. Therefore, it is important that every unit use one sedation protocol and that this protocol be adapted to each patient in each situation, based on the monitoring of his/her health status and level of sedation. The protocol should clearly establish the regimen for initial administration, dose escalation and reduction, indications for additional bolus doses and the method for discontinuation of sedation. Table 4 summarizes the protocol for sedation and analgesia adopted by the PICU of Gregório Maragnón hospital, in Spain.

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