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REVIEW

Procedural sedation and analgesia in the pediatric intensive care unit

Ivana Budic[1,2,*], Vesna Marjanovic[1,2], Ivona Djordjevic[2,3], Marija Stevic[4,5], Dragoljub Zivanovic[2,3], Dusica Simic[4,5]

[1]Clinic for Anesthesiology and Intensive Care, University Clinical Centre Nis, 18000 Nis, Serbia
[2]Medical Faculty, University of Nis, 18000 Nis, Serbia
[3]Clinic for Children's Surgery, University Clinical Centre Nis, 18000 Nis, Serbia
[4]University Children's Hospital, 11000 Belgrade, Serbia
[5]Medical Faculty, University of Belgrade, 11000 Belgrade, Serbia

***Correspondence**
md.ivanabudic@gmail.com
(Ivana Budic)

Abstract

Children frequently experience more painful, stressful, and traumatic medical procedures and treatments in the pediatric intensive care unit (PICU) than when they are hospitalized in general wards. An essential part of care in the PICU is providing critically ill children with appropriate sedation and analgesia. Finding the perfect combination of adequate analgesia and sufficient sedation in a patient group with a wide range of ages, sizes, and developmental stages can be challenging. Administration of sedatives and analgesics to critically ill patients may be challenging and complicated by unpredictable pharmacokinetics (PK) and pharmacodynamics (PD). It is important to keep in mind that optimal agents for procedural sedation and analgesia (PSA) differ from those used for long-term sedation in the PICU. In addition to pharmacological measures, different non-pharmacological methods can be applied and have been shown to be effective for pain relief in children. Efforts are being made to improve PSA management with the use of national surveys, recommendations and guidelines.

Keywords

Procedural sedation; Procedural analgesia; Neonate; Child; Intensive care unit

1. Introduction

Due to the nature of the pediatric intensive care unit (PICU), children frequently undergo more painful and stressful medical procedures and traumatic treatments than children who are hospitalized in general wards [1]. As opposed to adults, most children are unable to comprehend the necessity of medical intervention and often refuse to comply with medical professionals. Furthermore, children require invasive testing, monitoring, and challenging, frightful medical procedures in the PICU, requiring the administration of analgesics and sedatives [2]. Even in the PICU, pediatric patients have historically, for a long time, been restrained physically during procedures [3]. Because untreated pain frequently has both short- and long-term physiological, physical, and psychological consequences for children, it is practically necessary to relieve fear and procedural pain in children [4].

Procedural sedation and analgesia (PSA) are defined as the administration of amnestic, anxiolytic, or analgesic agents, which facilitates the completion of painful procedures, ensures the immobility and safety of the patient, and prevents the child from remembering or feeling the interventions [5, 6]. PSA practices need to be based on valid, high-fidelity research [7]. Finding the perfect combination of adequate analgesia and sufficient sedation in a patient group with a wide range of ages, sizes, and developmental stages can be challenging [2]. The added difficulties of critical illness in the pediatric population, such as evolving pathophysiology, impaired organ function, and changed pharmacodynamics and pharmacokinetics, must be considered [8].

Undersedation induces physical and psychological distress, may lead to adverse events such as unplanned extubation and unintended removal of catheters, and may also have long-term consequences. On the other hand, excessive sedation puts the child at risk of prolonged respiratory support, an extended stay in the intensive care unit, the development of tolerance to opioids and benzodiazepines, as well as an elevated possibility of withdrawal syndrome [9]. Interventions to reduce pain cannot be "one size fits all" due to the variability of this patient population. It is necessary to have a better grasp of the different types of pain and how they are identified and managed in PICUs [10]. Studies already conducted on PICUs have mostly used data gathered from adult intensive care unit (ICU) patients and have failed to take into account the heterogeneity of pediatric patients or the physiological, anatomical, and biological differences between children and adults [11].

With a focus on the issues that arise most frequently, the objective of this mini-review is to present the most recent and pertinent research that covers significant elements of procedural sedation and analgesia in the PICU.

2. Methods

The electronic search for this mini-review included three databases, PubMed, EMBASE, and Google Scholar, and used search terms: "procedural sedation", "procedural analgesia",

"pediatric", "neonate", "infant", "child", "intensive care". Articles containing full texts and studies involving newborns and children met the inclusion criteria. Articles that were not in English or that fell under the category of "gray literature" were excluded. A manual search among the cited references from the publications that were found in the initial round of searching led to the discovery of additional references. Seventy-one papers that were confirmed to be eligible for the study were found after the search was restricted to works published between 2010 and 2022. Due to a lack of available literature, papers published prior to 2010 were included for some issues.

3. Pharmacological aspects of PSA in PICU

3.1 Pharmacokinetics/pharmacodynamics

Very few studies have evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) properties of analgesic and sedative drugs in critically ill patients. Also, it is important to keep in mind that optimal agents for PSA differ from those used for long-term sedation in the PICU [6]. Despite the aforementioned, administration of sedatives and analgesics to critically ill patients may be challenging and complicated by unpredictable PK and PD due to internal factors (impaired organ function, drug interactions, altered protein binding, and fluctuating volumes of distribution) as well as external factors that can change the PK and PD of drugs (renal replacement therapy, extra-corporeal membrane oxygenation, therapeutic hypothermia) [2, 12]. The lowest dose of a drug with the highest therapeutic index for the procedure should be administered [7]. It should be emphasized that the PK and PD profiles of sedatives and analgesics in the PICU context have become even more complicated as a result of recent improvements in neonatal resuscitation and a significant decrease in mortality [2].

The PK of drugs in infants and children is strongly influenced by developmental changes in absorption, distribution, metabolism, and elimination. Children undergo many PK alterations as they grow and mature; drug distribution changes, hepatic enzymatic capacity matures, and renal function develops. P-glycoprotein expression is a cell membrane efflux transport protein crucial for the passage of opioids over the blood-brain barrier. The P-glycoprotein levels in the brain reach adult levels by the age of 3 to 6 months [13]. In comparison to adults and children, neonates and infants have higher fentanyl clearance and volume of distribution (Vd), which is likely due to increased hepatic blood flow and/or different protein binding [14]. The biotransformation capacities of all the phase I and II hepatic enzymes mature at different rates. For example, cytochrome P450 3A4 (CYP3A4) is responsible for primarily metabolizing midazolam. Because of the immature CYP3A4 enzyme activity in an infant, a decreased clearance of midazolam would be expected. As a result, the dosing regimen for adults cannot be simply or linearly extrapolated to children, especially in neonates and infants [15]. Polymorphisms of genes that participate in sedatives and analgesics metabolism promote the individual variability of drug response [16] and could contribute to the ontogenic alterations in drug disposition, drug response, and clinical application.

In everyday clinical practice it is noticed that the severity of the critical illness itself may have a significant impact on analgesia and sedation. For example, the underlying illness of a critically ill child (*e.g.*, sepsis) will influence the response to the administered drug to be different compared to a healthy child [17].

3.2 Pharmacological agents

The choice of drug and the route of administration used during PSA in the PICU should consider the criteria related to the type of procedure that the patient will undergo, as well as the criteria related to the baseline state and comorbidities. Benzodiazepines and opioids are traditionally used for PSA in the PICU, α-2 agonists and intravenous anesthetics are used as adjuncts in the therapeutic arsenal.

Benzodiazepines are hypnotic sedative agents. They bind to postsynaptic gamma-aminobutyric acid (GABA) receptors and increase the permeability to chlorine ions, leading to hyperpolarization and stabilization of the neuronal membrane. Benzodiazepines have hepatic metabolism and renal excretion and exhibit pharmacological effects such as sedation, hypnosis, anxiety reduction, amnesia, muscle relaxation, and anticonvulsant effects [18]. Concerns about benzodiazepines have recently emerged. Drugs acting on the γ-aminobutyric acid (GABA) receptor might promote a neurotoxic effect, especially in patients younger than 3 years [19, 20]. Additionally, it has been found that benzodiazepines directly and dose-dependently contribute to the emergence of delirium in critically ill children [21–23].

Opioids modulate the cortical perception of pain. At equianalgesic doses, all of the μ-opioid receptor agonists have similar pharmacodynamic effects that include analgesia, respiratory depression, sedation, nausea and vomiting, pruritus, constipation, miosis, tolerance, and physical dependence. Elimination half-life is prolonged in neonates due to reduced hepatic activity and blood flow [24]. Fentanyl is the most commonly used analgesic for procedures and pain control in the PICU.

In contrast to opioids and benzodiazepines, α-2 agonists like clonidine and dexmedetomidine induce relatively minimal respiratory depression [6]. Dexmedetomidine (DEX), an α-2 agonist with characteristics resembling those of clonidine, has just lately become a procedural sedation alternative. While still providing anxiolysis, dexmedetomidine enables children to cooperate during procedures and keeps their respiratory drive. A highly selective agonist of the α-2 adrenergic receptor, DEX has a better pharmacokinetic profile than clonidine [6].

Propofol, a diisopropyphenol anesthetic and a GABA receptor agonist, is useful for procedural sedation in the PICU, because of its quick onset (30 sec), high potency, constant production of the required sedative effect, and brief duration of action (4–10 min) [2]. Propofol has several cardiovascular effects, with hypotension being the most significant.

TABLE 1. The recommended doses of pharmacological agents used for PSA in the PICU [6, 18, 26, 27].

Drug class	Route	Dosage	Pharmacodynamic properties		Indications and special considerations	Adverse effects
			Onset of action	Duration of action		
Benzodiazepines						
Midazolam						
	IV	0.1–0.2 mg/kg	1–3 min	30–60 min	Minimal sedation	Accumulation in hepatic/renal failure
	IM	0.1–0.3 mg/kg	5–10 min		Fast acting	Paradoxical CNS stimulatory effect
	PO	0.4–0.5 mg/kg	10–30 min			
	IN	0.2–0.4 mg/kg	5–10 min			
	PR	0.3–0.5 mg/kg	10–30 min			
Diazepam						
	IV	0.04–0.3 mg/kg	1–3 min	25–60 min	Poor choice for PSA due to long half-life	Pain, phlebitis after IV administration
	PO	0.25–0.3 mg/kg	30–60 min	2–3 h		Accumulation in hepatic/renal failure
	PR	0.25–0.5 mg/kg	7–15 min	2–3 h		
Lorazepam						
	IV	0.02–0.1 mg/kg	1–5 min	3–4 h	Poor choice for PSA	Propylene glycol toxicity
	IM	0.05 mg/kg	10–20 min	3–6 h	Metabolism independent of liver and kidney function	Could cause acidosis seizures and renal failure
	PO	0.05 mg/kg	30–60 min	3–6 h		
Alpha-2 agonists						
Clonidine						
	IV	1–2 µg/kg	10 min	3–7 h	Anxiolysis	Bradycardia
	IN	3–4 µg/kg	>30 min		Slow onset	Rebound hypertension
	PO	2–4 µg/kg	90–120 min		Minimal effect on respiratory function	
Dexmedetomidine						
	IV	1 µg/kg over 10 min	5–10 min	1–3 h	Sedation (moderate and deep), small analgesic effect	Bradycardia
		0.2–0.7 µg/kg/h (continuous infusion)				
	IN	2–3 µg/kg	10–30 min	1–1.5 h	Minimal effect on respiratory function	Hypotension
	PO	2–3 µg/kg	25–35 min	1–2 h		Arrhythmia
Barbiturate						
Thiopental						
	IV	4–6 mg/kg	20–40 sec	5–15 min	Profound sedation Decreases intracranial pressure	Significant hypotension in hypovolemic patients Respiratory depression Apnea

TABLE 1. Continued.

Drug class	Route	Dosage	Pharmacodynamic properties		Indications and special considerations	Adverse effects
			Onset of action	Duration of action		
Other						
Propofol						
	IV	1–2 mg/kg (bolus) 6–10 mg/kg/h (continuous infusion)	30 sec	4–10 min	Sedation (moderate or deep) Fast-acting, short half-life	Injection pain Cardiovascular depressant Could cause propofol infusion syndrome (PRIS)
Esketamine						
	IV	0.5–2 mg/kg (bolus)	30–60 sec	5–15 min	Dissociative sedation (moderate or deep)	Nausea, salivation
		0.25–1.0 mg/kg repetition				
	IM	2–4 mg/kg	5–6 min	40–50 min	Analgesia No effect on respiratory drive	Raise intracranial pressure
	IN	2–4 mg/kg	4–6 min	30–70 min	May be combined with midazolam (“ketazolam”) or propofol (“ketofol”)	Hypertension
Etomidate						
	IV	0.2–0.3 mg/kg	30–60 sec	5–15 min	Fast and short sedation	Injection pain Myoclonus Transient adrenal suppression
Opioids						
Fentanyl						
	IV	1–2 µg/kg	1–2 min	30–60min	Analgesia	Bradycardia
	IN	1–2 µg/kg	2–3 min	30–60 min	Rapid onset Procedures with moderate to severe pain	Apnea Chest wall rigidity
Alfentanil						
	IV	5–10 µg/kg	1–2 min	30–60 min	Analgesia	Bradycardia
	IN	10 µg/kg	1–2 min	30–60 min	Rapid onset Procedures with moderate to severe pain	Apnea
Remifentanil						
	IV	1–3 µg/kg	<1 min	5–10 min	Analgesia	Bradycardia
		0.1–0.3 µg/kg/min (continuous infusion)			Rapid onset Procedures with moderate to severe pain	Apnea
Morphine						
	IV	0.05–0.2 mg/kg 10–40 µg/kg/h	20 min	60–90 min	Analgesia Procedures with moderate to severe pain	Histamine release Vasodilation Hypotension Nausea

PSA, procedural sedation and analgesia; CNS, central nervous system; IV, intravenous; IM, intramuscular; PO, oral route; IN, intranasal; PR, per rectum.

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist that has been available since the mid-20th century. It makes sense that ketamine is a useful opioid adjuvant because NMDA receptors have been proven to play a significant role in the development of central sensitization [25]. When administered intravenously, ketamine has a quick onset of 30 to 60 seconds; effective procedural sedation conditions are attained in 1 minute and last for up to 15 minutes.

Etomidate is a carboxylated imidazole ring-containing intravenous anesthetic agent used as an ultra-fast acting (onset 30–60 sec) sedative-hypnotic agent that binds to GABA receptors in the central nervous system (duration of action 5–15 min). As etomidate possesses limited analgesic properties, it should be coadministered with an analgesic drug [18].

The recommended doses of pharmacological agents used for PSA in the PICU are presented in Table 1. The key to success and safety is to titrate drugs based on the patient's response and the onset time of the drug(s) administered [27].

Combinations of different drugs can also be used to provide procedural sedation in the PICU. A combination of ketamine and propofol ("ketofol") allows a smaller dose of each one, thus potentially improving the quality, safety, and duration of recovery time [28]. With few side effects, procedural sedation in the PICU using ketamine and midazolam is considered generally safe [29].

Naloxone and flumazenil boluses are used for reversal of unwanted opioid- and benzodiazepine-induced respiratory depression and oversedation.

The use of potent inhalational anesthetics for sedation in the PICU environment is still relatively new. An alternative to current protocols of intravenous sedation for patients requiring intensive care is the Anesthetic Conserving Device, also known as "AnaConDa®" (ACD, Hudson RCI, Upplands Väsby, Sweden). It is a modified heat-moisture exchanger that may allow a streamlined method of administering inhalational anesthetic agents in the ICU setting [30]. One of the first to report the use of the AnaConDa device as an adjunct to extubation in a pediatric burn patient was Jung *et al.* [31] in 2008.

Most sedatives and analgesics in the PICU are administered intravenously. Enteral administration may lead to sub-optimal analgesia and sedation due to a slower onset or a prolonged and unpredictable duration [32]. In addition, in many children, especially in surgical intensive care units, enteral intake is stopped. Intranasal (IN) drug administration has become an alternative way to less invasive and quick delivery of drugs, mainly in pediatric emergency departments when intravenous access is not yet established. The dose of IN midazolam used in the different studies ranged between 0.2 mg/kg and 0.4 mg/kg or 0.5 mg/kg [33, 34]. Fentanyl is generally administered IN at a dose of 1.5–2 μg/kg [35]. Dexmedetomidine is administered at a dose of 2–4 μg/kg [36]. A wide dose range of IN ketamine is used in children (3–9 mg/kg) [37], compared to 2–4 mg/kg in neonates [38]. Drug administration via the IN route may be distressing to some children.

4. Non-pharmacological measures

The high safety profile of non-pharmacological measures is one of their main benefits. Most crucially, even though the benefits are modest, all non-pharmacological approaches have a very favorable benefit-to-risk ratio because the risk is extremely low. The main advantages of non-pharmacological therapies include simplicity of use, apparent safety, viability, and simplicity of learning, all of which would permit the universal application of any of these interventions [39].

Non-pharmacological measures could be divided into five main groups (Table 2).

TABLE 2. Non-pharmacological measures for procedural sedation and analgesia [23, 39–42].

Non-pharmacological measures	Methods and techniques
Environmental control	
	Skin-to-skin contact
	Swaddling
	Facilitated tucking
	Lighting optimization
	Minimization of noise
	Concentrating the procedures on daytime
Feeding methods	
	Non-nutritive sucking
	Sucrose/glucose solutions
Cognitive techniques	
	Distraction techniques
	Active distraction
	Video games, virtual reality goggles
	Passive distraction
	Audiovisual (music and cartoons)
	Acupressure
	Massage
Complementary techniques	
	Toy therapy
Physical methods	
	Comfort position
	Heat/cold therapy

Bucsea *et al.* [40] indentified proximal and distal nonpharmacological interventions in newborns. By giving soothing tactile stimuli prior to, during, and/or after the painful procedure, proximal approaches to pain management help newborns to reduce discomfort and achieve baseline states.

For the most common painful procedures in newborns, a lot of research supports the analgesic efficacy of sweet solutions [43, 44], non-nutritive sucking [45], breastfeeding [46], and skin-to-skin contact [47, 48]. The use of either approach alone

has been demonstrated to be less effective than combinations (*e.g.*, music therapy and sucrose). For many neonates receiving invasive or non-invasive ventilation in the ICU, breastfeeding may be impossible.

In order to reduce the neonate's pain response and pain-related suffering, distal pain management therapies involve altering the environment of the newborn [40]. Sedatives and analgesics can be reduced by optimizing the sleep-wake cycle with simple non-pharmacological interventions such as exposing them to sunlight during the day and reducing noise at night [6].

The use of non-pharmacologic pain therapy varies among PICUs and may be underreported or underutilized [41].

5. Discussion

Pain relief is a basic human right at any age. Children have historically received inadequate care for discomfort and invasive treatments. Many medical professionals held the opinion that children do not remember or feel pain to the same degree as adults. Due to the intrinsic difficulty in identifying pain in newborns and the widespread misconception that neonates lack the required physiological pathways for pain transmission, this age group has historically received less attention. Early neonatal exposure to untreated pain has been associated with a variety of deleterious short- and long-term effects, including the emergence of pain hypersensitivity, negative psychological symptomology, and altered neurodevelopment [49]. Researchers also found that intensive care units are the most common places where term and preterm newborns are exposed to uncontrolled and repetitive pain [50]. These exposures may affect the infants' perception of pain in later infancy and negatively impact their neurodevelopmental outcomes in terms of cognition [51], motor function [52], and brain development [53, 54].

It is already common knowledge that infants hospitalized to critical care units (ICU) endure a number of painful treatments during their stay. A newborn may require up to 14 attempts to successfully insert an intravenous cannula, according to the Epidemiology of Procedural Pain in Neonates (EPIPPAIN 1) study, which collected data in 2005–2006 [50]. According to available literature, the most frequently performed and most painful procedures in the PICU are listed in Table 3.

Courtois *et al.* [58] reported that neonates admitted to ICUs typically required 3.8 venipunctures over the course of an 8-day stay. Furthermore, one-quarter of neonates required more than five venipunctures, 76 percent of venipunctures required preprocedural specific analgesia, with wide variations in center practices, and only 61.7 percent of venipunctures were successful on the first attempt. According to their findings, 38.3 percent of venipunctures required more than one try, with 20% requiring three or more. A mean of 7.5–17.3 painful procedures per patient per day in the neonatal intensive care unit (NICU) setting were reported in a systematic review of 18 papers by Cruz *et al.* [59]. In an attempt to provide an in-depth analysis of the prevalence of painful and stressful procedures in the PICU, Barslaag *et al.* [12] conducted a prospective observational cohort study that included 229 patients, accounting for 955 patient days. Based on their research, the median number of painful and stressful procedures per patient per day was 11. The most prevalent procedure (45%) was endotracheal suctioning, which was followed by oral and nasal suctioning. The most painful procedures were rated as arterial and lumbar punctures, peripheral IV cannula insertion, and venipuncture. Mechanically ventilated patients underwent significantly more painful procedures than non-ventilated patients. They found that procedural analgesia or sedation was often not used during these most painful procedures.

TABLE 3. Most frequently performed and most painful procedures in PICU [12, 55–57].

Most frequently performed	Most painful
Endotracheal suctioning	Chest tube removal
Oral/nasal suctioning	Wound drain removal
Finger prick/heel prick	Arterial line insertion
Peripheral IV cannula insertion/removal	Lumbar puncture
Nasogastric tube insertion	Peripheral IV cannula insertion
Adhesive removal	Urinary catheter insertion
Wound dressing	Suctioning
Arterial line insertion	Finger prick/heel prick
Nasal flow cannula placement	Peripheral blood draw
Urinary catheter insertion	Subcutaneous injection

IV, intravenous.

Indeed, very little is known about international sedation and analgesia practices at the bedside. Efforts are being made to improve analgesia and sedation management with the use of recommendations [23], national surveys, and guidelines [60–66], but in practice, many guidelines are based on experts' consensus, experience, local protocols, or even personal preferences. Even more, studies show gaps between health professionals' knowledge and practice for the management of pain [50]. A secondary analysis of the EPIPPAIN 1 study found that the use of specific analgesics for painful procedures in ICUs was more frequent during the daytime than at night. Moreover, a sharp decrease in the use of analgesics from morning to afternoon, followed by a gentle decline thereafter, was described, which can be considered an indicator of poor quality care that needs to be overcome [67]. Despite the distribution of national guidelines, Lago *et al.* [68] discovered a generally common but incredibly varied use of procedural sedation and analgesia in Italian NICUs. In a level III NICU in India, pharmacological agents were used in 33.48 percent of the procedures, according to a study by Kothari *et al.* [56]. This suggests poor pain management practices and emphasizes the urgent need for education of NICU nurses, residents, fellows, and attendings. Almost two-thirds of the time, no pharmaceutical pain relief methods were used, and when administered, the pharmaceutical agents were rarely intended for pain relief.

There are global initiatives that are trying to overcome this problem. By giving special recognition to institutions that meet the requirements, the ChildKind program aims to raise

the standard of pediatric pain management in hospitals. It serves as an alternative to other models that could be more punitive in nature and frequently have less success in altering the institution's established culture [69].

It is important to keep in mind the numerous challenges associated with applying procedural sedation and analgesia, even in the PICU. Apnea, hypotension, laryngospasm, bradycardia, clinically evident pulmonary aspiration, total airway obstruction, lifelong neurological impairment, or even death, are examples of significant adverse events [4]. Green *et al.* [70] concluded that aspiration during procedural sedation appeared rare and idiosyncratic. Children treated with midazolam, propofol, and morphine were more likely to experience high levels of post-traumatic stress syndrome (PTSS) within one month of being released from the PICU [1].

Due to the fact that many sedatives given to children are used off-label or unlicensed and have not completed the strict testing requirements to be approved for pediatric usage, children represent an at-risk population [12, 71].

Limitations of the published studies should also be taken into account, as there is a risk of bias by under-reporting of painful and stressful procedures in the PICU. Baarslag *et al.* [12] pointed out that the painfulness of a procedure can vary within and between patients and that caregiver perceptions of pain may also affect pain management (*e.g.*, topical anesthesia is frequently used before peripheral IV cannula insertion but is rarely ever used before heel or finger sticks). On the other hand, it is possible that the caregivers, knowing that they are participating in the study, slightly modify their practices that result in greater attention to pain management [58].

6. Conclusion

Due to the fact that children often experience physiological, physical, as well as psychological effects from untreated pain, adequate procedural sedation and analgesia are morally necessary during painful and stressful procedures in the ICUs. A rational choice for a particular agent should be based on the desired effects of the drug, its pharmacokinetic properties, and its side-effects. Different non-pharmacological methods can be applied and have been shown to be effective for pain relief in children.

It would be wise to take steps to cut down on the number of painful and stressful procedures in the PICU. One of the measures would be re-evaluating the indications that should be supported by current evidence. Another way is to improve technical skills to reduce the number of attempts for certain procedures that require multiple attempts.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

IB, VM and MS—designed the research study; IB and VM—performed the research; ID, MS and DZ—analyzed the data; IB and MS—wrote the manuscript; DS—supervised and reviewed. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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