JPPT | Case Series

Propofol Sedation Washouts in Critically Ill Infants: A Case Series

Stephen Deptola, PharmD; Brianna Hemmann, PharmD; Trina Hemmelgarn, PharmD; Kyle DiPaola, PharmD; and DonnaMaria E. Cortezzo, MD

Medically complex infants are experiencing longer hospital stays, more invasive procedures, and increasingly involved therapeutic interventions that often require long-term analgesia and sedation. This is most commonly achieved with continuous intravenous infusions of opioids and benzodiazepines. There are times when patients develop a tolerance for these medications or the clinical scenario necessitates a rapid wean of them. A rapid wean of either class of medication can lead to increased signs of pain and agitation or withdrawal symptoms. As a result, when a rapid wean is needed or there has been a failure to control symptoms with conventional measures, alternative therapies are considered. Propofol, a sedative hypnotic typically used for general anesthesia and procedural sedation, is one such medication. It has effectively been used for short-term sedation in adults and children to facilitate weaning benzodiazepines and opioids. There is a paucity of data on the use of propofol in infants for this purpose. Here we describe the use of propofol to rapidly wean high-dose sedation and analgesia medications, a propofol sedation washout, in 3 infants. The washouts proved to be safe and efficacious. Based on institutional experience and a literature review, considerations and recommendations are made for propofol sedation washouts in infants.

ABBREVIATIONS CK, creatinine kinase; DOL, day of life; EKG, electrocardiogram; IV, intravenous; NICU, neonatal intensive care unit; PRIS, propofol-related infusion syndrome, VACTERL, vertebral anomalies, anorectal malformation, cardiovascular anomalies, trachea-esophageal fistula, renal and limb anomalies

KEYWORDS case series; neonates and infants; propofol washout; sedation and analgesia; sedation washout; sedation wean

J Pediatr Pharmacol Ther 2023;28(4):354–364

DOI: 10.5863/1551-6776-28.4.354

Introduction

Adequate sedation and analgesia are important aspects of care for critically ill infants in the neonatal intensive care unit (NICU). Appropriate analgesia and sedation can decrease stress responses, prevent dislodgement of invasive medical equipment, maximize synchrony with the ventilator, optimize hemodynamics, and improve clinical outcomes.[1–8] Although no consensus exists in the NICU regarding the optimal choice, route, dosing, or titration of analgesic and sedative medications in medially complex and critically ill infants, a combination of opioids and benzodiazepines is often used.[4,8,9] Recent guidelines from the Society of Critical Care Medicine highlight the importance of intentional practices for analgesia and sedation through protocols and specifically recommend minimizing benzodiazepines by using dexmedetomidine for infants in the pediatric intensive care unit.[8] With prolonged exposure to opioids and benzodiazepines, there can be challenges in maintaining optimal sedation and analgesia due to tolerance, hyperalgesia, delirium, and other potential adverse effects. Because infants' brains are in a critical period of development, they experience tolerance more frequently, reportedly up to 50% of the time.[10–12] As a result, they may require 2- to 5-fold increases in medication doses to achieve analgesia and sedation goals.[13] Additionally, recent studies have identified benzodiazepines as independent, dose-dependent, and modifiable risk factors for the development of delirium in critically ill children.[8,14–18] This, along with other adverse effects, requires that opioids and benzodiazepines be used cautiously and sparingly in infants. However, with longer hospital stays, more invasive procedures, and increasingly involved therapeutic interventions, medically complex infants often require these medications for extended periods of time. Weaning them can be challenging because of withdrawal or inadequate symptom control. Either of these factors can lead to increased morbidity and length of hospital stay.[10,19]

In order to combat tolerance, decrease the risk of delirium, provide adequate sedation, and improve overall outcomes for infants, providers have attempted to use alternative therapies and medications when there is prolonged opioid and benzodiazepine exposure or it becomes difficult to wean off of them.[8,10] One

rarely considered medication is propofol. Propofol (2-6-diisopropylphenol) is an alkylphenol intravenous (IV) sedative-hypnotic agent typically used for the induction and maintenance of anesthesia or procedural sedation.[20] Recently, with increased use for sedation outside of the operating room, propofol as a continuous infusion has been shown to be safe and effective in children.[8,21–23] The data in infants, however, are largely limited to procedural sedation with a wide range of reported outcomes.[22,24,25] Propofol has been used in older patients for sedation washouts. Rather than the sole purpose of providing sedation, a continuous propofol infusion is initiated with the subsequent rapid decrease of concomitant analgesic or sedative infusions. The opioids or benzodiazepines can, depending on the clinical scenario, be discontinued or reduced to lower doses. Although propofol washouts have been used successfully, there is a lack of data to guide appropriate dosing or duration of the propofol washout and weaning of associated medications.[26] In general, the use of propofol for long-term sedation is controversial because of reports of life-threatening complications, death, and variable pharmacokinetics in critically ill children.[27–34] Propofol-related infusion syndrome (PRIS) is a rare but potentially fatal complication associated with continuous infusions.[35] Although the true prevalence of adverse drug effects and PRIS remain low, even in children, the concern has led to limited use in pediatric patients outside of general anesthesia or procedural sedation.[20,36,37]

Although there are increasing reports of propofol for sedation in children, there is a paucity of data on propofol sedation washouts, especially in infants.[26,38,39] In this case series, we present our experience using propofol infusions for an opioid and benzodiazepine washout in medically complex infants. We aim to demonstrate the safety and efficacy of propofol sedation washouts in infants and recommend considerations and approaches to propofol washouts in this population.

Methods

This was a retrospective case series of all infants treated with a propofol sedation washout in a 75-bed level 4 NICU January 2017 to December 2021. We searched medication records to identify NICU patients treated with propofol and excluded patients who received it for other reasons, including anesthesia, procedural sedation, refractory seizures, and sedation without the intent to wean other medications. We extracted relevant clinical data from the electronic medical record and used standard descriptive statistics to delineate the study cohort. For the conversion of lorazepam to midazolam a conversion factor of 2:1 was used, ultimately converting mg/kg to mg/kg/hr. For the conversion of methadone to hydromorphone a conversion factor of 1:4 was used, ultimately converting mg/kg to mg/kg/hr.

Case Series. Three infants admitted to the NICU were treated with propofol for a sedation washout during the study period. Per unit guidelines, pain and agitation were assessed using the Neonatal Pain, Agitation, and Sedation Scale as well as clinical judgement.[40] Withdrawal was assessed using the Withdrawal Assessment Tool-1 and delirium was assessed using the Cornell Assessment of Pediatric Delirium.[41,42] A summary of patient characteristics are reported in Table 1.

Case 1. A female infant born at 35 weeks' gestation was admitted to the NICU for management of a giant omphalocele and pulmonary hypoplasia. She had a prolonged hospital course complicated by a severe pulmonary hypertensive crisis on day of life (DOL) 101 requiring reintubation and increased pulmonary vasodilatory support. Prior to this, she never required continuous opioid or benzodiazepine infusions. She was briefly on scheduled morphine 0.05 mg/kg every 4 hours in her first weeks of life and had not received any for several months. During this acute decompensation, she became critically ill and her sedation goals and medication requirements quickly escalated. Despite the appropriate titration of medications, adequate sedation was not achieved. This compromised her clinical stability and worsened her pulmonary hypertensive crisis.

During this time she had been receiving continuous IV infusions of midazolam for 63 days (DOL 101–164), dexmedetomidine for 62 days (DOL 102–164), and opioids for 11 days. Because of poor clinical effect, her opioids were rotated from morphine (DOL 154–158) to fentanyl (DOL 158–160), and ultimately to hydromorphone (DOL 160–164). Given her illness severity, sedation requirements, and decreased response to opioids and benzodiazepines she was started on multiple adjuvant medications and eventually a paralytic. Prior to the initiation of propofol, she was receiving midazolam 0.5 mg/kg/hr, dexmedetomidine 1 mcg/kg/hr, hydromorphone 0.2 mg/kg/hr, vecuronium 0.1 mg/kg/hr, methadone 0.05 mg/kg IV every 6 hours, and phenobarbital 4 mg/kg IV every 12 hours for sedation. She also had midazolam 0.5 mg/kg, hydromorphone 0.2 mg/kg, and ketamine 1 mg/kg IV as needed for sedation. She required premedication with these medications prior to cares and several additional times throughout the day. On DOL 164, propofol was initiated at 50 mcg/kg/minute and was continued at this dose for 57.6 hours (Table 2). This provided the adequate sedation needed to achieve clinical stability, perform necessary procedures, and to decrease benzodiazepines and opioids with improved clinical effect.

Three hours after the initiation of propofol, midazolam was decreased by 0.1 mg/kg/hr. An hour later vecuronium was discontinued and hydromorphone was decreased by 0.02 mg/kg/hr. Midazolam and hydromorphone were then incrementally decreased as tolerated

Table 1. Patient Characteristics

Case	Sex	Gestational Age at Birth, wk	Birth Weight, g	Primary Diagnosis	Other Diagnoses	CGA at Propofol Initiation, wk	DOL at Propofol Initiation	Propofol Dosing Weight, g
1	Female	35 5/7	2290	Congenital omphalocele	Pulmonary hypertension BPD Atrial septal defect	59 0/7	164	6450
2	Male	29 2/7	1490	Tracheal stenosis	VACTERL Duodenal atresia Imperforate anus Cardiac dextroposition Pulmonary hypoplasia Hypoplastic pulmonary artery Large PDA Vertebral anomalies Rectourethral fistula Grade I/grade II IVH Coagulopathy Acute kidney injury	47 6/7	129	5000
3	Female	26 1/7	617	Severe BPD	Pulmonary hypertension PDA Pulmonary vein stenosis	57 3/7	219	5100

BPD, bronchopulmonary dysplasia; CGA, corrected gestational age; DOL, day of life; IVH, interventricular hemorrhage; PDA, patent ductus arteriosus; VACTERL, vertebral anomalies, anorectal malformation, cardiovascul ar anomalies, trachea-esophageal fistula, renal and limb anomalies

Table 2. Propofol Washout Description

Case	Minimum Infusion Rate, mcg/kg/min	Maximum Infusion Rate, mcg/kg/min	Average Infusion Rate, mcg/kg/min	Total Duration of Infusion, hr
1	50	50	50.0	57.6
2*	25	200	96.5	39.6
3	25	175	137.8	65.5

* The infusion was discontinued at hour 30 and resumed at hour 41. It was discontinued again at approximately hour 52. Total infusion time was combined.

Figure 1. Titration of continuous medications hourly during and immediate after the propofol washout. The doses of midazolam and hydromorphone were converted from mg/kg/hr to mcg/kg/hr to aid in visualizing all medications on 1 graph. Likewise, other opioids (methadone) were converted to hydromorphone equivalent doses in mcg/kg/hr and other benzodiazepines (lorazepam) were converted to midazolam equivalent doses in mcg/kg/hr.

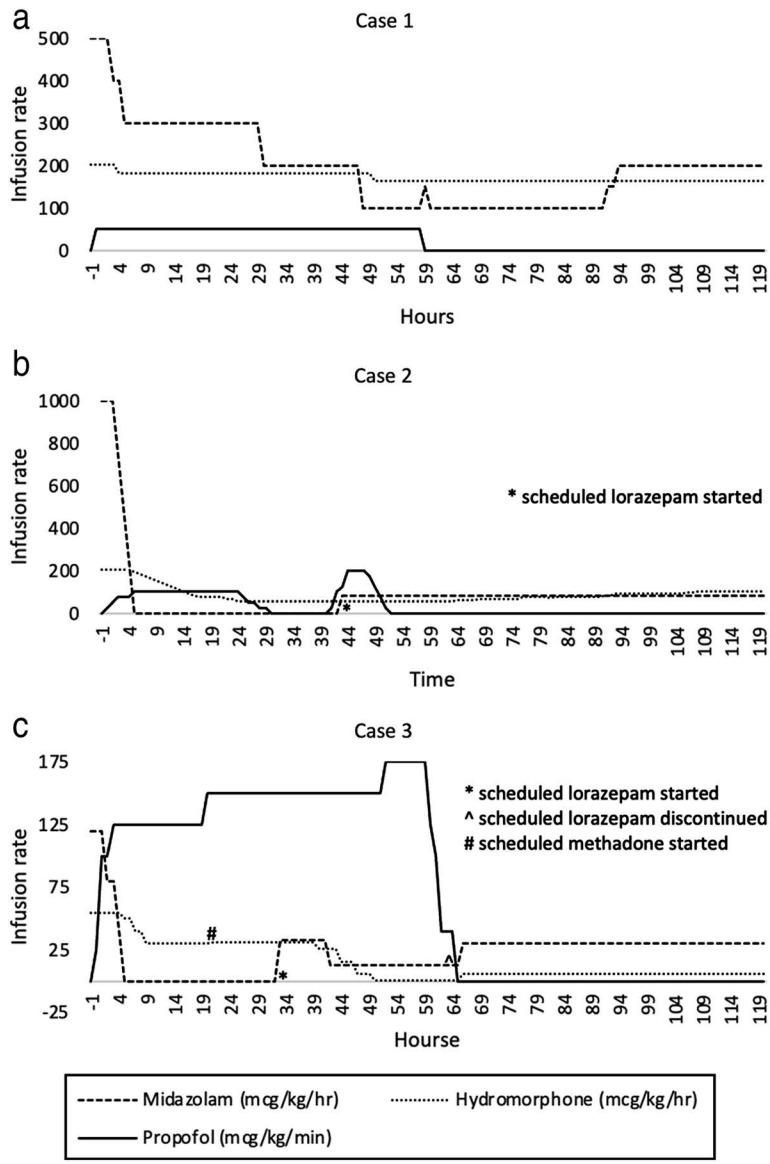

Table 3. Sedative and Analgesic Continuous Infusions Pre-propofol and Post-propofol Washout

Case	Hydromorphone			Midazolam			Dexmedetomidine			Vecuronium		
	Pre-propofol, mg/kg/hr*	Post-propofol, mg/kg/hr†	% Change	Pre-propofol, mg/kg/hr*	Post-propofol, mg/kg/hr†	% Change	Pre-propofol, mg/kg/hr*	Post-propofol, mg/kg/hr†	% Change	Pre-propofol, mg/kg/hr*	Post-propofol, mg/kg/hr†	% Change
1	0.203‡	0.163‡	−20	0.5	0.2	−60	1	1	0	0.1	0	−100
2	0.204‡	0.094‡	−54	1.000§	0.080§	−92	1.5	1.5	0	0.1	0	−100
3	0.055	0.006¶	−89	0.120§	0.030§	−75	1.5	1.5	0	0	0	0

* Value reflects infusion rate immediately prior to the propofol infusion.
† Value reflects infusion rate 48–72 hours after the end of the propofol infusion.
‡ Before the propofol infusion the infant was also on scheduled methadone, which was continued. The dose was converted to hydromorphone equivalents in mg/kg/hr for this table.
§ After the midazolam infusion was discontinued, smaller-dose scheduled lorazepam was started. The dose was converted to midazolam equivalents in mg/kg/hr for this table.
¶ Scheduled methadone was started during the propofol washout. The dose was converted to hydromorphone equivalents in mg/kg/hr for this table.

(Figure 1a). After a total of 56 hours, when propofol was discontinued, the infant was on a midazolam infusion at 0.1 mg/kg/hr and hydromorphone infusion at 0.16 mg/kg/hr (Figure 1a). She remained on methadone and dexmedetomidine. The midazolam dose was increased to 0.2 mg/kg/hr within 72 hours of propofol discontinuation (Table 3) with adequate symptom control. After the propofol washout, there was a 60% decrease in benzodiazepines and 20% decrease in opioids (Table 3). Midazolam, hydromorphone, and dexmedetomidine were slowly weaned off during a 2-month period. Intermittent scheduled phenobarbital was tapered off approximately 1 month after the propofol washout and methadone was slowly tapered during a 4-month period.

During the propofol infusion, to monitor for PRIS, serum triglycerides, creatine kinase (CK), and lactic acid levels were obtained twice daily. The serum triglyceride concentration was mildly elevated on the last day of propofol therapy at 123 mg/dL but rapidly decreased to 89 mg/dL the following day. Lactic acid and CK remained within normal limits. The infant did not experience metabolic acidosis, significant bradycardia, or hypotension.

Case 2. A male infant born at 29 weeks' gestation with vertebral anomalies, anorectal malformation, cardiovascular anomalies, trachea-esophageal fistula, renal and limb anomalies (VACTERL) association, now 47 weeks corrected gestational age, was transferred from an outside hospital for management of severe tracheal and bronchial stenosis. Intubation occurred at delivery and computed tomography angiography revealed right pulmonary hypoplasia, middle and distal tracheal stenosis, and a hypoplastic right pulmonary artery. He was critically ill with multiple additional comorbidities, including a coagulopathy and acute kidney injury (Table 1). The infant had received continuous IV infusions of hydromorphone for 91 days (DOL 33–124), dexmedetomidine for 92 days (DOL 32–124), midazolam for 87 days (DOL 37–124), and lorazepam as needed for 21 days (DOL 103–124) prior to transfer. On arrival, he was receiving dexmedetomidine at 1.5 mcg/kg/hr, midazolam at 1 mg/kg/hr, and hydromorphone at 0.2 mg/kg/hr. He was critically ill with cardiorespiratory failure and was started on methadone 0.08 mg/kg IV every 6 hours and vecuronium at 0.1 mg/kg/hr shortly after admission (Table 3).

Five days after transfer (DOL 129), a propofol washout was initiated because of a worsening clinical status and concerns for paradoxical adverse effects from the high dose of midazolam. Propofol was started at 25 mcg/kg/min and the vecuronium infusion was immediately discontinued. The propofol infusion was increased to 75 mcg/kg/min during a 2-hour period. Afterwards, midazolam was incrementally weaned as tolerated until it was discontinued 5 hours into the washout (Figure 1b). Then propofol was increased and during several hours hydromorphone was weaned to 0.05 mg/kg/hr (Figure 1b).

Subsequently, propofol was weaned by 25 mcg/kg/min every 1 to 2 hours until it was discontinued 30 hours after initiation. At that time, dexmedetomidine was weaned to 1 mcg/kg/hr. The patient was anuric and his respiratory and cardiovascular status continued to deteriorate. The decision was made to pursue dialysis catheter placement and cardiac catheterization for patent ductus arteriosus device closure in hopes of achieving stability to undergo tracheal and bronchial reconstruction. Eleven hours after the discontinuation of propofol it was restarted at 25 mcg/kg/min and escalated incrementally to 125 mcg/kg/min to achieve sedation and stability for the procedure. During the procedure, the dose was escalated to 200 mcg/kg/min. Afterwards, propofol was weaned by 25 mcg/kg/min every 30 minutes until it was discontinued. Around this time, he was started on scheduled IV lorazepam 0.25 mg/kg every 6 hours.

When propofol was discontinued, the infant was on hydromorphone 0.05 mg/kg/hr (Figure 1b). Approximately 12 hours later, he exhibited signs of withdrawal and hydromorphone was slowly increased to 0.07 mg/kg/hr with adequate symptom control and resolution of signs of withdrawal (Table 3). After the propofol washout, there was a 92% decrease in benzodiazepines and 54% decrease in opioids (Table 3). Several days later his clinical status deteriorated with increased ascites, fluid overload, near complete collapse of his airway, worsening mucous plugging, and possible sepsis. His multiple comorbidities led to multisystem organ failure with worsening respiratory failure, pulmonary hypertension, renal failure, metabolic acidosis, and new-onset seizures. He had several code events and was ultimately placed on extracorporeal membrane oxygenation. In the setting of his acute decompensation and need for extracorporeal membrane oxygenation cannulation, the goal was for him to be deeply sedated and paralyzed until recovery from a slide tracheoplasty and intertracheal stent placement. His medications were eventually escalated to hydromorphone 0.1 mg/kg/hr, dexmedetomidine 1.5 mcg/kg/hr, vecuronium 0.1 mg/kg/hr, methadone 0.1 mg/kg/dose IV every 6 hours, and lorazepam IV 0.25 mg/kg/dose every 6 hours. After recovery from surgery he was treated for delirium with quetiapine prior to weaning his opioids and benzodiazepines.

Laboratory markers for PRIS, including CK, triglycerides, and lactic acid, were monitored every 12 hours while on propofol. The triglyceride concentration increased from a baseline of 96 to 380 mg/dL during propofol infusion. Marked elevation in triglycerides was only noted toward the end of the washout and propofol was rapidly weaned off as planned. Triglycerides returned to 84 mg/dL within 96 hours after discontinuation of therapy. There was no clinically significant change in the lactic acid concentrations or CK during the propofol infusion. The infant did not experience metabolic acidosis, significant bradycardia, or hypotension.

Case 3. A former 26 weeks' gestation female now corrected to 32 weeks' gestation was transferred from an outside hospital for management of bacteremia, respiratory failure, and necrotizing enterocolitis (Table 1). At 54 weeks corrected gestational age she was reintubated for a pulmonary hypertensive crisis requiring inhaled nitric oxide, inhaled epoprostenol, and IV phenylephrine. She continued to receive significant escalation in respiratory support, cardiovascular support, and sedation medications to achieve clinical stability.

The patient was on a midazolam infusion for 21 days (DOL 198-219), dexmedetomidine for 13 days (DOL 206–219), and opioids for 21 days. During this time her opioids were rotated from morphine (DOL 198–205) to hydromorphone (DOL 205–219) because of a lack of clinical effect. She was also trialed on quetiapine DOL 214 because of concerns for delirium. This was discontinued on DOL 219 because there was no improvement in symptoms. Prior to the initiation of propofol on DOL 219, she was receiving midazolam 0.12 mg/kg/hr, hydromorphone 0.055 mg/kg/hr, and dexmedetomidine 1.5 mcg/kg/hr (Table 3). Additionally, she was receiving ketamine 1 mg/kg IV every 4 hours and gabapentin 5 mg/kg enterally every 8 hours for agitation. Scheduled ketamine was discontinued upon initiation of the propofol infusion. Propofol was initiated at 25 mcg/kg/min and increased every 15 minutes to 100 mcg/kg/hr. A further escalation to 125 mcg/kg/min was made 3 hours later (Figure 1c). Then, after appropriate sedation was achieved, the midazolam infusion was weaned by increments of 0.04 mg/kg/hr and discontinued approximately 5 hours after initiation of propofol (Figure 1c). Once midazolam was discontinued, the hydromorphone infusion was weaned by 0.005 to 0.01 mg/kg/hr every 1 to 2 hours as tolerated to a rate of 0.03 mg/kg/hr (Figure 1c). Twenty hours into the propofol washout, propofol was increased to 150 mcg/kg/min for worsening agitation with decreasing pulmonary compliance on the ventilator. The patient was started on methadone 0.05 mg/kg IV every 12 hours in anticipation of the need for long-term opioids. The hydromorphone was then incrementally weaned until it was discontinued approximately 50 hours from initiation of the propofol infusion. At 52 hours, propofol was increased to 175 mcg/kg/min for worsening agitation with decreasing pulmonary compliance on the ventilator (Table 2 and Figure 1c). At this time, the patient underwent cardiac catheterization with recanalization of her occluded left upper pulmonary vein. During the procedure, while under general anesthesia, propofol was weaned to 40 mcg/kg/min. Shortly after completion of the cardiac catheterization, approximately 65 hours after the start of the propofol washout, the propofol infusion was discontinued (Table 2). At this time, the patient was restarted on

midazolam 0.03 mg/kg/hr and hydromorphone 0.005 mg/kg/hr (Table 3). After the propofol washout, there was a 75% decrease in benzodiazepines and 89% decrease in opioids (Table 3). Several days after the washout, the midazolam infusion was discontinued and she was transitioned to scheduled lorazepam 0.05 mg/kg IV every 6 hours. The hydromorphone infusion was weaned off during a 12-day period with continuation of scheduled intermittent methadone dosing. The dexmedetomidine infusion was continued at a rate of 1.5 mcg/kg/hr for another 14 days and then was weaned off during a period of 12 days.

Laboratory markers for PRIS, including CK, triglycerides, and lactic acid, were monitored every 12 hours while on propofol. The serum creatinine remained within normal limits throughout the propofol infusion. The triglyceride concentration increased from a baseline of 210 to 301 mg/dL and returned to 130 mg/dL within 12 hours of discontinuation of therapy. The lactic acid concentration prior to initiation of propofol was 1.5 mmol/L and peaked at 2.96 mmol/L at approximately 36 hours of therapy. It returned to baseline of 1.34 mmol/L within 12 hours of discontinuing propofol. The infant did not experience metabolic acidosis, significant bradycardia, or hypotension.

Discussion

Given that medically complex infants in the NICU are increasingly requiring long-term sedation and analgesia, providers must be judicious in their use of opioids and benzodiazepines. By having analgesia and sedation protocols in place, providers can decrease the use of these medications, decrease the presence of delirium, and improve clinical outcomes.[8] When opioids or benzodiazepine are rapidly escalated, adjuvant medications should be considered. The α2 adrenergic agonists clonidine and dexmedetomidine have analgesic and sedative properties and can be considered safe as a primary sedative for mechanically ventilated patients.[8,9] Gabapentin, an anticonvulsant that works on the voltage-dependent calcium channel, can be beneficial for neonates with refractory agitation or neuroirritability.[43–46] Finally, ketamine, a dissociative anesthetic, has amnestic, analgesic, and sedative properties that can be beneficial when other agents have failed to provide adequate sedation.[8] Although there have been concerns for apoptosis in animal models, in human models and in the presence of painful stimuli, there is a possible protective effect.[47–49] These alternative therapies can safely provide adequate sedation with lower opioid and benzodiazepine requirements.

Decreasing opioid and benzodiazepine exposure in conjunction with environmental measures may decrease the likelihood of a patient developing delirium. When high-risk patients are experiencing signs of agitation despite escalation of opioids and benzodiazepines, delirium should be considered.[8] Two of our patients were treated with atypical antipsychotics for refractory delirium after exposure to high-dose benzodiazepines or deep sedation. One was not responsive to antipsychotics. Delirium prevention and treatment is important because of the associated morbidity and mortality.[14,16,17] Even with mindful practices and protocols, patients may require high doses of benzodiazepines and opioids, leading to unfavorable adverse effects, emergence of delirium, or development of tolerance. At times, a prolonged taper of medications, environmental measures, α2 agonists, or long-acting medications can successfully manage symptoms of withdrawal or facilitate medication weaning.[10] When these measures are unsuccessful or a rapid wean is indicated, providers should be knowledgeable about options for alternative therapies such as propofol.

Propofol may be beneficial in these circumstances because its mechanism of action is different than those of these other medications. When tolerance to opioids develops, there is a reduction in sensitivity of the mu-opioid receptor and a downregulation of receptor expression. With benzodiazepine tolerance, there is uncoupling and downregulation of the γ-aminobutyric acid type A receptor. Propofol directly activates the γ-aminobutyric acid type A receptor and is an *N*-methyl-D-aspartate receptor agonist.[20,50] It is thought that with a propofol washout, the rapid decrease of medications allows for the receptors to upregulate and increase their sensitivity. Additionally, the process may upregulate the expression of the mu-opioid receptors and enhance the activity of the endogenous mu-opioid system.[10,51–53] This should allow for the rapid wean of opioids and benzodiazepines with improved response to the medications after propofol is discontinued.

Although this theory of the mechanism of action is largely based on animal studies, it is plausible that propofol may be beneficial in minimizing benzodiazepine and opioid withdrawal. As a result, it has been used in the adult ICU to provide sedation while decreasing opioid and benzodiazepine requirements.[54] With the success of propofol sedation washouts in select patients, it has been more recently used to aid in detoxification for individuals with opioid addiction.[51,52,55] In pediatric patients, propofol has allowed for the rapid wean of opioids and benzodiazepines to aid in extubation.[26,38,39] The goal in these studies was to decrease the medications by half to allow for a new steady-state serum concentration while simultaneously providing sedation prior to extubation. There were no significant adverse effects from propofol and the children showed no signs of withdrawal with the subsequent medication wean. Similarly, because of its rapid onset and elimination, propofol has been successfully used as a sole agent to provide sedation periextubation.[39] A novel case report of a 16-month-old with cardiac disease demonstrated the successful use of a propofol infusion to facilitate the rapid wean of high-dose analgesia and sedation

medications postoperatively to aid in extubation.[26] The Society of Critical Care Medicine recently suggested the use of short-term propofol in pediatric patients as an adjuvant medication periextubation to facilitate weaning other analgosedative agents.[8]

Use of propofol has been limited in infants, largely because of concerns for safety, specifically the development of PRIS. PRIS is a constellation of symptoms, including bradycardia, cardiac failure, rhabdomyolysis, metabolic acidosis, liver enlargement, lipemic plasma, and kidney failure that can be fatal. It is the result of mitochondrial toxicity which leads to a lactic acidosis. This can cause profound cardiovascular collapse and death.[20,29,56,57] PRIS is thought to be dose and duration dependent. Although it has been reported that children are at higher risk for PRIS, a large retrospective study has shown when propofol is used for nonprocedural sedation in the pediatric ICU with predetermined guidelines for the dose range and duration of use, there were no cases of PRIS.[36] Furthermore, there have been no reported cases in the literature involving infants. It is unclear if this is because of the relative paucity of data on propofol in infants or if no cases of PRIS have been seen. In our case series, there was a transient elevation in triglycerides in all cases, but no severe or clinically relevant adverse effects or concern for PRIS were seen. Despite the rarity of these serious adverse effects, the use of propofol in infants is typically limited to intraoperative anesthesia or procedural sedation.[22,24,25]

There is currently no description of the successful use of propofol washouts in infants and no standard dosage recommendations or protocols. In our series, we describe 3 complex cases where the initiation of propofol therapy allowed for the rapid decrease of opioids and benzodiazepines in patients who were previously unable to achieve adequate sedation despite higher than conventional doses of analgosedative medications. In each case, opioids and benzodiazepines were weaned with improved clinical response to the medications after the discontinuation of propofol. On average, the patients remained on a propofol infusion for 54.2 hours with an average infusion rate of 96.7 mcg/kg/min. The maximum rate, for a transient period of time, was 200 mcg/kg/min (Table 2). Overall, benzodiazepines were weaned by 60% to 92% and opioids were weaned by 20% to 89% (Table 3). Two patients were started on lower equivalent doses of intermittent medications to facilitate continued medication weans. It is important to also consider, especially with case 2, that the presence of comorbidities and the acute change in clinical status likely factored in to the subsequent need to reinitiate and escalate continuous sedative and analgesic infusions. Some of the clinical symptoms could be partially explained by the emergence of withdrawal symptoms after propofol was discontinued. However, with a slight increase in medication, withdrawal symptoms resolved and the patient continued to deteriorate secondary to his underlying pathophysiology. Still, it is important to have protocols in place and to monitor patients for signs of withdrawal during and after a propofol washout. Although rarely reported in the literature, symptoms can appear hours or days later and should be treated with the same class of medications from which the patient is withdrawing.[8]

Based on institutional experience beyond this case series and an extensive literature review, we propose a general approach to propofol sedation washouts in infants. Treatment should be provided by experienced anesthesiologists or intensivists, qualified nurses, and multidisciplinary teams.[29] Prior to initiation, providers should be mindful of the glucose infusion rate because propofol inhibits fatty acid oxidation. A glucose infusion rate of at least 5 to 8 mg/kg/min is typically indicated. Also, because propofol contains lipids, 1 mL provides 0.1 g of lipids, and the amount of IV lipid emulsion a patient is on may need to be decreased to avoid hyperlipidemia or pancreatitis. Although none of our patients developed pancreatitis, they all had transient elevations in their triglycerides. Caution should be used when patients are on catecholamines or glucocorticoids because of the association with PRIS.[56,57] Given the dose-dependent concern for PRIS, propofol infusions of greater than 125 mcg/kg/min for more than 65 hours should be avoided. Doses can be escalated beyond that for short periods of time but should not remain there for the duration of the washout. Other sources suggest avoiding doses higher than 67 mcg/kg/min for more than 48 hours.[8,20,21,26,58] Although these recommendations are important considerations, we and another case report have found with close monitoring, higher doses and longer infusions appear to be safe.[26] Always, however, the goal should be to use the lowest possible dose of propofol for the shortest period of time. A 12-lead electrocardiogram (EKG), blood gas, lactate, electrolytes, CK, and triglycerides should be obtained prior to the initiation of propofol.[8] At the time of initiation of a propofol sedation washout, the infant should be monitored continuously with frequent blood pressure checks. Lab work should be monitored and a physical exam should be performed, to evaluate for hepatomegaly every 6 to 12 hours. Any abnormalities should be discussed in the context of the entire clinical scenario because specific criteria for continuing or discontinuing therapy may be tailored to each patient. See Figure 2 for specific indications for considering discontinuation of propofol. There are times when it is appropriate to continue a propofol washout with certain lab abnormalities, but the thresholds outlined at a minimum warrant discussion with the care team. Although the specific plan will need to be tailored to the patient based on their clinical scenario, their analgesia and sedation history, and the goal of the washout, a stepwise approach should be taken to increase propofol and decrease concomitant sedation and analgesia medications. The lowest amount of propofol needed should always be used. Propofol should be started at 25 mcg/kg/min and titrated

Figure 2. A general guide to a propofol washout in infants. The specific plan needs to be tailored to each patient based on their medication history, clinical course, and response to the washout. These steps give general guidance. A specific step-by-step plan should be determined for each patient prior to starting the washout.

- Initiate propofol at 25 mcg/kg/min
  - The propofol dose will be titrated up in 25 mcg/kg increments every hour until appropriate sedation is achieved
  - It is rare that the dose will need to be higher than 150 mcg/kg/min, and doses that high are typically only needed transiently. If this dose is needed, discuss with pharmacy prior to escalating further.
- If the patient is on a paralytic discontinue it 30 minutes after starting the propofol infusion
- Once the patient has an appropriate level of sedation (typically propofol dose is at least 50 mcg/kg/min), start to wean other sedatives
  - Wean benzodiazepines by 25% of the original dose every hour as tolerated until it is off
    - Consider increasing propofol by 25 mcg/kg increments each hour if the patient is agitated
    - The benzodiazepine can be decreased even if the propofol dose is increased
  - Once the benzodiazepine has been discontinued for 1 hour, start to wean the opioid
    - Wean the opioid by 5%–20% of the original dose every 1–2 hours as tolerated
    - Consider increasing propofol by 25 mcg/kg increments each hour if the patient is agitated. Discuss with pharmacy if the dose is exceeding 150 mcg/kg/min.
- Monitoring at initiation and every 6–12 hours
  - Continuous heart rate, pulse oximetry, blood pressure
  - 12-lead electrocardiogram
  - Blood gas, lactate, electrolytes, triglyceride, creatinine kinase
  - Physical exam assessing for hepatomegaly
- Indications for considering discontinuation
  - Lactate level >4 mmol/L or rise of >1.5 mmol/L
  - Creatinine kinase level >5000 units/L
  - Triglyceride level > 250–350 mg/dL
  - Extreme electrolyte abnormalities
  - Hepatomegaly
  - Signs or symptoms concerning for anaphylaxis
  - Electrocardiogram changes (T-wave inversion, widened QRS, prolonged QTc, PVCs, PACs, arrhythmia)

PACS, xxxx; PVC, xxxx.

in 25 mcg/kg increments every hour until appropriate sedation is achieved. Paralytics should be discontinued and then benzodiazepines and opioids can be weaned every 1 to 2 hours. A general recommendation to the stepwise approach based on institutional experience is outlined in Figure 2. Pain, agitation, withdrawal, and delirium should always be assessed using validated tools in addition to clinical judgment.[8,59]

Our case series has limitations that should be noted. This was a single-center, retrospective, observational study with a small sample size. As such, meaningful inferential statistics could not be performed. Also, the timing of and indication for a propofol sedation washout was determined based on a combination of subjective and objective information.

Overall, our experience indicates that propofol appears to be a safe and effective treatment option to decrease the doses and improve the efficacy of opioids and benzodiazepines for infants who develop tolerance to them. This treatment may be of benefit to neonates who are showing refractory symptoms of agitation, pain, or delirium despite escalation of conventional medications and adjuvant therapies. There is a need for larger, prospective studies to further evaluate the efficacy and safety of propofol sedation washouts in infants as well as to determine if there is a more appropriate protocol and dose titration regimen in this patient population.

Article Information

Affiliations. Division of Pharmacy (SD, BH, TH, KD), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Division of Neonatology and Pulmonary Biology (DEC), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Division of Pain and Palliative Medicine (DEC), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Department of Pediatrics (DEC), University of Cincinnati College of Medicine, Cincinnati, Ohio; Department of Anesthesiology (DEC), University of Cincinnati College of Medicine, Cincinnati, Ohio.

Correspondence. DonnaMaria E. Cortezzo, MD; DonnaMaria.Cortezzo@cchmc.org

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. The hospital Institutional Review Board declared this study exempt from full review and patient consent was not required.

Acknowledgments. The authors wish to acknowledge Dawn Butler, PharmD, for her care of these patients, assistance in developing the treatment plans, and review of the manuscript.

Submitted. June 2, 2022

Accepted. September 29, 2022

References

1. Barker DP, Rutter N. Stress, severity of illness, and outcome in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 1996;75(3):F187–F190.
2. Segura-Ramírez DK, Fernández-Castiñeira S, Gualotuña-Maigua DC, Martín-Ramos S, Lareu-Vidal S, Solís-Sánchez G. Neonatal unplanned extubations: an unsolved safety issue. *Bol Med Hosp Infant Mex.* 2021;78(4):259–264.
3. Pavlek LR, Dillard J, Ryshen G, Hone E, Shepherd EG, Moallem M. Short-term complications and long-term morbidities associated with repeated unplanned extubations. *J Perinatol.* 2021;41(3):562–570.
4. Anand KJ, Aranda JV, Berde CB, et al. Summary proceedings from the neonatal pain-control group. *Pediatrics.* 2006;117(3 pt 2):S9–S22.
5. Anand KS. Relationships between stress responses and clinical outcome in newborns, infants, and children. *Crit Care Med.* 1993;21(9 suppl):S358–S359.
6. Simons SH, Anand KJ. Pain control: opioid dosing, population kinetics and side-effects. *Semin Fetal Neonatal Med.* 2006;11(4):260–267.
7. Grunau RE, Whitfield MF, Petrie-Thomas J, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain.* 2009;143(1–2):138–146.
8. Smith HAB, Besunder JB, Betters KA, et al. 2022 Society of Critical Care Medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med.* 2022;23(2):e74–e110.
9. Hall RW, Anand KJ. Pain management in newborns. *Clin Perinatol.* 2014;41(4):895–924.
10. Anand KJ, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics.* 2010;125(5):e1208–e1225.
11. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hershenson MB. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology.* 1990;73(6):1136–1140.
12. Arnold JH, Truog RD, Scavone JM, Fenton T. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr.* 1991;119(4):639–643.
13. Anand KJ, Clark AE, Willson DF, et al. Opioid analgesia in mechanically ventilated children: results from the multicenter Measuring Opioid Tolerance Induced by Fentanyl study. *Pediatr Crit Care Med.* 2013;14(1):27–36.
14. Dechnik A, Traube C. Delirium in hospitalised children. *Lancet Child Adolesc Health.* 2020;4(4):312–321.
15. Meyburg J, Dill ML, Traube C, Silver G, von Haken R. Patterns of postoperative delirium in children. *Pediatr Crit Care Med.* 2017;18(2):128–133.
16. Mody K, Kaur S, Mauer EA, et al. Benzodiazepines and development of delirium in critically ill children: estimating the causal effect. *Crit Care Med.* 2018;46(9):1486–1491.
17. Patel AK, Bell MJ, Traube C. Delirium in pediatric critical care. *Pediatr Clin North Am.* 2017;64(5):1117–1132.
18. Patel AK, Biagas KV, Clarke EC, et al. Delirium in children after cardiac bypass surgery. *Pediatr Crit Care Med.* 2017;18(2):165–171.
19. Franck LS, Vilardi J, Durand D, Powers R. Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation. *Am J Crit Care.* 1998;7(5):364–369.
20. Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. *CNS Drugs.* 2015;29(7):543–563.
21. Cornfield DN, Tegtmeyer K, Nelson MD, Milla CE, Sweeney M. Continuous propofol infusion in 142 critically ill children. *Pediatrics.* 2002;110(6):1177–1181.
22. Filho EM, Riechelmann MB. Propofol use in newborns and children: is it safe?: a systematic review. *J Pediatr (Rio J).* 2020;96(3):289–309.
23. Kruessell MA, Udink ten Cate FE, Kraus AJ, Roth B, Trieschmann U. Use of propofol in pediatric intensive care units: a national survey in Germany. *Pediatr Crit Care Med.* 2012;13(3):e150–e154.
24. Smits A, Thewissen L, Caicedo A, Naulaers G, Allegaert K. Propofol dose-finding to reach optimal effect for (semi-) elective intubation in neonates. *J Pediatr.* 2016;179:54–60.e9.
25. Shah PS, Shah VS. Propofol for procedural sedation/anaesthesia in neonates. *Cochrane Database Syst Rev.* 2011;(3):CD007248.
26. Loomba R, Ramsingh S, Rausa J, Dorsey V. Propofol infusion for rapid opiate and benzodiazepine wean to extubation in a child after cardiac surgery with residual mitral regurgitation: lessons from a unique case. *EC Paediatr.* 2020;9(4):3–9.
27. Cray SH, Robinson BH, Cox PN. Lactic acidemia and bradyarrhythmia in a child sedated with propofol. *Crit Care Med.* 1998;26(12):2087–2092.

28. Mehta N, DeMunter C, Habibi P, Nadel S, Britto J. Short-term propofol infusions in children. *Lancet*. 1999;354(9181):866–867.
29. Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet*. 2001;357(9256):606–607.
30. Kataria BK, Ved SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology.* 1994;80(1):104–122.
31. Saint-Maurice C, Cockshott ID, Douglas EJ, Richard MO, Harmey JL. Pharmacokinetics of propofol in young children after a single dose. *Br J Anaesth.* 1989;63(6):667–670.
32. Jones RD, Chan K, Andrew LJ. Pharmacokinetics of propofol in children. *Br J Anaesth.* 1990;65(5):661–667.
33. Rigby-Jones AE, Sneyd JR. Propofol and children–what we know and what we do not know. *Paediatr Anaesth.* 2011;21(3):247–254.
34. Rigby-Jones AE, Nolan JA, Priston MJ, Wright PM, Sneyd JR, Wolf AR. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. *Anesthesiology.* 2002;97(6):1393–1400.
35. Fudickar A, Bein B, Tonner PH. Propofol infusion syndrome in anaesthesia and intensive care medicine. *Curr Opin Anaesthesiol.* 2006;19(4):404–410.
36. Koriyama H, Duff JP, Guerra GG, Chan AW; Sedation Withdrawal and Analgesia Team. Is propofol a friend or a foe of the pediatric intensivist?: description of propofol use in a PICU. *Pediatr Crit Care Med.* 2014;15(2):e66–e71.
37. Morse J, Hannam JA, Cortinez LI, Allegaert K, Anderson BJ. A manual propofol infusion regimen for neonates and infants. *Paediatr Anaesth.* 2019;29(9):907–914.
38. Sheridan RL, Keaney T, Stoddard F, Enfanto R, Kadillack P, Breault L. Short-term propofol infusion as an adjunct to extubation in burned children. *J Burn Care Rehabil.* 2003;24(6):356–360.
39. Bhalala US, Patel A, Thangavelu M, Sauter M, Appachi E. Propofol infusion is a feasible bridge to extubation in general pediatric intensive care unit. *Front Pediatr.* 2020;8:255.
40. Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol.* 2008;28(1):55–60.
41. Silver G, Kearney J, Traube C, Hertzig M. Delirium screening anchored in child development: the Cornell Assessment for Pediatric Delirium. *Palliat Support Care.* 2015;13(4):1005–1011.
42. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med.* 2008;9(6):573–580.
43. Burnsed JC, Heinan K, Letzkus L, Zanelli S. Gabapentin for pain, movement disorders, and irritability in neonates and infants. *Dev Med Child Neurol.* 2020;62(3):386–389.
44. Abdi HH, Maitre NL, Benninger KL, Hester ME, Slaughter JL. Gabapentin use for hospitalized neonates. *Pediatr Neurol.* 2019;97:64–70.
45. Edwards L, DeMeo S, Hornik CD, et al. Gabapentin use in the neonatal intensive care unit. *J Pediatr.* 2016;169:310–312.
46. Sacha GL, Foreman MG, Kyllonen K, Rodriguez RJ. The use of gabapentin for pain and agitation in neonates and infants in a neonatal ICU. *J Pediatr Pharmacol Ther.* 2017;22(3):207–211.
47. Anand KJ. Anesthetic neurotoxicity in newborns: should we change clinical practice? *Anesthesiology.* 2007;107(1):2–4.
48. Anand KJ. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *J Perinatol.* 2007;27(suppl 1):S4–S11.
49. Anand KJ, Garg S, Rovnaghi CR, Narsinghani U, Bhutta AT, Hall RW. Ketamine reduces the cell death following inflammatory pain in newborn rat brain. *Pediatr Res.* 2007;62(3):283–290.
50. Kingston S, Mao L, Yang L, Arora A, Fibuch EE, Wang JQ. Propofol inhibits phosphorylation of N-methyl-D-aspartate receptor NR1 subunits in neurons. *Anesthesiology.* 2006;104(4):763–769.
51. Kienbaum P, Scherbaum N, Thürauf N, Michel MC, Gastpar M, Peters J. Acute detoxification of opioid-addicted patients with naloxone during propofol or methohexital anesthesia: a comparison of withdrawal symptoms, neuroendocrine, metabolic, and cardiovascular patterns. *Crit Care Med.* 2000;28(4):969–976.
52. Subramaniam K, Gowda RM, Jani K, Zewedie W, Ute R. Propofol combined with lorazepam for severe poly substance misuse and withdrawal states in intensive care unit: a case series and review. *Emerg Med J.* 2004;21(5):632–634.
53. Feng JQ, Kendig JJ. Propofol potentiates the depressant effect of alfentanil in isolated neonatal rat spinal cord and blocks naloxone-precipitated hyperresponsiveness. *Neurosci Lett.* 1997;229(1):9–12.
54. Barr J, Egan TD, Sandoval NF, et al. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic-pharmacodynamic model. *Anesthesiology.* 2001;95(2):324–33.
55. Hensel M, Kox WJ. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anaesthesia: a prospective study in methadone, heroin, codeine and morphine addicts. *Acta Anaesthesiol Scand.* 2000;44(3):326–333.
56. Schroeppel TJ, Fabian TC, Clement LP, et al. Propofol infusion syndrome: a lethal condition in critically injured patients eliminated by a simple screening protocol. *Injury.* 2014;45(1):245–249.
57. Krajčová A, Waldauf P, Anděl M, Duška F. Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. *Crit Care.* 2015;19:398.
58. Meyers RS, Thackray J, Matson KL, et al. Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List. *J Pediatr Pharmacol Ther.* 2020;25(3):175–191.
59. Castagno E, Fabiano G, Carmellino V, et al. Neonatal pain assessment scales: review of the literature. *Prof Inferm.* 2022;75(1):17–28.