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Sedation-analgesia, Muscle Relaxant Applications in Pediatric Intensive Care Units and Guidelines for the Management and Environment Optimization of Clinical Statements Such as Withdrawal, Delirium Developed During These Applications

Çocuk Yoğun Bakım Ünitelerinde Sedasyon-analjezi, Kas Gevşetici Uygulamaları ve Bu Uygulamalar Esnasında Gelişen Yoksunluk, Deliryum gibi Klinik Tabloların Yönetimi ve Ortam Optimizasyonuna Yönelik Rehber

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Regardless of the patient's age or underlying clinical condition, painful interventions are frequently performed during admission and follow-up in intensive care units. Pain may be caused by the underlying disease or may develop due to care. In intensive care units, pain caused by endotracheal tubes and mechanical ventilation is important. Factors such as separation from family, disturbances in the day and night cycles, noise of machines and monitors, unfamiliar people, and fear of death may cause emotional stress, anxiety, and insomnia in pediatric intensive care units (PICU). The aim of using sedation and analgesia in pediatric patients is to ensure that the patient is comfortable, to minimize physical discomfort and pain, to prevent psychological trauma by reducing anxiety, to create amnesia, to increase the success of assisted ventilation by keeping the level of consciousness and movement of the patient under control, and to ensure a safe return to the pre-consciousness level after the application.[1-3]

Methodology

"Pediatric Intensive Care Sedation-Analgesia and Muscle Relaxant Group" was established, and a guideline was planned to be prepared in order to make a common regulation in light of current information in the sedation-analgesia management,

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the use of muscle relaxants and the management of clinical pictures in PICUs, to provide standardization among centers and to prepare a resource that will shed light on new studies. For this purpose, the "Pediatric Intensive Care Sedation-Analgesia and Muscle Relaxants Group" met for six times. While forming the recommendations, firstly, the literature on the subject was reviewed in order to create evidence, the results of the surveys conducted in our country were evaluated, and the evidentiary data obtained were grouped with the GRADE methodology. In order to ensure consensus, voting was held for a maximum of two times. Finally, these recommendations and statements were renewed to be compatible with each other. As a result, recommendations with 80% or more consensus were considered strong recommendations, while 50-80% were considered weak recommendations.

Sedation is used to describe the reduction of consciousness or awareness: analgesia is used to describe the reduction of pain sensation; and amnesia is used to describe the absence of subsequent recollection of events. The American Society of Anesthesiologists defines interventional sedation on a scale from the mildest sedation to general anesthesia. Medically induced mild loss of cognitive and motor functions is anxiolysis. Moderate sedation and analgesia, also defined as conscious sedation, is a state of moderate sedation in which children can respond appropriately to verbal commands with mild tactile stimulation or alone. Respiratory and cardiovascular functions are not affected in these two stages. Deep sedation and analgesia are a medically induced suppressions of consciousness in which the child can only respond to repetitive or painful stimuli. General anesthesia is a medically induced loss of consciousness with no response to painful stimuli (Table 1). Respiration is affected in deep sedation and general anesthesia.[1-3]

In recent years, the negative effects of inadequate sedation-analgesia in intensive care units, especially in mechanically ventilated patients, have been frequently emphasized. Failure to provide effective sedation-analgesia in patients monitored in intensive care units may lead to an increase in oxygen consumption and carbon dioxide production. Changes in respiratory parameters such as increased respiratory rate and minute ventilation, decreased tidal volume, maximum expiratory volume and vital capacity may develop. Neuroendocrine events developing with the release of catecholamine, cortisol, glucagon and other catabolic hormones may lead to negative nitrogen balance and catabolic state with hyperglycemia. Hemodynamically, heart rate and blood pressure may increase.[4-7]

All these findings are related to the sensation of pain as a result of inadequate sedation-analgesia. Therefore, pain and sedation levels should be measured. Assessment and measurement of pain in children is difficult. Especially for infants, non-verbal (2-7 years old) and pediatric patients in intensive care, it is difficult to define pain. This difficulty causes some of the available tests to be inapplicable to children, and adequate pain control cannot be achieved. Many objective and observation-based methods are used in the assessment of pain. The methods used to determine the level of pain are based on the observer's assessment or measurement of certain characteristics or changes in the patient (Type I measurements) or on the patient's self-rating of pain (Type II measurements). Type I methods include physiological (increased plasma cortisol and catecholamine levels, changes in cardiovascular and respiratory parameters), non-pharmacological (inverse relationship with plasma β-endorphin levels, changes in skin temperature) and neurological (nerve conduction velocity, evoked responses, special micrographs and tomographs) measurements. Type II methods include category numerical and visual analog scales, the McGill Pain Questionnaire or Wesh Haven-Yale Inventory, rehabilitation tests. The choice of method should be based on the child's general condition, age and level of pain recognition. In infants, body response, facial expression, crying and pulling reflex can be used to get an idea. Among these, facial expression is considered to be the most reliable. While evaluating facial expression, eyebrow raising, eye squeezing, nasolabial groove formation, opening of the lips, vertical or horizontal stretching of the mouth, puckering of the lips, stretching of the tongue, and trembling of the chin are taken into consideration. The duration and tone of the crying sound can also be evaluated. However, these symptoms indicate the presence of pain rather than its degree. Most children over the age of three years can express their pain and its degree, and can indicate the intensity of pain by choosing from a series of colors or pictures, or by selecting

Table 1. Sedation and analgesia stages

State	Anxiolysis/mild sedation	Conscious sedation/moderate sedation and analgesia	Deep sedation/analgesia	General anesthesia
Non-response	Normal response to verbal stimulation	Appropriate response to verbal or mild tactile stimulation	Appropriate response to repetitive or painful stimuli	Unresponsive to painful stimuli
Airway patency	Maintained	Maintained	Can require intervention	Often require intervention
Respiration	Normal	Sufficient	Can require support	Often require support
Cardiovascular functions	Normal	Maintained	Generally maintained	Can impair

one of the rungs of a ladder. The intensity and severity of pain can be assessed in children aged three years and older using the Oucher scale or the visual scales developed by McGrath. The applicability of these tests is difficult especially for the patients hospitalized in intensive care units.[4-7]

Determining the level of sedation during sedation-analgesia use is also necessary for dose adjustment in non-cooperative PICU patients. The most commonly used sedation scores in the PICU are scales assessing physiologic variables or depth of sedation or both. The most commonly used scale is the COMFORT score, which is assessed by patient response or physiologic parameters. Here, patient alertness, respiration, blood pressure, muscle tone, agitation, mobility, heart rate and facial tension are assessed (Table 2). Tachycardia or hypertension may not be observed despite pain and agitation, especially in patients with cardiovascular instability and those taking vasoactive drugs. COMFORT-B scoring was developed due to the limitations mentioned. In the COMFORT scoring, which is most commonly used in children, a score between 6 and 10 indicates excessive sedation, and a score between 23 and 30 indicates inadequate sedation levels. The other sedation grading system is the RAMSAY scoring used in adults (Table 3). Many scoring systems are subjective and adversely affected by differences in assessment between observers. Methods with high objectivity may be difficult to apply routinely. Based on this, the Brussels sedation scale, which was developed as a simple scoring system, is easy to use and reduces subjectivity and inter-observer variability (Table 4). Scoring systems have been shown to be cost-effective for PICUs. With good control of the sedation level of the patient, weaning from the ventilator is accelerated and the number of ventilator-dependent days decreases.[5-8]

A major problem with clinical sedation systems is the difficulty in determining the depth of sedation in patients receiving paralytic agents. A bispectral index (BIS) is a monitor that measures the hypnotic effects of sedative and anesthetic agents based on the electroencephalogram. The measurement of brain electrical activity with the BIS monitor is integrated into a single numerical value between 0 and 100. The results are not clear, but most reports have found a good correlation between the COMFORT score and the BIS. The BIS has been found to correlate particularly well in patients undergoing inhalation anesthesia or in assessing the efficacy of some specific agents.[9,10]

The BIS can be applied to a group of patients for whom intensive care scoring systems using muscle relaxants and/or agents that can alter the heart rate and blood pressure response would be difficult to assess. The main problem associated with the use of BIS is the recording of highly variable values.

Table 2. Comfort and comfort B sedation scales

Comfort scale	Score
Alertness	
Deeply asleep	1
Lightly asleep	2
Drowsy	3
Fully awake and alert	4
Hyperalert	5
Calmness	
Calm	1
Slightly anxious	2
Anxious	3
Very anxious	4
Panicky	5
Heart rate	
Heart rate below baseline	1
Heart rate consistently at baseline	2
Infrequent elevations of 15% or more above baseline (1-3 during observation)	3
Frequent elevations of 15% or more above baseline (more than 3 during observation)	4
Sustained elevations of 15% or more	5
Facial appearance	
Facial muscles totally relaxed	1
Facial muscle tone normal, no facial muscle tension evident	2
Tension evident in some facial muscles	3
Tension evident throughout muscles	4
Facial muscles contorted and grimacing	5
Blood pressure baseline	
Blood pressure below baseline	1
Blood pressure consistently at baseline	2
Infrequent elevations of 15% or more above baseline (1-3 during observation)	3
Frequent elevations of 15% or more above baseline (more than 3 during observation)	4
Sustained elevations of 15% or more	5
Respiratory response (only in patients undergoing mechanical ventilation)	
No coughing and no spontaneous respiration	1
Spontaneous respiration with little or no response to ventilation	2
Occasional cough or resistance to ventilator	3
Active respiration against ventilator	4
Fights ventilator, coughing or choking	5
Muscle tone	
Muscles totally relaxed, no muscle tone	1
Reduced muscle tone	2
Normal muscle tone	3
Increased muscle tone and flexion of fingers and toes	4
Extreme muscle rigidity	5
Physical movement	
No movement	1
Occasional, slight movements	2
Frequent, slight movements	3
Vigorous movement limited to extremities	4
Vigorous movements including torso and head	5

Main Principles for the Selection of Drugs

Adequate control of pain and/or anxiety requires an accurate assessment of patient and environmental factors. Before sedation and increasing analgesia doses, it is imperative to determine that the agitation is treatable and not due to life-threatening causes such as hypoxemia, hypercarbia, cerebral hypoperfusion, necrotic bowel syndrome or compartment syndrome. Non-pharmacologic interventions are very important for pain control, sedation and the prevention of physical and emotional stress.

It is important to identify the factor causing the stress in determining the correct agent. Analgesic drugs should be used in the presence of tissue damage or pain, and sedative, anxiolytic and amnestic agents should be used in times of emotional stress. Unfortunately, a very limited number of drugs have both sedative and analgesic effects. The half-life of the agent to be used should be taken into consideration when choosing the right drug. Some interventions may take days and weeks starting in 5 minutes and lasting 12 hours. In addition, there are not enough studies on the pharmacology and pharmacodynamics of sedative/analgesic drugs in critically ill children and they are not evidence-based. Especially in the PICU, organ damage, respiratory and circulatory imbalance, low protein levels and drug interactions make this situation more complex. In addition to pharmacokinetic and pharmacodynamic properties, pharmacogenic factors should also be considered in agent selection. The efficacy and side effects of sedatives and analgesics may vary individually. In some patients, adequate efficacy can be achieved with low doses, whereas high doses may be needed in others. Drug doses should be adjusted according to the patient's level of sedation and analgesia. Drugs with few side effects should be preferred. Incorrect use of sedatives and analgesia without examination of the patient and effective monitoring may lead to negative results. Institutions should make a sedation-analgesia plan, have monitoring criteria, personnel accreditation and quality improvement protocols to ensure safe sedation and analgesia practices in children.[1-5] The use of guidelines published by the American Pediatric Association in the management of sedation and analgesia in these patients may increase efficacy and safety.[9,10]

Table 3. RAMSAY scale

Grade	Describing
1	Patient is awake, anxious, restless and/or disturbed
2	Patient is awake, cooperative, oriented and calm
3	Patient awake, responding only to commands
4	Patient is asleep, responds vividly to loud vocalization and glabellar stimulation
5	Patient is asleep, responds poorly to loud vocalization and glabellar stimulation
6	The patient is asleep, unresponsive to loud vocalization and glabellar stimulation

Table 4. Brussels sedation scale

Grade	Describing
1	Unable to wake up
2	No response to verbal stimuli, responds to painful stimuli
3	Responds to verbal stimuli
4	Awake and alert
5	Agitated

Clinics of Turkey; Non-invasive and Invasive mechanical ventilation special issue: Sedation and Analgesia During Non-invasive and Invasive Mechanical Ventilation pages; 51-60

The parameters to be considered in patients planned to be sedated in PICUs are:

1. Always exclude the treatable cause of agitation

- Hypoxia and hypercarbia
- Cerebral hypoperfusion
- Bladder distortion
- Surgical lesion: Necrotic bowel and compartment syndrome

2. Adequate sedation-identify the cause of pain and agitation if you want to provide analgesia

3. Follow the recommendation of the American Pediatric Association

4. Administer the first loading dose, and then the infusion dose according to the clinical response

5. Monitor for physiological effects, including the development of tolerance, and increase the dose or switch to another drug if necessary.

Agent, Route and Management Procedure

The choice of medication should be based on the type of intervention and the patient's underlying medical condition. Procedures that are not painful but require the child to remain still can usually be performed with sedation alone. Children undergoing painful procedures require additional analgesia in addition to sedation. Before starting sedation-analgesia treatments, three basic issues should be decided: 1) the agent to be used, 2) the route of administration, 3) the method of administration. There is no single agent that will be effective for every patient. The intravenous route is usually chosen. Very rarely, inhaled anesthetics or subcutaneous drugs can be used for analgesia. The inhaled route is preferred if there are side effects or problems with the intravenous route. Not every drug may have an alternative route. Chlorhydrate is administered orally and rectally, isoflurane is inhaled, and propofol is administered only intravenously. Midazolam and ketamine can be used by any route. Finally, the method of administration (continuous, intermittent or patient-controlled) should be decided. In a mechanically ventilated children, long-

acting agents (lorezepam, phentobarbital, and morphine) may provide adequate sedation when administered intermittently and bolus. However, the most common and best practice is to infuse short-acting agents (midozalom-fentanyl) continuously to provide normal serum concentrations. Patient-controlled analgesia is more commonly used outside of intensive care.

Various drugs with advantages and disadvantages are used for sedation and analgesia in the PICU. Healthcare workers should select the agents that they think will be effective based on the clinical characteristics of the patient and should know the characteristics of all of them in order to be able to switch between drugs when necessary.

Pharmacological Agents Used for Sedation and Anesthesia

Opioids

The limbic system, periaquaductal structures and posterior laminae of the spinal cord contain specific pain receptors and are involved in pain perception. The identified sites are stereospecific binding sites for opioids and opioid-related drugs. There are multiple types of receptors specific to these drugs. Table 5 shows the physiologic effects of opioids.

Morphine

It means "god of sleep" in Greek. It provides analgesia by agonist effect on μu receptors in the central nervous system. Because morphine is a lipid soluble drug, and the blood-brain barrier is immature in newborns, its permeability to morphine is high. It is metabolized in the liver. Its half-life is three hours but it is prolonged in neonates and premature infants. Morphine can cause nausea, vomiting, pruritus, miosis and convulsions at high doses. The likelihood of side effects is high, especially in neonates. Although morphine causes peripheral vasodilatation and venous pooling, it has little effect on hemodynamic parameters. It may cause hypotension when used with the sedative drug diazepam. It may cause respiratory depression by decreasing the sensitivity of the respiratory center in the brain stem to hypoxia and hypercarbia. It causes biliary colic, contraction of the ureter, bladder, and bladder detrusor muscles and increased tonus. It is contraindicated in asthma crises because it increases histamine release.[11]

Fentanyl

Its effect starts quickly and its duration of action is short; for these reasons, it is used quite frequently. It is the most commonly used opioid group drug in mechanically ventilated patients. It is 100 times stronger than morphine. There are four commonly used agents: fentanyl, sulfentanil, alfentanil and remifentanil. When they are compared clinically, they have no obvious superiority over each other. Fentanyl-sulfentanil-alfentanil are hepatically metabolized. Their half-lives are prolonged in the presence of hepatic dysfunction. Sulfentanil is 10 times more potent than fentanyl. Alfentanil is 5-10 times less potent than fentanyl. Fentanyl has little negative effect on the cardiovascular system. Remifentanil, one of the new opioids, is less affected by liver dysfunction than other opioids. Remifentanil's half-life is 5-10 minutes. It causes deep sedation. When the drug is discontinued, its effect subsides rapidly and the patient wakes up in a short time.

Opioids may increase intracranial pressure and cause chest wall rigidity. Studies in adults have shown that they decrease mean arterial pressure, increase intracranial pressure and decrease cerebral perfusion pressure. These effects are explained by reflex cerebral vasodilation in response to decreased mean arterial pressure. Chest wall rigidity is dose, rate of administration-, and age-related. The side effect of chest wall rigidity is reversed with the administration of naloxone and muscle relaxants. Fentanyl and similar group drugs are highly lipophilic and cross the blood brain barrier rapidly. Fentanyl's half-life is 233±137 minutes in infants and

Table 5. Physiological effects of opioids

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CNS	**Respiratory system**	**Cardiovascular system**	**Gastrointestinal system**	**Urinary system**
Analgesia, sedation	Antitussive	Bradycardia (fentanyl-morphine)	Motility-persistaltism ↓	Ureter, bladder, bladder detrusor muscle tone ↑
Nausea, vomiting	Minute ventilation ↓	Histamine release (morphine)	Sphincter tone ↑	
Myosis	Respiratory rate-tidal volume ↓	Little effect on cardiac output		
Seizure	Suppresses the response to CO_2 and O_2			
Dysphoria				
Euphoria				

CO_2: Carbon dioxide, O_2; Oxygen, CNS: Central nervous system, Clinics of Turkey; Non-invasive and Invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

244±79 minutes in older children. Fentanyl can be easily used as a continuous infusion in intensive care units. It can be administered as a bolus dose or continuous infusion as needed. Other fentanyl group drugs have recently started to be used in pediatric patients, and information on their efficacy and side effects is limited.[1-3,11]

Benzodiazepines

Benzodiazepines are the most commonly used agents to provide sedation in the PICU. Benzodiazepines provide sedation, anxiolysis and amnesia and do not have analgesic properties. They bind to the alpha-subunit of the inhibitory amino acid gamma-aminobutyric acid (GABA) receptor. This association leads to tight binding of the GABA molecule to the beta-subunit, chloride transmission through the neuronal membrane is accelerated and hyperpolarization occurs.

Midazolam

Midazolam is a water-soluble benzodiazepine with a rapid onset of action and a short half-life after bolus administration. It has good anxiolytic, amnestic and muscle relaxant properties. Midazolam is often used to provide mild sedation in children or combined with fentanyl or dexmedetomidine in patients targeting moderate sedation. Midazolam is metabolized by the hepatic P450 enzyme system to 1-OH midazolam, which has the same potency as the parent compound. Subsequently, 1-OH midazolam-glucronide is formed in the liver by the glucronyl transferase system, which dissolves in water and is excreted through the kidneys. Midazolam pharmacokinetics can be altered by many factors, including age and underlying disease. The metabolism of midazolam is dependent on the hepatic P450 system, and the half-life is shortened while clearance increases from infancy to adulthood. The presence of hepatic insufficiency increases the free fraction 2-3-fold, leading to the accumulation of active metabolites and prolonged duration of drug action. Renal dysfunction leads to the accumulation of 1-OH midazolam-glucronide, which increases the efficacy of midazolam. Midazolam has a high protein binding rate. Free levels of midazolam may vary significantly with various factors such as heparin affecting its protein binding. Awakening time is fast in short-term use (<12 hours) and slow in long-term use. Midazolam clearance is decreased by many commonly used drugs such as calcium channel blockers, erythromycin and triazole antifungals. Midazolam is water soluble and can be administered parenterally (intravenously or intramuscularly), rectally (PR), intranasally (IN), sublingually (SL) or orally (PO). Doses, onset and duration of action vary depending on the patient's age and route of administration. Midazolam has the fastest onset of action via the V route.

Midazolam may cause respiratory depression and apnea, especially when used in combination with opioid drugs such as fentanyl or morphine. When midazolam is used as a single agent, paradoxical reactions such as inconsolable crying, hyperactivity and aggressive behavior may occur in approximately 1% to 3% of patients. Both respiratory depression and paradoxical reactions can be reversed with flumazenil.[1-5,12-14] Flumazenil should not be used in patients with seizure disorders or who are taking chronic benzodiazepines because of the risk of triggering withdrawal symptoms.[1-3,11]

Lorazepam

Lorazepam is metabolized by glucuronyl transferase and is a water-soluble benzodiazepine with no active metabolites. It is well absorbed orally and intramuscularly. It shows sedation effect for 4-8 hours after a single dose. Its half-life is approximately 14 hours. Lorazepam pharmacokinetics are not altered by drugs known to affect the P450 system (e.g., anticonvulsants, rifampicin, and cimetidine). Its metabolism is not affected by age and critical illness.

Due to the toxic effects of propylene glycol, which is a diluent in the intravenous form of lorazepam, caution should be exercised in high doses or in the newborn population. In propylene glycol toxicity, symptoms and signs such as metabolic acidosis, renal failure, mental changes, hemolysis and an increased osmolar gap are observed. Propylene glycol is metabolized to lactic and pyruvic acid in the liver; it should be used with caution in the presence of lactic acidosis. Propylene glycol is also excreted unchanged in the urine and the risk of toxicity increases in the presence of renal insufficiency. Neonatal infants, especially preterm ones, cannot metabolize propylene glycol sufficiently due to hepatic and renal immaturity; continuous infusion of lorazepam is not recommended in this population.[12]

Etomidate

It is an intravenous anesthetic agent. Its half-life is 2.9-5.3 hours. It decreases cerebral metabolic O_2 requirement, blood flow and intracranial pressure. The induction dose in children is 0.2-0.3 mg/kg. Especially at doses of 0.2-0.4 mg/kg, cardiovascular effects are low. The infusion dose is 40-50 µg/kg/min. Respiratory suppression and apnea may develop dose-dependently and may be prominent when used in combination with other drugs. It may cause myoclonus. Its myoclonus side effect can be prevented by administering low doses of fentanyl-benzodiazepine and etomidate before treatment. With prolonged use, etomidate reduces endogenous corticosteroid production by blocking the enzyme 11 β hydroxylase. This enzyme is required for the production of cortisol, aldosterone and corticosterone. Even a single dose reduces corticosteroid production but is of no clinical significance. In addition, it suppresses neutrophil function. A continuous infusion of etomidate is known to

increase the development of infection and mortality. It may cause pain, anaphylaxis, nausea and vomiting. Etomiodate is the frequently preferred agent for rapid sequence intubation because it has no adverse effects on the cardiovascular system. It is also an ideal sedative agent for the patients with increased intracranial pressure. However, prolonged infusions and repeated doses are not recommended.[2,3]

Ketamine

Ketamine is a sedative, amnesic and analgesic drug. It increases mean arterial pressure, heart rate and cardiac output regardless of the route of administration and can be used in shock and in hemodynamically unstable patients. Ketamine is a potent bronchial smooth muscle relaxant, making it an ideal sedative-analgesic agent for asthmatic patients. Its effect on pulmonary vascular resistance is controversial. It may increase intracranial pressure due to its effect on CO_2 or directly on cerebral vascularity. For years, ketamine was not used in patients with increased intracranial pressure because it was thought to increase intracranial pressure further by vasodilatation. However, recent experimental studies have shown no change or even a decrease in intracranial pressure following ketamine injection in mechanically ventilated subjects. Ketamine may cause vertical or horizontal nystagmus and hallucinations. Administration of benzodiazepine before ketamine treatment prevents hallucinations. It increases salivary and bronchial mucus secretion; atropine can be used in cases where it causes an increase in secretions.

Ketamine has high lipid solubility; it rapidly crosses the blood-brain barrier with a single intravenous dose and causes loss of consciousness. It has a half-life of 2-3 hours and is metabolized in the liver by microsomal enzymes. There are few studies on its use in mechanically ventilated patients. The ketamine bolus dose is 0.5-1 mg/kg and infusion dose are 1-2 mg/kg/hour. Ketamine is not the first agent to be used in patients undergoing mechanical ventilation in PICUs. Ketamine should be used especially 1) when cardiovascular side effects due to opioid and benzodiazepine use have developed, 2) when spontaneous breathing needs to be maintained while applying non-invasive ventilation, 3) due to its bronchodilator properties in the presence of status asthmaticus 4) as a low dose in cases where increasing the opioid dose and developing tolerance is not desired and 5) in short painful interventions where spontaneous breathing is desired.[2,3,13]

Propofol

It is a general anesthetic agent. Its chemical structure is similar to etomidate and barbiturate but the mechanism of action is different. It has sedative and amnestic effects, but no analgesic effect. In recent years, it has been frequently used in intensive care units because its onset and termination are rapid, and it has no active metabolites. This agent causes cerebral vasoconstriction like barbiturates, and decreases cerebral metabolic oxygen demand and intracranial pressure. Propofol has been reported to decrease intracranial pressure and improve cerebral perfusion pressure in vasogenic edema, but not in cytotoxic edema. In human studies, it was found that it decreased intracranial pressure but mean arterial pressure and cerebral perfusion pressure decreased simultaneously. However, it has been shown that if mean arterial pressure is kept normal by using vasopressors, intracranial pressure decreases and cerebral perfusion pressure is maintained. Propofol is one of the agents used in rapid sequence intubation; it reduces airway reactivity. Propofol is used in the treatment of refractory status epilepticus.

It causes peripheral vasodilation, it is a negative inotrope and hypotension may develop during administration. This side effect is prominent in patients with rapid injections and suppressed cardiovascular function. Adverse hemodynamic effects may improve with calcium therapy. Propofol may increase vagal tone and cause bradycardia, conduction disturbances and asystole. The possibility of these side effects increases when used with other drugs (such as fentanyl, succinylcholine). Propofol may cause respiratory suppression-apnea and airway obstruction. It may cause neurologic side effects such as opisthotonos, myoclonic movements and seizure-like activity. Propofol is diluted with a lipid emulsion. Lipid emulsion content is 10% lipid compound used in parenteral nutrition fluids. The daily caloric intake of the patient should be calculated taking into account the lipid content of propofol. Lipid content may cause anaphylactic reactions, pain during administration, an increase in triglyceride levels in prolonged infusions and may create a favorable environment for the growth of bacteria. Pain during administration may be reduced if given with lidocaine or low dose ketamine. It may cause a trace element deficiency. Due to propofol infusion syndrome, it is not recommended for use in children aged 3 years and younger. Syndrome may develop in patients receiving a propofol infusion for more than 48 hours and at a dose of more than 4 mg/kg/hour. Propofol is thought to impair mitochondrial function. The findings of this syndrome include metabolic acidosis, bradycardia, dysrhythmia, rhabdomyolysis and fatal heart failure. Blood gas, creatine phosphokinase and lactate levels should be checked in patients receiving propofol. If the syndrome develops, propofol infusion should be terminated and supportive therapies should be administered. If long-term use of propofol is required, a cost-benefit analysis should be performed carefully.[2,3]

Barbiturates

Barbiturates are classified according to their chemical structure or duration of action. Hepatic metabolism of short-acting

agents is slow, but their redistribution-induced effects end rapidly. The clinical duration of action of short-acting agents such as methohexital, thiopental and thiamylal is between 5 and 10 minutes. Long-acting agents such as phenobarbital and pentobarbital have half-lives of 6-12 hours. Short-acting barbiturates are used in situations where rapid onset and termination of action are targeted, such as induction of anesthesia and endotracheal intubation.

The cardio-respiratory effects of barbiturates are similar to those of propofol. In healthy subjects, sedative doses minimally affect cardiovascular function, respiration and airway protective reflexes, while higher doses may cause respiratory depression, apnea and hypotension, especially in patients with myocardial dysfunction. Hypotension is caused by peripheral vasodilation and direct negative inotropic effects. Pentobarbital is an alkaline solution; it is incompatible with other medications and parenteral nutrition fluids and should be administered through a separate infusion line. The high pH of the barbiturate solution may cause localized erythema with subcutaneous infiltration and thrombophlebitis. It is not recommended to use barbiturate as the first agent for sedated patients to be monitored in the PICU. However, they may be preferred in cases where the agents used are not effective or undesirable side effects occur. In the retrospective evaluation of 50 infants and children aged between 1 month and 14 years who were on mechanical ventilation and who could not achieve the desired level of sedation despite the combination of benzodiazepines (midazolam dose 0.4 mg/kg/h) and opioids (fentanyl dose 10 micrograms/kg/h, morphine dose 100 micrograms/kg/h), it was shown that effective sedation was achieved with pentobarbital treatment, and the dose of other agents was reduced. Barbiturates do not have analgesic properties and should be used together with opioids in patients requiring pain treatment.[2,3]

Alpha-2 Adrenergic Agonists

Alpha-2 adrenergic agonists achieve their sedative effects by stimulating central parasympathetic signals and inhibiting central sympathetic signals. Noradrenergic impulses originating from the locus coeruleus decrease, a number of inhibitory neurons involving the GABA system are stimulated, and sedative and anxiolytic effects begin. This effect is similar to the changes seen during the non-REM period of sleep. The mechanism of action of alpha-2 adrenergic drugs is different from that of other agents used for sedation in the PICU. When other agents are used for prolonged periods, non-REM sleep periods are reduced and the likelihood of delirium increases significantly. Alpha-2 adrenergic agonists exert analgesic effects by regulating the release of substance P and enhancing the effects of opioids. The affinity of dexmedetomidine for alpha-2 adrenergic receptors is 8 times higher than that of clonidine, the alpha 1/alpha 2 agonism ratio is 1:1600, and the half-life is two hours, allowing dose adjustment in intravenous infusion. Dexmedetomidine is approved by the FDA for short-term (less than 24 hours) sedation in mechanically ventilated adults. Dexmedetomidine has been used for sedation in adult patients requiring mechanical ventilation after cardiac surgery and general surgery caused an 80% reduction in midazolam dose and a 50% reduction in morphine dose compared to placebo. Currently, there is no prospective study using dexmedetomidine in pediatric patients undergoing mechanical ventilation. In this study, dexmedetomidine, when administered at a dose of 0.25 microgram/kg/h, provided a similar level of sedation to midazolam administered at an infusion rate of 0.22 mg/kg/h, and was more effective than midazolam when administered at a higher dose (0.5 microgram/kg/h). Dexmedetomidine is less effective in children younger than 6-12 months. Five of the six patients who could not achieve the desired level of sedation during dexmedetomidine use were younger than 12 months. In the same study, it was reported that bradycardia developed in one patient who was using digoxin as a side effect. Dexmedetomidine may have a negative effect on respiratory and cardiovascular function. Clonidine has a low probability of respiratory depression side effects. There are different results on the effects of dexmedetomidine on ventilatory function. There are studies reporting mild respiratory depression, decreased minute ventilation, suppression of CO_2 response and no adverse effect. In PICUs, clonidine can be administered orally to prevent the development of withdrawal symptoms during discontinuation of other sedative drugs.[2,3,14]

Withdrawal Syndrome

Hospitalization periods in PICUs can be long. Sedation-analgesia applications in patients requiring long hospitalization may lead to long-term effects. It was first described in 1980-1990 that withdrawal or withdrawal syndrome developed after the discontinuation of most sedation-analgesia drugs.[15]

Tolerance, withdrawal and physical dependence develop after prolonged sedation-analgesia. Withdrawal syndrome symptoms are drug-independent and similar. The time of onset of withdrawal symptoms varies depending on the half-life and active metabolites of the sedative and/or analgesic drug administered. Some of the withdrawal symptoms and signs include CNS irritability, GI dysfunction and autonomic dysfunction (Table 6). Convulsions have also been described. Withdrawal syndrome remains a serious problem in long-term hospitalizations despite the development of new sedation techniques.[1,15]

Guidelines should be used to recognize withdrawal syndrome early in patients taking sedation-analgesic drugs for a long-time.[1,15,16] The presence of withdrawal symptoms should be evaluated at twenty-four hour intervals (Table 7) and an appropriate treatment strategy should be determined (Table 8).

Table 6. Typical signs of withdrawal syndrome

CNS irritability	GIS dysfunction	Autonomic dysfunction
Poor sleep pattern	Diarrhea	Tachypnea
Tremor	Vomiting	Piloerection
Convulsion	Abdominal pain	Fever
Fever	Inadequate nutrition	Tachycardia
Myoclonic pulse		Hypotension
		Tachypnea
		Sneezing

GIS: Gastrointestinal, CNS: Central nervous system

Table 7. Sedation withdrawal score

Tremor	Sneezing
Irritability	Respiratory distress
Hypertonicity	Fever
Hyperactivity	Diarrhea
Vomiting	Sweating
Loud crying	Convulsion

For each parameter none=0, mild=1, severe=2. Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

The protocols used in our unit are summarized in Table 9, Figures 1 and 2.

Improper use of sedation-analgesic drugs leads to prolonged mechanical ventilation and intensive care unit stays and increased mortality and morbidity. The quality of sedation-analgesia is improved, and side effects are reduced with the administration of appropriate drugs based on the correct protocols and careful monitoring. Different sedative-analgesic drugs have advantages and disadvantages. The ideal sedative analgesic drug should have a rapid onset of action, a short half-life, low metabolism and elimination, limited hemodynamic or respiratory side effects, a specific antidote and should not interact with other drugs. Pharmacodynamics, route of administration, secondary effects, patient's age, other diseases, need for mechanical ventilation, nutritional status, renal and hepatic function and cost should be taken into consideration when choosing the right agent.

In recent years, it has been reported that daily awakenings can be performed in children receiving sedation and analgesia as well as in adults. However, there are still no clear data on this issue.

There is no single ideal agent for sedation analgesia. In most cases, treatment is started with a combination of benzodiazepines and opioids. The most preferred drugs are midazolam and fentanyl. Hemodynamic balance is maintained during fentanyl treatment, and the risk of developing tolerance is low in morphine treatment. Opioid infusion may be useful in the modulation of pulmonary vascular resistance. Especially in patients with pulmonary hypertension, opioid infusion may prevent the development of crisis. Ketamine, pentobarbital and dexmedetomidine may be used if first-line drugs are inadequate. Ketamine may be useful in patients with hemodynamic instability or airway reactivity. There are very limited reports on the use of pentobarbital for sedation. Propofol is a commonly used agent in adult intensive care units. Propofol is not preferred in PICUs because of the risk of propofol infusion syndrome. Doses of sedative and analgesic drugs are given in Tables 10 and 11.

Table 8. Strategy to be implemented

Score (6 hours)	Strategy
<6	Continue with the current application
6-12	Do not reduce current practice
12-18	Turn back to previous status
>18	Get suggestion

Table 9. Scoring of withdrawal syndrome

Criteria	Score
Crying/agitation	
25%> of the 4-hour period	2
26-75% of the 4-hour period	3
75%< of the 4-hour period	5
Sleeping	
25%> of the 4-hour period	1
26-75% of the 4-hour period	2
75%< of the 4-hour period	3
Hyperactivated moro (for newborns)	2
Apparent hyperactivity (for newborn)	3
Tremor	
Mild	1
Moderate	3
Severe	5
Tonic-clonic seizure	5
Hallucinations (in verbal children)	1
Extubated or IMV-ventilated patient	
Respiratory rate 60< for <2 years	2
Respiratory rate 60< for >2 years	2
Vomiting	2
Diarrhea	2
Other symptoms	1
Total score	32

IMV: Intermittent mandatory ventilation. Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

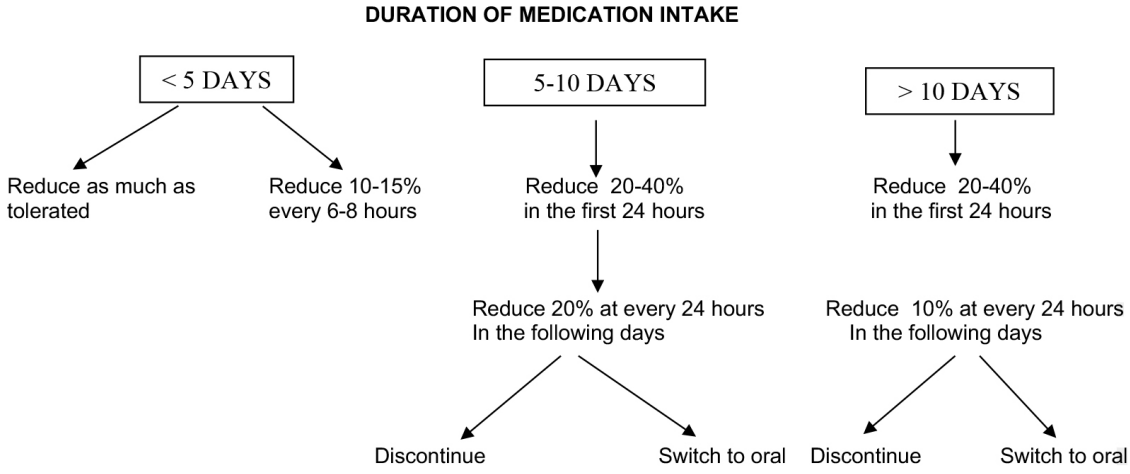
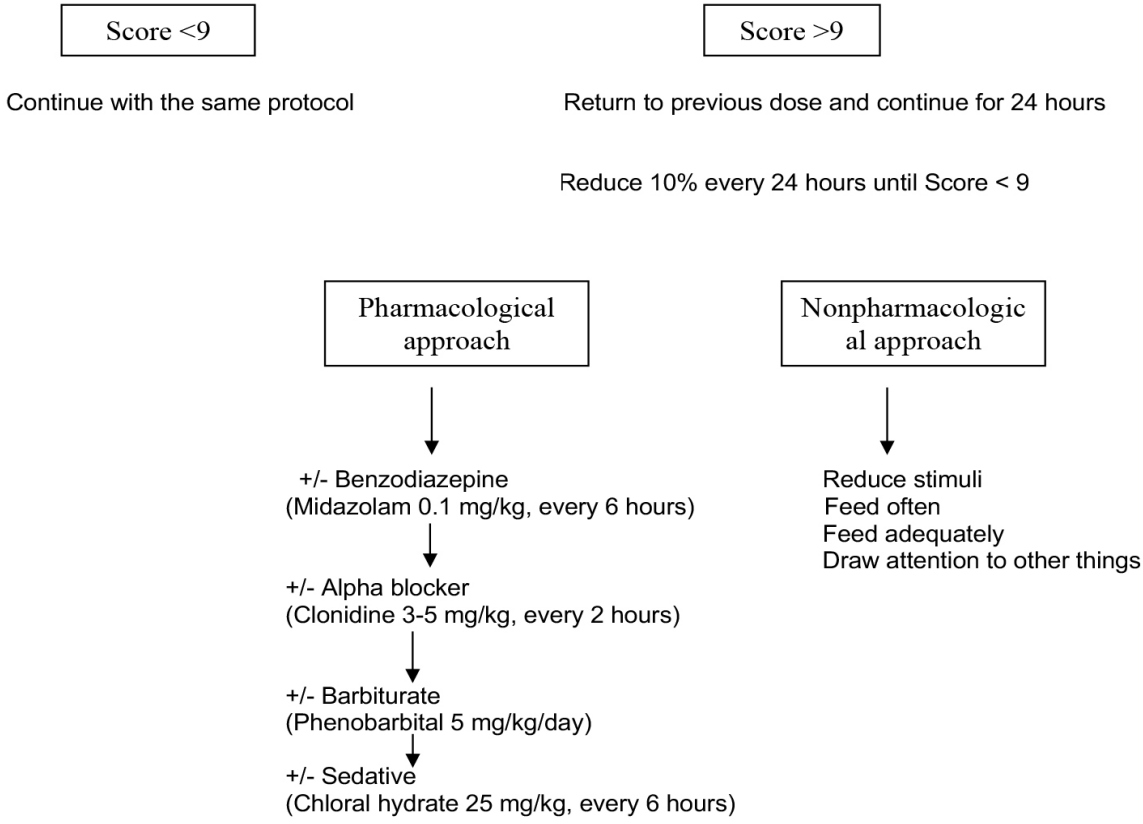


Figure 1. Strategies to prevent withdrawal syndrome during the discontinuation period of sedation and analgesic drugs
Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60



Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60.

Figure 2. Withdrawal syndrome treatment protocol

As a result, the ideal level of sedation is when the patient is conscious, breathing in compliance with the ventilator and tolerant to therapeutic interventions. The ideal level of sedation in each patient varies according to the underlying disease and its severity. The ideal level of sedation is achieved by titrating the doses of sedative drugs using observational sedation scales. The steps to be followed in the clinic to ensure the ideal individual sedation level and to recognize and treat withdrawal symptoms early are summarized in Table 12.

Recommendations for Sedation:

1- We recommend that sedation assessments of critically ill children in the pediatric intensive care unit be performed every 4-8 hours (STRONG RECOMMENDATION)

2- We recommend the use of comfort B or state behavioral scale (SBS) scales in the sedation assessment of intubated patients in the pediatric intensive care unit (STRONG RECOMMENDATION)

Table 10. Characteristics of sedative agents used in PICUs

Drug	Dose (mg/kg)	Beginning	Indication	Suggestion
Midazolom	Or, Rec: 0.5-0.75 IN, SL: 0.2-0.5 IV: 0.2 Inf: 0.05-0.6 mg/kg/h	2-3 min	Short intervention Prolonged mechanical ventilation	Tolerance Abstinence Liver and kidney failure, reduce dose Risk of hypotension with bolus dose
Lorezepam	IV loading: 0.02-0.06 Inf: 0.02-0.1 mg/kg/h	5-20 min	Prolonged mechanical ventilation Withdrawal syndrome	Limited
Propofol	IV loading: 2-3 Inf: 1-4 mg/kg/h	1-2 min	Short mechanical ventilation Short intervention	Propofol infusion syndrome Hypertriglycemia
Ketamine	IM: 3-5 IV loading: 1-3 Inf: 0.7-3 mg/kg/h	0.5-1	Short intervention During intubation in an acute asthma attack	Endogenous catecholamine release
Etomidate	IV 0.2-0.3	Immediately	Intubation in hemodynamic instability	Surrenal insufficiency
Thiopental	IV loading: 3-5 Inf: 1-5 mg/kg/h	Immediately	Intubation at ICP ↑	(-) Inotrope vasodilation
Dexmedetomidine	IV loading 1 µg/kg Inf: 0.2-1.0 µg/kg/h	2-5	Short intervention At withdrawal syndrome	
Chloralhydrate	OR, PR: 25-75 mg/kg	5-20	Short intervention	Agitation
Clonidine	OR, IV 1-4 µg/kg Inf: 0.1-02 µg/kg/h	5-20	Prolonged mechanical ventilation Withdrawal syndrome	At sudden withdrawal
Chlorpromazine	OR, PR: 0.5-1.5 mg/kg IV: 0.5 mg/kg	-	Agitation Delirium	Extrapyramidal reaction

ICP: Intracranial pressure, Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

Table 11. Characteristics of analgesic drugs used in PICUs

Drug	Dose (mg/kg)	Beginning	Indication	Suggestion
Morphine	IV: 0.1-0.2 mg/kg Inf: 10-40 µg/kg/h	20	Mechanical ventilation Acute and chronic pain Pulmonary edema	Liver and kidney failure, reduce dose Histamine release Nausea and vomiting
Fentanyl	IV: 1-3 µg/kg Inf: 1-10 µg/kg/h	1-2	Short procedures Similar to morphine	Prolonged clearance Good hemodynamics Thoracic rigidity after rapid bolus
Remifentanil	IV: 1 µg/kg Inf: analgesic 0.5-6 µg/kg/s Sedation: 6-12 µg/kg/h	1	Mechanical ventilation Postoperative	Fast clearance Good hemodynamics Thoracic rigidity
Alfentanyl	IV: 15-25 µg/kg Inf: 0.4-2 µg /kg/h	1-2	Short procedure	High price Do not use in liver failure
Methadone	IV: 0.1-0.2 mg/kg/4-6 h	45	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 hemodynamics Less respiratory depression
Paracetamol	IV 10-15 mg/kg/6 h	30	Moderate pain Hyperthermia	Hepatotoxicity

Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

3- We recommend that a written sedation protocol should be available for patients monitored on mechanical ventilators in the intensive care unit (STRONG RECOMMENDATION)

4- We recommend the use of dexmedetomidine and/or ketamine (STRONG RECOMMENDATION) in the first order and midazolam (WEAK RECOMMENDATION) in the second order as the first choice sedative agent in patients we monitor using non-invasive mechanical ventilation.

5- We recommend the use of midazolam or dexmethothimidine as the first choice sedative agent in intubated patients on mechanical ventilator (WEAK RECOMMENDATION)

6- We recommend adding a new agent in patients who are monitored on mechanical ventilator and who are not sufficiently sedated despite reaching the adequate dose for the agent we use (WEAK RECOMMENDATION). We recommend the use of ketamine as an adjuvant drug (STRONG RECOMMENDATION).

7- In patients intubated on mechanical ventilator, if only a sedative drug is used, we recommend adding a drug with analgesic effect to the treatment (STRONG RECOMMENDATION)

8- If you think that your team has sufficient experience and expertise, we recommend routine awakening on a daily basis in patients who are sedated in the intensive care unit (WEAK RECOMMENDATION)

9- We suggest that ketamine can be used in patients with increased intracranial pressure (WEAK RECOMMENDATION)

Recommendations for Pain/Analgesia

10- We recommend routine pain assessment in patients monitored in the intensive care unit (STRONG RECOMMENDATION)

11- We recommend that pain assessments be performed every 4-8 hours in patients monitored in the intensive care unit (STRONG RECOMMENDATION)

12- We recommend the use of the Wong-Baker face scale and visual analog scale (VAS) for pain assessment in patients aged 6 years and older who can communicate (STRONG RECOMMENDATION)

13- We recommend the use of FLACC and COMFORT- B facial scales for pain assessment in patients younger than 6 years of age or in patients who cannot communicate (STRONG RECOMMENDATION)

14- We recommend that a written protocol regarding analgesic applications in the intensive care unit be established/available (STRONG RECOMMENDATION)

15- We recommend the use of iv opioids as the primary analgesic in the treatment of moderate to severe pain in pediatric critically ill patients (STRONG RECOMMENDATION), and we recommend the use of fentanyl as the opioid agent of first choice (STRONG RECOMMENDATION).

16- We recommend that ketamine should be administered first as a sedoanalgesic agent in short-term interventions (catheter insertion, lumbar puncture, thoracic tube application, etc.) in pediatric patients who are extubated in the intensive care unit (STRONG RECOMMENDATION)

Table 12. Approach steps for ideal sedation in clinical practice

First step: Evaluate
Use a sedation scale with proven efficacy and train your nurses in its use
Determine the level of sedation every eight hours in a critically ill child
Define the targeted level of sedation in the patient according to individual needs, avoid excessive or inadequate sedation
Second step: Non-pharmacological treatment
Minimize stress by ensuring nurse care and parental presence
Third step: Pharmacological treatment
Titrate doses of sedative medications to provide the ideal level of sedation for the patient according to individual needs
Start with one drug
If under stress, add the second drug
If the goal of sedation level is not achieved, add one more drug. If there is no hemodynamic instability in the patient, increase the infusion rate of the drugs and make a bolus dose to reach the stable blood level quickly
Consider pentobarbital if adequate sedation is not achieved despite all medications. Stop other sedative drugs when pentobarbital is started
Fourth step: Discontinuation and delirium
Reduce doses of sedative drugs according to targeted sedation score
Assess withdrawal and delirium scores at regular intervals
If the patient has been sedated for more than five days, slowly reduce doses or add a long-acting oral medication
If delirium is diagnosed, consult with psychiatry
If antipsychotic treatment is needed, start with a low dose, increase slowly and monitor side effects

17- We recommend the use of dexmedetomidine and ketamine as sedative and sedoanalgesic if needed in patients with respiratory failure in the intensive care unit who are followed up with respiratory failure and YANKOT (STRONG RECOMMENDATION)

18- We recommend the use of Paracetamol or NSAIDs for mild-to-moderate pain in pediatric surgical patients followed postoperatively in the intensive care unit (STRONG RECOMMENDATION)

19- We recommend the use of Paracetamol or NSAIDs for mild to moderate pain in trauma patients monitored in the intensive care unit (STRONG RECOMMENDATION)

20- We recommend the use of Dexmedetomidine as the first line sedation and sedoanalgesic in postoperative cardiac surgery patients monitored in the intensive care unit (STRONG RECOMMENDATION)

21- In critically ill children being monitored in the intensive care unit, if sedative and analgesic drugs are used in the form of continuous infusion for more than 3-5 days and at high doses, we recommend that these drugs should be discontinued carefully and gradually decreased during the termination of treatment (STRONG RECOMMENDATION)

Recommendations for Withdrawal

22- We recommend that withdrawal assessment should be routinely performed in critically ill pediatric patients followed in the intensive care unit (STRONG RECOMMENDATION)

23- We recommend withdrawal assessment every 12-24 hours (STRONG RECOMMENDATION)

24- We recommend the use of the withdrawal assessment tool-1 (WAT-1) scale for withdrawal assessment in critically ill pediatric patients followed up in the intensive care unit (STRONG RECOMMENDATION)

25- We recommend the establishment of a written protocol to prevent the development or mitigate the effects of withdrawal (STRONG RECOMMENDATION)

26- We recommend opioid replacement therapy to alleviate opioid-related withdrawal symptoms, regardless of previous dose and/or duration or opioid exposure (WEAK RECOMMENDATION)

27- We recommend that non-pharmacologic methods (breastfeeding, swaddling, music, watching TV in appropriate patients, etc.) should be applied first to patients observed in the intensive care unit with withdrawal symptoms (STRONG RECOMMENDATION)

28- We recommend benzodiazepine replacement therapy to alleviate symptoms regardless of the benzodiazepine-related pre-withdrawal dose and/or duration of benzodiazepine exposure (WEAK RECOMMENDATION)

DELIRIUM

Delirium is a neuropsychiatric syndrome that can be triggered by various medical, surgical, pharmacologic and traumatic causes. While it can be seen at any age, it develops especially in critically ill patients. The pathogenesis has not yet been elucidated, but a decrease in acetylcholinergic activity is blamed. Patients should be evaluated carefully because iatrogenic withdrawal syndrome, excessive sedation and pain may be confused with the findings.[1,17,18]

While the frequency of delirium has been reported to be high in adult studies, the frequency of studies evaluating the frequency, management and long-term outcomes of delirium in children is increasing day by day. While delirium develops at a rate of 10-30% in pediatric intensive care units, this rate reaches 50% in patients receiving invasive mechanical ventilation support. There are various risk factors that may contribute to the development of delirium. Factors such as disease severity, age <5 years, mechanical ventilation, vasopressors, benzodiazepines, antiepileptic and narcotic agents, and physical restraint increase the risk of delirium.[18-20]

Various scoring systems have been produced to be used in screening for childhood delirium. Among these, the Cornell Assessment of Pediatric Delirium (CAP-D) scoring, which is most commonly used, has been presented as a Grade A recommendation by the European Society for Pediatric and Neonatal Intensive Care (ESPNIC). Patients with ≥9 points in CAP-D scoring are considered to have delirium (Table 13).[1,20]

There are three types of delirium: hypoactive, hyperactive and mixed. Hypoactive delirium is the most difficult type to diagnose; it needs to be differentiated from mood disorders, nonconvulsive status epilepticus and catatonia. The patient has slowed or infrequent speech, slow motor activity, lethargy, decreased awareness and apathy. In hyperactive delirium, hyperactivity, talkativeness, psychomotor agitation, irritability, paranoid delusions, and visual and auditory hallucinations may be observed. In mixed type delirium, findings of hypoactive and hyperactive delirium develop in the same patient.[21]

Delirium is controlled with the treatment of the underlying disease, psychosocial interventions and pharmacologic agents. The aim of treatment is to reduce agitation, treat psychosis, prevent harm, and increase comfort. Psychosocial practices constitute the most important step in the prevention and treatment of delirium. Reducing intensive care lighting at night to ensure the sleep cycle, waking children at the same time in the morning, placing the beds in a sitting position, preventing unnecessary alarm sounds of medical devices, providing television and tablets are environmental arrangements that can be applied. Allowing family members to stay with the patient, ensuring active participation of family members in the treatment process, bringing the child's favorite toys and

Table 13. Cornell assessment of pediatric delirium scoring

	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
Does the child make eye contact with the caregiver?						
Are the child's actions purposeful?						
Is the child aware of his/her surroundings?						
Does the child communicate needs and wants?						
	Never 0	**Rarely 1**	**Sometimes 2**	**Often 3**	**Always 4**	
Is the child restless?						
Is the child inconsolable?						
Is the child underactive-very little movement while awake?						
Does it take the child a long-time to response to interactions?						
					Total	

photographs of family members, ensuring that they use glasses and hearing aids, and calling patients by their names are psychosocial interventions that can be implemented.[18-21]

Pharmacologic treatment should be applied in case of delirium that cannot be controlled with psychosocial interventions. Haloperidol (0.05-0.25 mg/dose for loading, 0.05-0.5 mg/kg/day 3-4 doses for maintenance) in hyperactive delirium and risperidone (0.1-0.2 mg/dose once daily for <5 years, 0.5-2.5 mg/day 2-4 doses for ≥5 years) in hypoactive delirium are recommended agents. However, patients on antipsychotic treatment should be carefully monitored for acute dystonia, swallowing problems, dysarthria, akathisia, neuroleptic malignant syndrome and QT prolongation. Cardiac side effects of antipsychotic treatment should be considered in patients with existing cardiac disease, and the necessity of treatment should be questioned. In patients who develop side effects, biperiden (50 mcg/kg, IV over 15 minutes) should be administered.[20-22]

The development of delirium increases the length of hospitalization, costs, morbidity and mortality. It has been shown to affect social life even after hospital discharge. Neurocognitive impairment may develop in the long term, and one third of patients develop post-traumatic stress disorder. Patients should be evaluated every 8-12 hours for delirium from the 24-48th hour of pediatric intensive care unit admission. Early recognition and treatment of delirium will increase the patient's compliance with treatment and decrease the duration of intensive care unit stay, morbidity and mortality.[20-23]

Recommendations for Delirium

29- We recommend that delirium evaluation should be performed routinely in critically ill pediatric patients followed up in the intensive care unit (STRONG RECOMMENDATION)

30- We recommend delirium assessment every 12-24 hours (STRONG RECOMMENDATION)

31- We recommend the use of the Preschool and Pediatric Confusion Assessment Methods (ps/pCAM- ICU) or Cornell Assessment for Pediatric Delirium (CAPD) scales as the most valid and reliable delirium monitoring tool for delirium assessment in critically ill pediatric patients followed up in the intensive care unit (STRONG RECOMMENDATION)

32- Given the potential patient benefit to reducing the incidence, duration and/or severity of delirium, we recommend non-pharmacological peripheral implementation strategies; such as optimization of sleep quality, and direct family involvement in patient care (STRONG RECOMMENDATION)

33- We recommend early mobilization if possible to reduce the development of delirium in critically ill pediatric patients followed in the intensive care unit (STRONG RECOMMENDATION)

34- We recommend minimizing the use of benzodiazepine-based sedation whenever possible in critically ill pediatric patients to reduce the incidence, duration and/or severity of delirium (STRONG RECOMMENDATION)

35- Considering possible drug side effects in critically ill pediatric patients with refractory delirium, we recommend that haloperidol or antipsychotics be considered for the treatment of severe delirium symptoms (WEAK RECOMMENDATION)

Environmental Optimization

The environment in the PICU can negatively affect patients during critical illness management and recovery. Although the technological environment of the PICU provides benefits in terms of biological balance, it also has negative physical and psychological effects. Critically ill infants and children are at high risk of developing stress-related behavioral disorders, and the PICU environment contributes significantly to these changes.

Although data on the effects of environmental optimization is limited, the risks of implementing such changes are generally low, with potentially beneficial effects for patients and their families. Providing family-centered care and sleep hygiene can contribute significantly to environmental optimization.[24]

Presence of the Family

Promoting an environment of parent and caregiver interaction with patient care is likely to directly benefit patients and may reduce parents' levels of stress and anxiety. Studies specific to pediatric intensive care show that when parents/caregivers are involved in family-centered care, their anxiety and stress levels are reduced, they are more satisfied with the care their child receives, and when they are allowed to be present for procedures or resuscitations, it helps the parent or caregiver to cope with the situation while maintaining both quality care and patient safety.[25,26]

The presence of parents or caregivers in the PICU during routine care and interventional procedures is recommended for providing comfort to the child, decreasing the stress and anxiety levels of parents and increasing the level of satisfaction with care.[1] However, we think that this is difficult to achieve under the current conditions in our country.

Sleep Hygiene

The environment directly affects the quality and quantity of a patient's sleep. Sleep deprivation is a major stressor reported by survivors of critical illnesses. In addition to patient-related factors such as the presence of invasive devices and procedures, the need for mechanical ventilation, immobility, drug effects and poorly controlled pain, environmental factors such as ambient noise and light levels can also negatively affect sleep.[1,27]

PICU teams are recommended to make environmental and/or behavioral changes to reduce excessive noise and thus improve sleep hygiene and comfort in critically ill pediatric patients.[4] To reduce the effect of ambient noise that cannot be changed, patients are recommended to use noise-reducing devices such as earplugs or headphones. Adjusting the lights in patient rooms in accordance with daylight and using a sleep mask may also contribute to sleep patterns.[1]

Early Mobilization

Early mobilization defines rehabilitation exercises of varying degrees as any passive or active activity that is initiated within the first 72 hours of the patient's admission to the pediatric intensive care unit, is clinically safe and appropriate to the patient's development, and aims to maintain or restore musculoskeletal strength and function. The feasibility of implementing early mobilization has been demonstrated in various ways in pediatric medical, neurological and postoperative patients, including cardiac ones.[28]

Mobilization of critically ill children is associated with potential risks and complications associated with central catheters, endotracheal tubes and other life-saving devices. Safety concerns often drive staff perceptions. Conditions such as hemodynamic instability, accidental tube dislodgement, and falls create anxiety in staff. It is important to educate all healthcare personnel who have a role in patient care about the harms of immobilization.[28-30]

Early mobilization is a complex and multi-step process that facilitates PICU culture. A multicomponent and interdisciplinary approach to early mobilization can be applied to minimize the effects of immobility in critically ill pediatric patients. Early mobilization planning that prioritizes patient safety, sedation minimization, delirium recognition and family participation should be encouraged.[28]

Recommendations for Optimization of the Environment

36. In the care of critically ill pediatric patients in the intensive care unit, we recommend the presence of a parent-caregiver during routine care in appropriate patients (STRONG RECOMMENDATION)

37. We recommend early mobilization to minimize the effects of immobility in critically ill children (STRONG RECOMMENDATION)

38. We recommend environmental and/or behavioral modifications to reduce excessive noise and thus improve sleep hygiene and comfort in the care of critically ill children in the intensive care unit (STRONG RECOMMENDATION)

39. To reduce the impact of ambient noise that cannot be modified, we recommend that patients wear noise-reducing devices such as earplugs or headphones (WEAK RECOMMENDATION)

40. Since the doses, duration of use and costs of sedative and analgesic agents used by providing an appropriate environment in the follow-up of critically ill children followed up in the intensive care unit will be significantly reduced, we recommend that the necessary importance should be given to environmental optimization (STRONG RECOMMENDATION)

Muscle Relaxants

Neuromuscular blockers are drugs that cause paralysis in skeletal muscles by blocking impulse transmission at the neuromuscular junction and do not have sedative, amnestic or analgesic properties. In intensive care, these agents are used for purposes other than intubation preparation, such as decreasing patient-ventilator incompatibility and intra-abdominal pressure in patients receiving mechanical ventilator support, and facilitating gas exchange by increasing chest wall compliance, decreasing the risk of barotrauma in the lungs, decreasing the contribution of muscles to oxygen

Table 14. Indications for the use of muscle relaxants during mechanical ventilation

To prevent patient ventilator incompatibility
To prevent hyper- or hypoventilation
In patients on non-conventional mechanical ventilation,
To reduce respiratory work and metabolic demand
In agitated patients who do not respond to maximum sedation and analgesia
During therapeutic hypothermia
To facilitate the treatment of increased intracranial pressure
Status epilepticus>facilitating treatment*

*: If continuous (24 hours) EEG monitoring is available, EEG: Electroencephalogram

consumption by preventing tremor, and limiting retching and consequently intracranial pressure. Muscle relaxants can be used as continuous infusions or intermittent doses. Since these agents do not have sedative and analgesic properties, sedative and analgesic agents should be used concomitantly. Hypo-hyperventilation is prevented with the administration of muscle relaxants; oxygen consumption decreases and gas exchange improves.[31,32] Indications for muscle relaxants during mechanical ventilation are given in Table 14.

Muscle relaxants are divided into two groups: Depolarizing and non-depolarizing. Succinylcholine is the only depolarizing agent available. This drug, which may have serious side effects, is contraindicated in some cases, and its use in pediatric intensive care is extremely rare because of the potential hazards (Table 15). Non-depolarizing muscle relaxants are used during mechanical ventilation in intensive care units. Non-depolarizing drugs are competitive antagonists of acetylcholine receptors. When they compete with acetylcholine and bind to the 2 alpha subunit of the acetylcholine receptor, they do not cause structural changes in the receptor and the ion channel in the middle is not opened.[31-33]

Therefore, acetylcholine cannot trigger contractions. The most commonly used of these are medium- and long-acting non-depolarizing muscle relaxants. In this group, d-tubocurarine, doxacurium and pancuronium are long-acting, while atracurium, cisatracurium, vecuronium and rocuronium are intermediate-acting. Tables 16 and 17 show the properties and potential side effects of non-depolarizing drugs.

Long-acting non-depolarizing drugs may cause hypotension and tachycardia-bradycardia. Doxacurium does not cause histamine release and has no harmful effects on the cardiovascular system. Pancuronium causes tachycardia, hypotension and increased cardiac output.

Medium-acting drugs are the most commonly used group of drugs during mechanical ventilation. Their effects start in 1-3 minutes and last for 30-60 minutes. Atracurium can cause histamine release and hypotension. When it causes histamine release, the patient develops itching and increased bronchial secretion and wheezing. Vecuronium is the most commonly used drug during mechanical ventilation in intensive care units. Unlike pancuronium, vecuronium does not cause

Table 15. Conditions in which succinylcholine is contraindicated

Burns 3 days to 6 months
Massive trauma: 3 days to 1 year
Stroke/paraplegia: 3 days to 1 year
Myotonia
Duchene muscular dystrophy
Friedreich's ataxia
Amyotropic lateral sclerosis
Multiple sclerosis
Guillain-Barré syndrome
Spinal cord trauma
Penetrating injuries of the ocular globe
History of malignant hyperthermia
Increased intracranial pressure
Chronic renal failure
Hyperkalemia
Prolonged effect expected due to pseudocholinesterase deficiency, hypomagnesemia, malnutrition and hepatic failure

histamine and catecholamine release. Cisatracurium is a steroisomer of atracurium and is 3-4 times more potent than atracurium in humans. Unlike atracurium, it does not cause histamine release.

If very high doses are not used, it does not change heart rate and blood pressure. Rocuronium has been increasingly used in intensive care units in recent years. Even very high doses do not cause histamine release and side effects in the cardiovascular system. Therefore, it can be used in very high doses.

There are a number of drugs that decrease and increase the effects of muscle relaxants. The interaction between muscle relaxants and other drugs should be well known in mechanically ventilated patients because they may increase the existing complications of muscle relaxants. Corticosteroids are the most frequently interacting agents with muscle relaxants, followed by other drugs. Drugs that antagonize or potentiate the effect of muscle relaxants are given in Table 18.

One of the biggest problems caused by muscle relaxants is muscle weakness. This problem is more common in patients with renal failure and in the female gender. Muscle weakness

Table 16. Dosage and duration of action of non-depolarizing muscle relaxants

Drug	Initial dose (µg/kg)		Infusion dose (µg/kg)		Start time of the effect (min)		Duration of clinical effect (min)		Time to return of clinical effects (min)	
	Infant	Older	Infant	Older	Infant	Older	Infant	Older	Infant	Older
Doxacurium	-	50	-	0.1-0.2	-	3-6	-	44	-	107
Pancuronium	100	150	0.4-0.6	0.5-0.1	2-5	2-4	-	24	-	33
Atracuronium	300	500	10-20	10-20	1-3	1-3	22	25	33	40
Vecuronium	100	150	1-1.5	1.5-2.5	-	1-3	-	22	73	35
Rokuronium	500	800	-	-	-	0.8-1.5	-	27	-	42

Table 17. Potential side effects of drugs used in mechanical ventilation

Drugs	Histamine release	Cholinergic properties	Ganglion blockade	Active metabolite	Prolonged blockage
Doxacurium	-	-	-	No	?
Pancuronium	-	Moderate	-	Yes	Yes
Atracuronium	Mild	-	Mild	No	Rarely
Vecuronium	-	-	-	Yes	Yes
Rokuronium	-	-	-	?	?
Cisatracurium	-	-	-	No	?

Table 18. Interaction of muscle relaxants with other drugs

Drugs/conditions that antogonize the effect	Drugs/conditions that potentiate the effect
• Hyperkalemia	• Inhalation anesthetics
• Alkalosis	· Antibiotics
• Phenytoin	· Vancomycin
• Carbamazepine	· Aminoglycosides
• Motor neuron lesions	• Others (clindamycin-tetracycline)
• Burn	• Antiarrhythmics
• Cerebral palsy	· Procainamide
• Sympathomimetic drugs	· Quinidine
• Theophylline	• β Adrenergic blockers
	• Calcium channel blockers
	• Hypermagnesemia
	• Local anesthetics
	• Myastenia gravis
	• Lithium carbonate
	• Diuretics
	· Furosemide
	· Thiazide
	• Cyclosporine

Table 19. Complications of muscle paralysis during mechanical ventilation

Complications caused by immobilization
Deep venous thrombosis and pulmonary embolism
Peripheral nerve injuries
Decubitus ulcer
Complications of cough reflex disappearance Secretion accumulation and atelectasis
Prolonged paralysis after muscle relaxant withdrawal
Resistant neuromuscular blockade
Steroid-related myopathy
Motor neuropathy **Neuromuscular dysfunction** **Central nervous system effects**

can easily develop in patients who use vecuronium for more than two days. This is caused by the active metabolite 3-deacetyl vecuronium. Besides myopathy, muscle relaxants can also cause motor neuropathy. Especially vecuronium and pancuronium used for a long-time can cause this condition. There is a loss of deep tendon reflexes and muscle wasting in the affected upper and lower extremities. Motor neuropathy is correlated with dose increase and duration. Another problem with muscle relaxants is prolonged paralysis. The risk factors for this are renal failure, female gender, concomitant use with high dose corticosteroids and high dose and prolonged use of muscle relaxants.[34-36] Other complications are given in Table 19.

Non-depolarizing Drugs

Short Effects

Mivacurium (Mivacron)

Since it is completely hydrolyzed in plasma by pseudocholinesterase, its duration of action is short. Mivacurium 0.2-0.25 mg/kg intravenously allows intubation within 1 minute and reverses its effect within 20 minutes. It is metabolized by plasma cholinesterases. Its effect may be prolonged in patients with severe renal or hepatic insufficiency due to plasma cholinesterase activity. It may cause histamine

release. Its typical uses are: Rapid sequential intubation or laryngospasm.

Moderate Effects

Vecuronium

It is an analog of pancuronium. When 0.1 mg/kg is used intravenously, it allows intubation within 1.5 minutes and reverses its effect within 20 minutes. At a dose of 0.4 mg/kg, the initial effect is shorter than 30 seconds, and the reversal time is within 90 minutes. In infants and newborns, this effect is longer. It is metabolized mainly in the liver. Metabolites accumulate in the presence of renal failure and prolonged paralysis. Its advantage is that it has few hemodynamic effects and does not cause tachycardia.

Atracurium

Like vecuronium, it is a moderately effective muscle relaxant. It is highly metabolized in circulation. It is metabolized in two different ways: Ester hydrolysis (non-specific esterases) and Hoffman elimination (spontaneous non-enzymatic chemical degradation at physiologic pH and temperature). Paralysis develops 2 minutes after intravenous administration of atracurium 0.4 mg/kg and reverses in 30 minutes. When metabolites accumulate, it causes central nervous system depression. High doses may cause histamine release, which may result in bronchospasm or hypotension. The duration of action may be prolonged in hypothermic and acidotic patients. It may form precipitate when administered intravenously with alkaline drugs such as thiopental.[1,37]

Long Effects

Pancuronium

An intravenous dose of 0.06-0.1 mg/kg causes paralysis within 3 minutes and reverses within 1 hour. It is primarily eliminated from the kidney, and its effect may be prolonged in renal failure. In hepatic failure, drug resistance may develop and prolong its effect. Tachycardia and hypertension are common side effects.

Metocurine

The dose of metocurine is 0.2-0.3 mg/kg. Its action and elimination are similar to pancuronium but without cardiovascular side effects.

Pipecuronium

It is a derivative of pancuronium and 20-30% more potent than pancuronium. It is preferred in operations that do not require early extubation that last >3-4 hours and requires cardiovascular stability because it has no vagolytic effect, does not affect the autonomic ganglia, and does not cause histamine release. It is not metabolized. Its main excretion is by the kidneys and to a lesser extent by the liver.[38] There are insufficient data on its pediatric use.

Reversing the Effects of Muscle Relaxants

When residual paralysis develops secondary to muscle relaxants, it is possible to antagonize their effects (e.g., extubation). For this, less than 90% of the receptors must be blocked.

Neostigmine 0.05-7 mg/kg or edrophonium 1 mg/kg combined with atropine 0.02 mg/kg or glycopyrrolate 0.01 mg/kg is used for this procedure, and reverses the effect of muscle relaxants in 10 minutes.[39]

Among the non-depolarizing muscle relaxants, the specific antagonist of vecuronium and rocuronium is Bridion (sugammadex), which is very effective in eliminating neuromuscular block, especially in non-intubated cases. If repeated applications of rocuronium and vecuronium are necessary in patients receiving Bridion, these applications should be performed after 24 hours, but if muscle relaxants are required before 24 hours, non-steroidal muscle relaxants (atracurium or cisatracurium) can be tried. Bridion is currently of limited use in children under two years of age due to a lack of sufficient data. It is recommended to use 2-4 mg/kg by dilution (1 mL drug + 9 mL saline) in the reversal of rocuronium-induced block only in children aged 2-17 years.[40]

Recommendations for Muscle Relaxants

41. We do not recommend the routine use of muscle relaxants in patients on Mechanical Ventilation in the intensive care unit (STRONG RECOMMENDATION).

42. If it is necessary to use muscle relaxants for various reasons (patient-ventilator incompatibility, to reduce work of breathing and metabolic demand in ARDS, bronchospasm, during rapid successive intubation, etc...) in patients undergoing mechanical ventilation in the intensive care unit, we recommend the use of rokuronium, vekuronium at the lowest required doses (STRONG RECOMMENDATION).

43. We recommend the use of bispectral index instead of validated clinical scoring tools to assess the depth of sedation in patients receiving muscle relaxants (STRONG RECOMMENDATION).

44. We recommend routine passive eyelid closure and use of lubricant to prevent corneal abrasions in critically ill pediatric patients receiving muscle relaxants (STRONG RECOMMENDATION).

As a result, it is the duty and obligation of all physicians and auxiliary health personnel working in these units to ensure the

correct sedation and analgesia application in the treatment management of the sick child hospitalized in the PICU, the use of appropriate muscle relaxants when necessary, the prevention and/or correct management of withdrawal and delirium pictures that may occur, and the correct arrangement of intensive care units in order for all these applications to be more effective under appropriate conditions, in other words, to ensure the correct "environmental optimization". When all these practices are carried out in accordance with certain standards based on up-to-date information, improvement and recovery in the clinical picture of the patient will be faster, unwanted situations and complications will be minimized, and the treatment and management of the patient will become easier for the intensive care team. We hope that the guideline we have prepared in order to organize all these practices and regulations in the most up-to-date and best conditions in the PICUs in our country will be a guide and will be beneficial to our patients by helping all healthcare professionals.

Ethics

Authorship Contributions

Concept: D.Y., Design: D.Y., Data Collection or Processing: G.B., E.K., A.K., Ü.A., Analysis or Interpretation: G.B., E.K., A.K., Ü.A., D.Y., Literature Search: G.B., E.K., A.K., Ü.A., Writing: G.B., E.K., A.K., Ü.A., D.Y.

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