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Review

Sedation level with midazolam: A pediatric surgery approach

Carmen Flores-Pérez [a,b,*], Luis Alfonso Moreno-Rocha [c], Juan Luis Chávez-Pacheco [a], Norma Angélica Noguez-Méndez [d], Janett Flores-Pérez [a], María Fernanda Alcántara-Morales [a], Luz Cortés-Vásquez [e], Lina Sarmiento-Argüello [e]

[a] Laboratorio de Farmacología, Instituto Nacional de Pediatría (INP), Ciudad de México, México
[b] Doctorado en Ciencias Biológicas y de la Salud, Universidad Autónoma Metropolitana (UAM), Ciudad de México, México
[c] Laboratorio de Farmacocinética y Farmacodinamia, UAM Xochimilco, Ciudad de México, México
[d] Laboratorio de Farmacia Molecular y de Liberación Controlada, UAM Xochimilco, Ciudad de México, México
[e] Departamento de Anestesiología, INP, Ciudad de México, México

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ABSTRACT

Midazolam (MDZ) is a short-acting benzodiazepine that is widely used to induce and maintain general anesthesia during diagnostic and therapeutic procedures in pediatric patients due to its sedative properties. The aim of this study was to perform a systematic review without a meta-analysis to identify scientific articles and clinical assays concerning MDZ-induced sedation for a pediatric surgery approach. One hundred and twenty-eight results were obtained. After critical reading, 37 articles were eliminated, yielding 91 publications. Additional items were identified, and the final review was performed with a total of 106 publications.

In conclusion, to use MDZ accurately, individual patient characteristics, the base disease state, comorbidities, the treatment burden and other drugs with possible pharmacological interactions or adverse reactions must be considered to avoid direct alterations in the pharmacokinetics and pharmacodynamics of MDZ to obtain the desired effects and avoid overdosing in the pediatric population.

Contents

Abbreviations: MDZ, Midazolam; Vd, Distribution volume; CL, Clearance; $t_{1/2}$, Elimination half-life; PopPK, Population pharmacokinetics; NONMEM, Nonlinear mixed effects modeling; GABA, Gamma-aminobutyric acid; BIS, Bispectral index; EEG, Electroencephalogram; CNS, Central nervous system.

* Corresponding author at: Laboratorio de Farmacología, Instituto Nacional de Pediatría, 04530 Ciudad de México, México.
E-mail addresses: afloresp@pediatria.gob.mx (C. Flores-Pérez), lamoreno@correo.xoc.uam.mx (L.A. Moreno-Rocha), jchavezp@pediatria.gob.mx (J.L. Chávez-Pacheco), nanoguez@correo.xoc.uam.mx (N.A. Noguez-Méndez), mfloresp@pediatria.gob.mx (J. Flores-Pérez), mafer.alcmor27@gmail.com (M.F. Alcántara-Morales), acortesv@pediatria.gob.mx (L. Cortés-Vásquez), lsarmientoa@pediatria.gob.mx (L. Sarmiento-Argüello).

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1. Introduction

Midazolam (MDZ) is a drug that belongs to the benzodiazepine category; it was approved for clinical use in 1976 as a hypnotic sedative drug and for the treatment of refractory seizure crises, as well as for the induction and maintenance of general anesthesia, with the purpose of achieving sedation in diagnostic or therapeutic procedures (Olkkola and Ahonen, 2008; Young and Mangum, 2010).

Anesthesiologists are directly responsible for anesthesia during surgical procedures, including pediatric surgeries in which extremely careful medication dosage is required.

Due to the higher probability of adverse reactions such as hypotension and cardiorespiratory depression, among others, when higher doses are administered, it is important to consider all of these factors before calculating and administering the dosage.

On the other hand, it is essential to consider the patient's own characteristics, such as age and nutritional status of the child, that could have a relationship with the administration of midazolam.

Because of the widespread intrahospital use of MDZ for sedation and anesthesia induction in pediatric patients undergoing surgical procedures, the purpose of this review is to discuss various topics related to its classic and population pharmacokinetics, pharmacodynamics, pharmacological interactions, adverse reactions and sedative properties for the benefit of pharmacologists and anesthesiologists who require basic knowledge of this drug and consider these concepts when making decisions in their daily practice.

2. Material and methods

A systematic review without a meta-analysis was performed using biomedical databases, including the Cochrane Database of Systematic Reviews, Embase, Medline (PubMed and Ovid), Scopus and LILACS, to identify articles concerning the use of MDZ in children. No language or time filters were applied, and the following medical subject heading terms were used: midazolam, pharmacokinetics, pharmacodynamics, population pharmacokinetics, sedation, surgery, pediatrics, pharmacological interactions and adverse effects. Preclinical studies and studies involving pregnant, oncologic or neurological patients were excluded.

Thus, one hundred and twenty-eight results were obtained through the database search. After critical reading, 37 articles were eliminated because of irrelevance to the topic, yielding 91 publications. Additional items were identified, and the final review was performed with a total of 106 publications.

3. Results

3.1. MDZ pharmacokinetics

The pharmacological action of MDZ is characterized by a rapid onset due to its fast metabolic transformation. As a result of its low toxicity, MDZ has a wide therapeutic range; moreover, it has rapid and highly intense sedative and soporific effects (Miller et al., 2015). The drug is well absorbed following intramuscular, oral, rectal or intranasal administration. Although MDZ is manufactured as an acid molecule (pH 4) to make it more water soluble, the drug is highly lipophilic within the physiological pH range and rapidly passes through the blood–brain barrier, quickly gaining access to benzodiazepine receptors in the central nervous system (CNS) (Blumer, 1998; García, 2003).

MDZ provides effective sedation with a dose of 0.07 to 0.15 mg/kg in 20-year-olds, with a recommended dose reduction of 15% for each decade younger. Sedation is likely to be effective 20–40 min after administration (Miller et al., 2015). When administered intravenously (IV), the plasma concentration–time curve exhibits one or two distinct distribution phases. The distribution volume (Vd) in the steady state is approximately 0.7–1.2 L/kg, and approximately 96–98% of the drug is bound to plasma proteins, with albumin being the major protein. The MDZ clearance (CL) interval ranges from 6 to 11 mL/kg/min, with an elimination half-life ($t_{1/2}$) of approximately 2.5 h (2.1 h-3.4 h) (Greenblatt et al., 1981; Reves et al., 1985). The MDZ $t_{1/2}$ in children aged < 12 months ranges from 0.8 h to 1.8 h with a renal CL rate of 4.7–19.7 mL/min/kg. In the pediatric population, because of physiological metabolism changes in different life stages, the IV sedative dose is administered according to age and must be calculated according to children's weight and indicated in mg/kg (Table 1). Furthermore, a single intramuscular dose of 0.1 to 0.15 mg/kg is effective for sedation induction, anxiolysis and amnesia before anesthesia (Blumer, 1998).

MDZ undergoes extensive hepatic metabolism by cytochrome *CYP450*, and its major active metabolite is 1-hydroxy-midazolam (Fig. 1) (Link et al., 2007; Reves et al., 1985). This metabolite is con-

Table 1
IV midazolam doses used for sedation in children.

Age (years)	Initial dose (mg/kg)	Total dose (mg/kg)
0.5 to 5	0.05–0.1	$\leq$ 0.6
6 to 12	0.025–0.05	$\leq$ 0.4
>12	0.1	$\leq$ 0.4

jugated with glucuronic acid to form 1-hydroxy-midazolam glucuronide, which lacks biological activity (Blumer, 1998).

Approximately 60% to 80% of the excreted dose in urine is in the form of alpha-hydroxy-midazolam-conjugated glucuronide with a $t_{1/2}$ of 1 h, and <1% of the excreted drug is in its unaltered form (Oldenhof et al., 1988).

Nevertheless, 1-OH-midazolam glucuronide is recognized as having apparent sedative properties at higher concentrations, as observed in adult patients with end-stage kidney disease (Bauer et al., 1995).

3.2. Population pharmacokinetics

Population pharmacokinetics (PopPK) is the study of variability in drug concentrations within a patient population receiving clinically relevant doses of a drug of interest. PopPK methods use mathematical models to describe pharmacokinetics data and draw conclusions. Therefore, this model approaches the inter- and intraindividual variability of serum concentrations of the drug as well as the parameters that determine them when MDZ is administered in standardized conditions in a population group with well-defined characteristics. The elements of this model are a structural model and a variance model.

The structural model consists of a pharmacokinetic model and a regression model. The first model is a conventional pharmacokinetic model, commonly compartmental, while the second model correlates the pharmacokinetic model parameters (CL, Vd, etc.) with continuous variables (age, weight, creatinine CL, etc.) and/or categorical variables (gender, diagnosis, habits, etc.).

On the other hand, the variance model quantifies the magnitude of interindividual pharmacokinetic variability (pharmacokinetic parameters) and residuals (concentrations); the latter variable quantifies the magnitude of the discrepancy between the observed concentration in each individual and the value predicted using the individually obtained pharmacokinetic parameters (Lanao, 2003).

3.3. Methods for the estimation of population parameters

3.3.1. Two-stage models

The first phase separately analyzes the kinetics of each individual, adjusted by concentration/time with a nonlinear regression curve to the selected kinetic model, using a conventional nonlinear regression program that implements weighted least squares.

The second phase statistically analyzes the individual parameters obtained in the first phase, with the aim of estimating the average values of the parameters (fixed effects) and their corresponding variances (random effects).

3.3.2. Mixed-effect models

Mixed-effect models are an alternative to the two-stage methods. The resolution of the model is computationally performed in one stage using specific programs.

A simultaneous estimation is realized with the same adjustment of fixed-effect and random-effect parameters, including interindividual as well as intraindividual ones.

Nonlinear mixed effects modeling (NONMEM) is a computer program for parametric estimations from population data.

Validation for a population program requires the definitive acceptance of a model for its subsequent utilization in clinical practice. Validation can be achieved using type I (prospective) data; it is designed according to the population model, a dosage regimen that allows the obtainment of a certain serum level in the stationary stage. This model works with certain individual data from each patient and takes a complex process to generate.

Data types II and III (retrospective) come from individuals who have received treatment in the past but were not included in the construction of the population model. The information is considered type II when there is only one data point per patient and type III when there are 2 or more data points per patient. Type III is the most frequently used data type for validation.

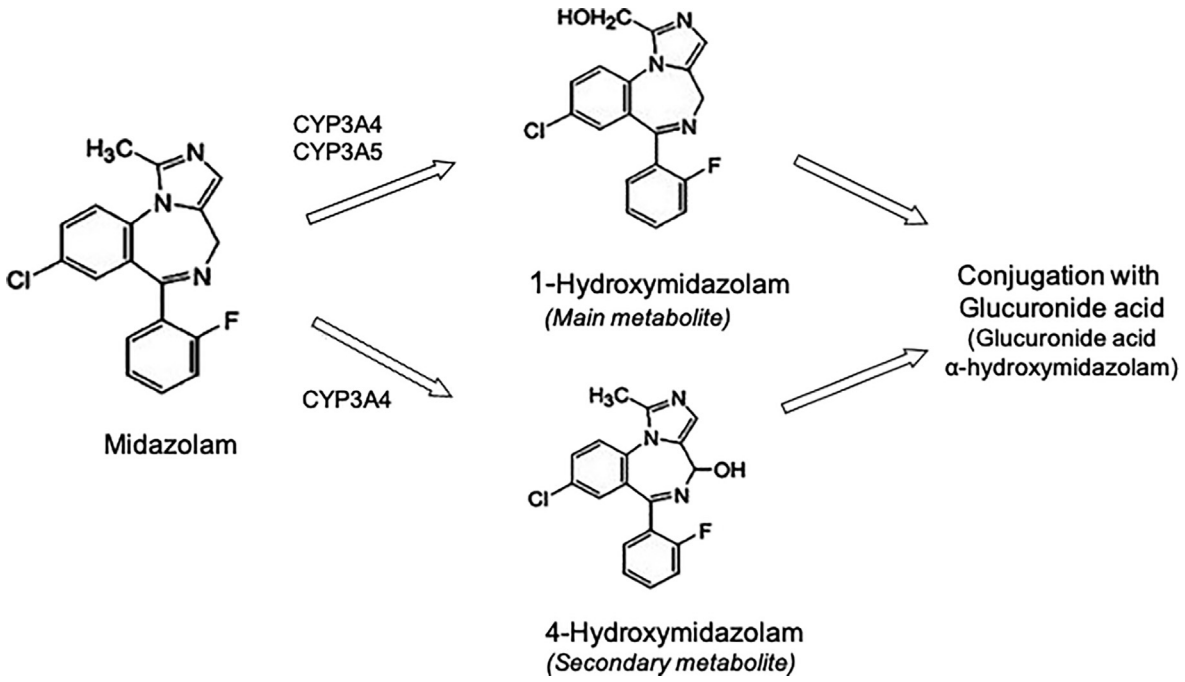

Fig. 1. Metabolic route and metabolites of midazolam (modified from Link et al., 2007; Reves et al., 1985).

Population prediction is based on predicted serum levels in the validation population, while the Bayesian type is based on individual pharmacokinetic parameter estimation in the population using one or two data points per patient with nonlinear Bayesian regression.

Finally, other aspects must be considered, such as average prediction error, which can be evaluated using the average of differences between predicted and observed values, named prediction errors, and standardized prediction errors, which refer to the correlation between prediction errors in the same patient (Lanao, 2003).

On the other hand, there are few studies reported in the literature about clinical trials using a MDZ pediatric population model (Brussee et al., 2019; de Wildt et al., 2003; van Groen et al., 2019; Vet et al., 2016; Völler et al., 2019), which have contributed to this type of population pharmacotherapy within the hospital environment.

3.4. MDZ pharmacodynamics

MDZ exerts a clinical effect by binding to a complex receptor to facilitate the inhibitory effect of the neurotransmitter gamma-aminobutyric acid (GABA). Through this mechanism, MDZ is capable of exerting sedating, anxiolytic, anticonvulsant, muscle-relaxing and amnestic effects in adults as well as in children (Fig. 2) (Bauer et al., 1995; Blumer, 1998; de Wildt et al., 2003; Flores-Pérez et al., 2019; García, 2003; Greenblatt et al., 1981; Link et al., 2007; Oldenhof et al., 1988; Reves et al., 1985).

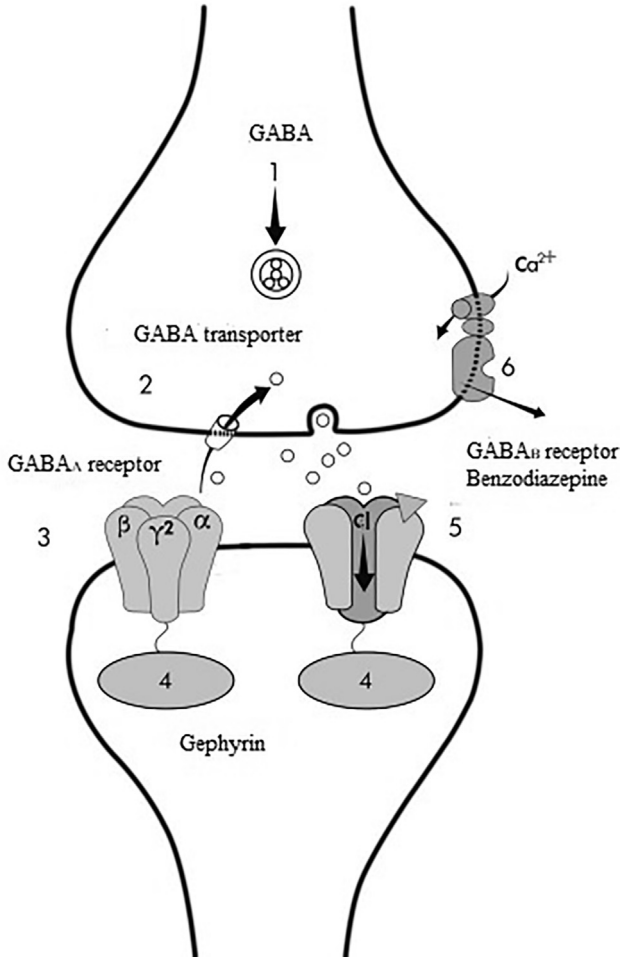

Fig. 2. GABAergic synapse. The neurotransmitter GABA is stored in presynaptic vesicles and later released by exocytosis. When released into the synaptic space, it binds, among others, to postsynaptic GABA-A receptors, which is a pentameric macromolecular complex consisting of 5 subunits around a chloride channel, and in the cytoplasm, the GABA receptor binds to a protein called Gephyrin (modified from Flores-Pérez et al., 2019).

The sedative power of MDZ is approximately 3–4 times stronger than that of diazepam. Thus, it has been associated with a higher amnesia level and major adult patient acceptability with regard to diazepam (Bardhan et al., 1984; Carrougher et al., 1993; Ginsberg et al., 1992; Bianchi Porro et al., 1988).

MDZ allows superior sedation control and prompt recuperation compared to other benzodiazepines, including diazepam, in children (Lloyd-Thomas and Booker, 1986).

The onset time of MDZ IV in adults is approximately 2–2.5 min without premedication with opioids and 1–1.5 min when premedication is administered. The peak effect occurs between 2 and 3 min in healthy adult patients (Kanto, 1985). The lifespan of MDZ action ranges from 2 to 6 h, and patients generally start recovering from the sedative effect after 5–30 min (Booker et al., 1986).

In a clinical trial with children undergoing esophagogastroduodenoscopy, researchers found a positive correlation between plasma MDZ concentrations and the grade of sedation on the COMFORT scale, thus noticing that maximum sedation correlated to a peak plasmatic concentration of 229 μg/L. The sedation peak occurred 5 min after drug administration, and sedation decreased with the plasmatic concentration (Tolia et al., 1991).

Anxiolytic and anticonvulsant effects are achieved with <20% drug–receptor binding. An occupancy rate of 30 to 50% will provoke sedative and amnestic effects, and a hypnotic effect will appear at values higher than 60% (Boussofara and Raucoules-Aimé, 2016).

It is important to consider that the intensity of the clinical effects is related not only to the drug affinity for its receptors but also to the administered dosage. This date must be considered when administering MDZ due to the possible requirement of a dosage adjustment to obtain the desired effect, where overdosing and other adverse effects in the immune and central nervous systems are limited.

Other factors that are responsible for the diversity of the answer secondary to MDZ administration can include some other drugs administered, patient age, other comorbidities (hepatic or renal diseases), general health condition, alcoholism, smoking and hormonal profile (Cheng et al., 2002). Because of the reported difference in *CYP3A4* gut and liver activity and expression in different age groups, it has been observed that MDZ CL is lower in children than in adults (Marcon et al., 2017). In children, the time needed to obtain a clinical effect is greater for MDZ than for any other sedative agent (Sagarin et al., 2002).

3.5. Clinical factors that alter MDZ pharmacokinetics and pharmacodynamics

There are factors inherent in patients who are involved in the metabolism of midazolam. The duration of the effects, the elimination time and the dose necessary to achieve the desired effect are influenced by the presence of active metabolites, interaction with other drugs, metabolism of the medicine, patients premedicated with opioid analgesics, etc. These same aspects are altered by the patient's own characteristics, such as age or nutritional status. Therefore, the patient should be assessed to identify what may increase or decrease the sensitivity to the anesthetic and sedative effects of midazolam. This would help to determine the adequate administration and dosage of the medication for each patient (Checketts et al., 2016; Gan, 2006).

3.5.1. Age

The disposition of the drug can vary between children and adults due to age and to differences in the processes of absorption,

distribution, metabolism and excretion, since children have a smaller intestine and intestinal permeability is altered with advancing age (Brussee et al., 2019; van Groen et al., 2019).

Due to the differences observed in the expression and activity of *CYP3A4* in the liver and intestine in different age groups, it has been observed that the CL of midazolam is lower in children than in adults. In children, the time for the clinical effect is greater for midazolam than for any other sedative agent (Marcon et al., 2017; Sagarin et al., 2002).

Newborns have reduced or immature organ function, so they are vulnerable to the deep and/or prolonged respiratory effects of midazolam. In these patients, the elimination $t_{1/2}$ is from 6 to 12 h on average, and the CL is diminished. Pediatric patients under 6 months of age are particularly vulnerable to obstruction of the airways and to hypoventilation; therefore, it is essential to adjust the doses with small increments as a function of the clinical effects and close control of the respiratory frequency and oxygen saturation. In 3- to 10 year old children, the $t_{1/2}$ after intravenous or rectal administration is shorter (1–1.5 h) than that in adults. The difference is due to the elevated metabolic CL in children of this age group. The high metabolic rate observed in children compared to adolescents is explained by a decrease in the renal CL of α-hydroxy-midazolam related to an early age (Marcon et al., 2017; Sakata, 2010; Spanish Agency of Medicines and Health Products, 2018).

Elderly individuals have diminished liver function due to a decrease in the size of the liver and a reduction in hepatic blood flow. The reduction in metabolic capacity depends on the affected enzymatic system, which supposes interindividual variability in the hepatic CL. In adults older than 60 years, $t_{1/2}$ can be extended up to four times. As a consequence, the interactions are associated with more serious symptoms and have more important consequences than in the young population (Sakata, 2010).

3.5.2. Sex

Midazolam is used for premedication, induction and maintenance of general anesthesia to achieve conscious sedation during diagnostic or therapeutic procedures (Lu et al., 2015; Olkkola and Ahonen, 2008). Regarding the difference by sex, it is known that women have lower cardiac output and therefore lower liver blood flow; however, it is the activity of liver enzymes that is mainly responsible for the differences in metabolism and, consequently, in drug clearance.

Among the differences related to sex in pharmacokinetics and pharmacodynamics include those that refer to physiology, such as body fat content and hormonal influence, among others (Farkouh et al., 2020). Variations in the menstrual cycle occur in the renal, cardiovascular and hematological systems, with the potential to affect protein binding and volume of distribution (Nicolas et al., 2009).

Physiological differences between men and women can explain variations in pharmacokinetics, which have been widely described (Anderson, 2005; Buchanan et al., 2009; Campesi et al., 2012; Franconi et al., 2007, 2011; Marino et al., 2011; Soldin et al., 2011; Spoletini et al., 2012). In fact, in humans, it is estimated that there is a 40% difference in pharmacokinetics between men and women (Anderson, 2005). In general, women are smaller, have more fat and less muscle than men and have lower total body water (~15–20%) than men.

Some of these differences may be related to genetically determined responses (metabolism) to drugs, but most are related to the effect of sex hormones on pharmacokinetics (Franconi et al., 2011).

Sex hormone-dependent physiological differences that can affect drug kinetics include the effect on body mass index and body fat deposition, on absolute and relative water compartments and on plasma proteins. These gender differences in volumes of distribution are especially relevant when drugs are administered in fixed doses (mg) rather than considering body weight or body surface area (mg/kg or mg/m^2), as is frequently observed with agents of premedication and postoperative analgesics (Booij, 2008).

In women, the volume of distribution of lipophilic drugs is increased (Buchanan et al., 2009; Jochmann et al., 2005; Pleym et al., 2003), including benzodiazepines such as diazepam (Greenblatt et al., 1980; Ochs et al., 1982) and midazolam (Greenblatt et al., 1984). The same dose of a lipophilic drug will have a lower serum concentration in a woman compared to a man of the same weight because there is a relatively larger lipophilic compartment in which the drug resides. There are differences in metabolism and transport proteins (Franconi et al., 2007, 2011; Schwartz, 2007; Soldin et al., 2011).

In fact, many of the sex differences could be due to the differential expression of drug metabolism genes between men and women (Restrepo et al., 2009; Scandlyn et al., 2008).

Most studies have failed to find significant sex differences in midazolam metabolism (Greenblatt et al., 1984; Kashuba et al., 1998; Nishiyama et al., 1998; Thummel et al., 1994), with the exception of greater clearance in women (Greenblatt et al., 1986; Kinirons et al., 1999), despite having considered a small sample size.

One reason that may help explain the contradictory results obtained for *CYP3A4* substrates in terms of sex differences in liver metabolism is the presence of the P-glycoprotein transporter (Gandhi et al., 2004). This is a transport protein bound to the membrane that reduces the intracellular concentrations of many types of drugs by promoting drug exit. As a drug must be intracellularly metabolized by *CYP3A4*, more P-glycoprotein in the membrane of hepatocytes will reduce the rate of drug metabolism (Gorski et al., 1998). Men have been found to have more liver P-glycoprotein (Cummins et al., 2002).

This results in higher intracellular drug concentrations in female hepatocytes, with consequent increased metabolism of *CYP3A4*-specific drugs and clearance of those that are substrates for both *CYP3A4* and P-glycoprotein (Gorski et al., 1998). This may therefore explain the sex-based differences in *CYP3A4* activity between midazolam and verapamil, since verapamil is a substrate for both *CYP3A4* and P-glycoprotein, whereas midazolam is only a *CYP3A4* substrate (Gandhi et al., 2004).

3.5.3. Nutritional status

In patients with malnutrition, there is a decrease in plasma proteins, e.g., albumin, which is responsible for the transport of many drugs, including midazolam. This situation leads to alterations in the pharmacokinetics of this drug, which, among others, produces a decrease in its CL (Celis-Rodríguez et al., 2013).

Midazolam accumulates in adipose tissue when it is administered in repeated doses. Hence, obese patients accumulate a greater amount of the drug, which increases the risk for significantly prolonged sedation effects. The $t_{1/2}$ is longer in obese patients than in nonobese patients (5.9 h compared with 2.3 h). This is associated with an increase in the Vd observed in obese adolescents compared with normal weight adolescents. On the other hand, the difference in CL between obese and nonobese patients is not significant (Gan, 2006; Sakata, 2010; van Rongen et al., 2015).

3.5.4. Pharmacological interactions

Pharmacokinetic interactions have been reported with *CYP3A4* inhibitors or inductors and are more markedly seen with oral MDZ administration rather than IV administration specifically because *CYP3A4* is also present in the upper gastrointestinal tract.

This is because systemic CL and bioavailability seem to be altered through oral administration; meanwhile, with the parenteral route, only systemic CL is altered (Spanish Agency of Medicines and Health Products, 2018).

The main MDZ pharmacological interactions are atorvastatin, *CYP3A4* inductors and moderated inhibitors such as dexamethasone, verapamil, propofol, selective serotonin reuptake inhibitors, buprenorphine, and clozapine. Strong *CYP3A4* inductors include carbamazepine, phenytoin, rifampin, azithromycin, erythromycin, mifepristone, oxycodone, theophylline, itraconazole, ketoconazole (systemic), olanzapine, or phenadrine, indinavir, nelfinavir, ritonavir and saquinavir. Table 2 shows some drugs used during minor surgical procedures in pediatric patients. When administered simultaneously, these drugs can interact with MDZ (Ashton, 1994; Fragen, 1997; Nelson and Chouinard, 1999; Spanish Agency of Medicines and Health Products, 2018).

3.5.5. Adverse reactions

The following adverse reactions have more commonly been reported: hiccups, nausea, vomiting, laryngeal spasms, dyspnea, hallucinations, dizziness, ataxia, and involuntary movements. It also produces hypotension, low oxygen saturation and changes in heart rate and respiratory rate (Amrein et al., 1988; Dundee et al., 1984; Reves et al., 1985).

With an overdose, cardiorespiratory depression may occur, as well as apnea, areflexia, respiratory or cardiac failure (usually in combination with other CNS depressor drugs) (Reves et al., 1985).

The complications following insufficient sedation that have been reported are anxiety, fear, agitation, risk of remembering disgusting situations or being conscious of them and the possibility of unintended tearing off medical devices (Fraser et al., 2001). Table 3 shows the main midazolam adverse reactions (Hegenbarth, 2008; Hughes et al., 1994; Nordt and Clark, 1997).

Table 2
Main drugs used in concomitant therapy with midazolam during sedation in pediatric patients undergoing minor surgical procedures.

Drug name	Pharmacological group	CYP3A4 metabolism
Fentanyl	Analgesic, opioid	Substrate (major)
Lidocaine	Antiarrhythmic agent, Class Ib; local anesthetic	Substrate (major)
Propofol	General anesthetic	Substrate (minor), Inhibitor (weak)
Vecuronium	Neuromuscular blocker agent	None known
Ranitidine	Histamine H_2 antagonist	NA
Ketorolac	Analgesic, nonopioid	None known
Dexamethasone	Anti-inflammatory agent, corticosteroid	Substrate (major), Inducer (weak)
Acetaminophen	Analgesic, nonopioid	Substrate (minor)
Ondansetron	Antiemetic, selective 5-HT_3 receptor antagonist	Substrate (major)
Buprenorphine	Analgesic, opioid	Substrate (major)
Morphine	Analgesic, opioid	NA, avoid concomitant use with benzodiazepines when possible
Tramadol	Analgesic, opioid	Substrate (major)
Omeprazole	Proton pump inhibitor	Substrate (minor)

NA = not applicable, the drug metabolism is different from the CYP3A4 pathway.

Table 3
Main midazolam adverse reactions.

System	Adverse reactions
Respiratory system	Bradypnea (>10%), decreased tidal volume (1% to 10%), apnea (children: 3%), cough (1%) and dyspnea, hyperventilation, laryngospasm, bronchospasm and wheezing (<1%)
Cardiovascular system	Hypotension (children: 3%) and bigeminy, bradycardia, tachycardia, premature ventricular contractions (<1%)
Central nervous system	Dizziness (1%), headache (1%), epileptic activity on EEG (children: 1%), dependence (physical and psychological with prolonged use), myoclonus (preterm children), severe sedation, acidic taste, agitation, amnesia, confusion, delirium, euphoria, hallucinations, sialorrhea (<1%)
Gastrointestinal tract	Hiccups (adults: 4%; children: 1%), nausea (3%), vomiting (3%)
Skin and tegument	Injection site reaction (IM: ≤4%, IV: ≤5%; less severity than diazepam), injection site pain (IM: ≤4%, IV: ≤5%; less severity than diazepam) and rash (<1%)
Eyes	Nystagmus (children: 1%)

3.6. Sedation with midazolam

The sedation objective is to generate a status where the patients remain relaxed, calmed and in rational verbal contact with the personnel in charge of their care, i.e., anesthesiologists and surgeons (Rojas-Rivera and Camacho-Aguilar, 2004).

The ideal sedative agent would have a rapid onset of action, be effective in providing adequate sedation and allow prompt recuperation after suspending it, be easy to administer without appreciable accumulation, have minimal adverse reactions, lack any severe pharmacological interactions and be inexpensive (Hansen-Flaschen, 1991).

As mentioned before, benzodiazepines bind to the alpha subunit of the receptor to inhibit GABA. This interaction increases the binding of GABA to the beta subunit, which facilitates chloride conduction through the neuronal membrane, resulting in a hyperpolarized membrane. This primary mechanism of action through the GABA system route is shared with many sedative agents, such as propofol and barbiturates.

Midazolam has the advantage of being a rapid action benzodiazepine with a short $t_{1/2}$. In addition, this drug is water soluble and therefore has no need for propylene glycol in its parenteral fabrication. Propylene glycol is a component widely used along with other benzodiazepines, such as diazepam or lorazepam, and it is related to some adverse effects, such as phlebitis (Blumer, 1998; Reed et al., 2001).

Midazolam can be used for perioperative sedation to reduce anxiety in patients before surgery, especially in regard to pediatric patients who are distressed when separated from their parents to be taken into the operating room. This drug is used in combination with other agents, such as opioids, propofol or barbiturates, to induce general anesthesia. Additionally, it can be administered during surgery to aid anesthesia maintenance in combination with other agents and, if required, can be used in postoperative sedation (Blumer, 1998).

3.7. Sedation scales

Consciousness, sedation and analgesic status evaluation are very subjective, and available tools for monitoring are scant. The most commonly used methods to assess the level of sedation are clinical scales that analyze different physiological parameters. In children, the Ramsay and COMFORT scales are the two major scales used for this purpose, although they have low sensitivity to changes in sedation depth (De Jonghe et al., 2000; Ista et al., 2005).

3.7.1. Ramsay scale

Used since 1974 and modified over time, this scale has remained the same in essence and thus seems to be one of the most applied scales in clinical practice. It has the advantage of being easy and fast to use and indicates the patient's degree of sedation (Table 4) (Concha et al., 2009).

Similar to the COMFORT scale, the Ramsay scale distinguishes 3 levels of sedation, where 0 means no sedation, 2–3 means conscious sedation, and 4–6 means deep sedation.

3.7.2. COMFORT scale

This scale has the advantage of being independent of age, since it uses age-adapted physiological parameters and does not require patient stimulation. The scale is divided into 3 sedation ranges: a score of 8–6 points indicates deep sedation, a score of 17–26 points indicates optimal sedation, and a score of 27–40 points indicates inadequate sedation (Table 5) (Bu and Fuentes, 2007).

3.7.3. COMFORT behavior scale

The COMFORT-Behavior (COMFORT-B) scale is recommended either for assessing pain in non-communicative critically ill pediatric patients or to assess the level of sedation in mechanically ventilated pediatric patients (Smith et al., 2022).

The COMFORT score was initially developed and validated to assess general distress in critically ill pediatric patients but has additionally been shown valid in differentiating pain from other sources of distress. The modified COMFORT-B scale removed the vital sign elements of the COMFORT scale due to concerns regarding their reliability in the assessment of pain and distress during critical illness (Ambuel et al., 1992; Carnevale and Razack, 2002; Ista et al., 2005; Smith et al., 2022; van Dijk et al., 2000).

The COMFORT-B scale consists of the following six behavioral items: alertness, calmness, respiratory response (for ventilated children) or crying (for spontaneously breathing children), body movements, facial tension and muscle tone. Each item has five response alternatives rated 1 to 5 describing the different intensities of the behavior in question. Summing the six ratings lead to a total score theoretically ranging from 6 to 30 (Boerlage et al., 2015). The COMFORT-B scale items are shown in Table 6 (van Dijk et al., 2000, 2005).

The COMFORT-B score can be used to assess both the pain and sedation level, rendering it a reliable tool able to help to prevent over- and undersedation and unnoticed pain (Boerlage et al., 2015; Ista et al., 2005; Johansson and Kokinsky, 2009).

3.7.4. State behavioral scale

The Martha A. Curley group developed the State Behavioral Scale (SBS) to assess sedation in infants and young children aged between 6 weeks and 6 years using mechanical ventilators. This tool can be implemented in cognitively immature patients and includes scores related to the following different dimensions: respiratory drive, cough, response to mechanical ventilation, response to stimulation, response to care provider, tolerance to care, comfortability, and movement after being comforted (Curley et al., 2006). The RESTORE clinical trial showed that the SBS has a good agreement and construct validity in patients aged $\geq$ 2 weeks to < 18 years (Lebet et al., 2017).

In the SBS, negative values are associated with a more sedated state, and a score of −3 reflects an unresponsive patient. A zero score reflects a patient with effective breathing who responds to voices. Positive values are related to agitation, and a score of + 2 reflects a patient who may have difficulty breathing on a ventilator, responds without an external stimulus and can be unsafe to be left alone (Table 7).

Despite the usefulness and applicability of several of the sedation scales, according to the survey (Kudchadkar et al., 2014), most intensivists do not use any. Among those who use them, COMFORT is the most used worldwide; however, the use of the SBS and the Richmond Agitation-Sedation scale is increasing among intensivists in North America.

3.7.5. Richmond agitation-sedation scale

The Richmond Agitation-Sedation Scale (RASS) was developed at Virginia Commonwealth University in Richmond in 2012. The

Table 4
Ramsay sedation scale.

Level 0	Agitated, anxious, restless
Level 1	Relaxed, awake and cooperative
Level 2	Asleep, opens eyes to ambient noise
Level 3	Asleep, brisk response to loud auditory stimuli
Level 4	Asleep, sluggish response only to tactile stimuli
Level 5	Asleep, open his or her eyes but does not talk
Level 6	Hypnosis: unconscious and unresponsive

Table 5
COMFORT sedation scale.

Alertness	
Deeply asleep (eyes closed, no response to any ambient stimuli)Lightly	1
sleep	2
(eyes closed, only slight head movements)Drowsy	3
(closes his or her eyes frequently)Fully awake and alert	4
(sensitive to ambient stimuli)Hyperalert	5
(exaggerated responses to stimuli)	
Agitation	
Calm (serene and relaxed)	1
Slightly anxiousAnxious	2
(child seem to be agitated but calms down when comforted)Very	3
anxious	4
(agitated, difficult to calm down)Panicky	5
(loses control)	
Respiratory response	
No coughing, no spontaneous respiration	1
Spontaneous respirations	2
Resistance to ventilator	3
Resistance to ventilator, regular coughing	4
Fights ventilator; coughs or chokes	5
Physical movement	
No movements Occasionally	1
(<3)Frequent (3 or more)	2
, slight movements	3
Vigorous movements in extremities only	4
Vigorous movements including head and trunk	5
Muscle tone	
Relaxed muscles	1
Reduced muscle tone	2
Normal muscle tone	3
Increased tone with flexion of fingers and toes	4
Greatly increased muscle tone, rigidity in fingers and toes	5
Facial tension	
Facial muscles totally relaxed	1
Facial muscle tone normal	2
Tension evident in some facial muscles	3
Tension evident throughout facial muscles	4
Facial muscles contorted and grimacing	5
Blood pressure (BP)	
Blood pressure under baseline	1
Blood pressure constantly at the arterial baseline	2
Infrequent BP elevations > 15% from baseline	3
Frequent BP elevations > 15% from baseline	4
Persistent BP elevation > 15% from baseline	5
Heart rate (HR)	
Heart rate under baseline	1
Heart rate constantly at baseline	2
Infrequent HR elevations > 15% from baseline	3
Frequent HR elevations > 15% from baseline	4
Persistent HR elevation > 15% from baseline	5

Table 6
COMFORT behavior scale (COMFORT-B).

Alertness	Deeply asleep (eyes closed, no response to changes in the environment)	1
	Lightly asleep (eyes mostly closed, occasional responses)	2
	Drowsy (child closes his or her eyes frequently, less responsive to the environment)	3
	Awake and alert (child responsive to the environment)	4
	Awake and hyperalert (exaggerated responses to environmental stimuli)	5
Calmness-Agitation	Calm (child appears serene and tranquil)	1
	Slightly anxious (child shows slight anxiety)	2
	Anxious (child appears agitated but remains in control)	3
	Very anxious (child appears very agitated and is barely in control)	4
	Panicky (child appears severely distressed with the loss of control)	5
Respiratory response (score only in mechanically ventilated children)	No spontaneous respiration	1
	Spontaneous and ventilator respiration	2
	Restlessness or resistance to ventilator	3
	Active breathing against ventilator or regular coughing	4
	Fighting against ventilator	5
Crying (score only in children breathing spontaneously)	Quiet breathing, no crying sounds	1
	Occasional sobbing or moaning	2
	Whining (monotone)	3
	Crying	4
	Screaming or shrieking	5
Physical movement	No movement	1
	Occasional slight movements (≤3)	2
	Frequent slight movements (≥3)	3
	Vigorous movements limited to extremities	4
	Vigorous movements including the torso and head	5
Muscle tone	Muscles totally relaxed, no muscle tone	1
	Reduced muscle tone, less resistance than normal	2
	Normal muscle tone	3
	Increased muscle tone and flexion of the fingers and toes	4
	Extreme muscle rigidity and flexion of the fingers and toes	5
Facial tension	Facial muscle totally relaxed	1
	Normal facial tone	2
	Tension evident in some facial muscles (not sustained)	3
	Tension evident throughout facial muscles (sustained)	4
	Facial muscles contorted and grimacing	5

Table 7
State behavioral scale (SBS).

Score	Description	Definition
−3	**Unresponsive**	No spontaneous respiratory effort No cough or coughs only with suctioning No response to noxious stimuli Unable to pay attention to care providerDoes not show distress with any procedures (including nausea) Does not move
−2	**Responsive to noxious stimuli**	Spontaneous yet supported breathing Coughs with suctioning/repositioning Responds to noxious stimuli Unable to pay attention to care provider Shows distress during a noxious procedure Does not move/occasional movements of the limbs of shifting of position
−1	**Responsive to gentle touch or voice**	Spontaneous but ineffective nonsupported breaths Coughs with suctioning/repositioning Responds to touch/voices Able to pay attention but drifts off after stimulation Shows distress during procedures Able to calm with comforting touch or voice when stimulus is removed Occasional movements of the limbs or shifting of position
0	**Awake and able to calm**	Spontaneous and effective breathing Coughs when repositioned/occasional spontaneous cough Responds to voices/no external stimulus is required to elicit a response Spontaneously pays attention to care provider Shows distress during procedures Able to calm with comforting touch or voice when stimulus is removedOccasional movements of the limbs or shifting position/ increased movement (restless, squirming)
+1	**Restless and difficult to calm**	Spontaneous effective breathing/having difficulty breathing with ventilator Occasional spontaneous cough Responds to voices/no external stimulus is required to elicit a response Drifts off/spontaneously pays attention to care provider Intermittently unsafe Does not consistently calm, despite 5-min attempt/unable to consoleIncreased movement (restless, squirming)
+2	**Agitated**	May have difficulty breathing with ventilator Coughing spontaneously No external stimulus required to elicit a response Spontaneously pays attention to care providerUnsafe (biting endotracheal tube, pulling catheters, cannot be left alone) Unable to consoleIncreased movement (restless, squirming, or thrashing side-to-side, kicking legs)

RASS is a 10-point scale using 3 defined steps for the levels of sedation and agitation. The RASS uses the duration of eye contact following verbal stimulation as the principal means of titrating sedation. This scale relates to both arousal and content of thought, which are the 2 components of consciousness (Rojas-Gambasica et al., 2016; Sessler et al., 2002).

The steps applied to perform the scale are as follows: *Step 1)* observe patient: patient is alert, restless, or agitated (Score 0 to + 4); *Step 2)* if not alert, state patienťs name and ask the patient to open their eyes and look at the speaker: patient awakens with sustained eye opening and eye contact (Score −1); patient awakens with eye opening and eye contact but not sustained (Score −2), and the patient has any movement in response to voices but no eye contact (Score −3); and *Step 3)* when a response to verbal stimulation is lacking, physically stimulate the patient by shaking their shoulder and/or rubbing the sternum patient has some movement in response to physical stimulation (Score −4) or no response to any stimulation (Score −5). The items are shown in Table 8 (Ely et al., 2003).

In the adult population, the RASS has excellent validity comparable to that of a visual analogue scale and selected sedation scales when used by bedside physicians, nurses, and researchers with minimal training (Sessler et al., 2002). In the pediatric population, there are two studies. One author validated the RASS and compared it to both a visual analog scale and the University of Michigan Sedation Scale in critically ill children. The RASS may allow for more accurate assessments of responsiveness and could improve the ability to conduct research investigating the risk factors and outcomes associated with various levels of sedation and agitation (Kerson et al., 2016). Other work conducted in a Spanish pediatric

Table 8
Richmond agitation-sedation scale (RASS).

Score	Term/Description
+4	**Combative**: Overtly combative or violent, immediate danger to staff
+3	**Very agitated**: Pulls or removes tube(s), has aggressive behavior towards staff
+2	**Agitated**: Frequent nonpurposeful movement, patient-ventilator dyssynchrony
+1	**Restless**: Anxious or apprehensive but movements not aggressive or vigorous
0	**Alert and calm**
−1	**Drowsy**: Not fully alert but has sustained > 10 s awakening with eye contact to voice
−2	**Light sedation**: Briefly < 10 s awakens with eye contact to voice
−3	**Moderate sedation**: Any movement, but no eye contact, to voice
−4	**Deep sedation**: No response to voice but any movement to physical stimulation
−5	**Unarousable**: No response to voice or physical stimulation

population analyzed the RASS's inter-rater reliability and construct validity by comparing the RASS to the COMFORT behavior (COMFORT-B) scale and the numeric rating scale (NRS) and demonstrated that the RASS can distinguish whether a child is agitated, but this scale may not be accurate enough in determining the exact level of agitation in the pediatric population (Tapia et al., 2022).

3.7.6. Bispectral index (BIS)

In recent years, several methods have been developed that allow a more objective analysis of patients' degree of awareness by means of electroencephalogram (EEG) analysis. The most commonly used tools are auditory evoked potentials and the Bispectral index™ (BIS™) (Rampil, 1998; Saboya et al., 2009; Weber et al., 2004). This last method estimates the brain electrical activity degree and therefore the patient sedation degree by means of EEG wave frequency analysis. (Synch-FastSlow %, rapid frequencies/% slow frequencies) (Rampil, 1998).

The BIS™ has been widely used as an objective and continuous patient conscious level measure. EEG information is obtained through an electrode placed in the patient's forehead. Values can oscillate between 0 and 100, understanding 0 as a complete EEG suppression case and 100 when the patient is completely awake. BIS™ monitoring has been validated as a hypnosis measure in children older than 1 year old and adults (Bannister et al., 2001; Denman et al., 2000).

Physician BIS™ interpretation must accompany the assessment of other clinical signs available. BIS™ values are directly related to the sedation scales habitually utilized, such as the Ramsay scale, Sedation-Agitation scale (SAS), Richmond Sedation-Agitation Scale and COMFORT punctuation (Ely et al., 2001; Fraser et al., 2001; Riker et al., 2001; Shah et al., 1996; Takeda et al., 2000; Triltsch et al., 1999; Venn et al., 1999).

It is well known that most published data are related to trials in volunteers (early validation studies) and patients in the operating room. Publications show that the BIS™ functions adequately in the measurement of some drug sedative effects (Shah et al., 1996; Simmons et al., 1999; Triltsch et al., 1999). BIS™ values and intervals are shown in Fig. 3 (Aspect Medical Systems™).

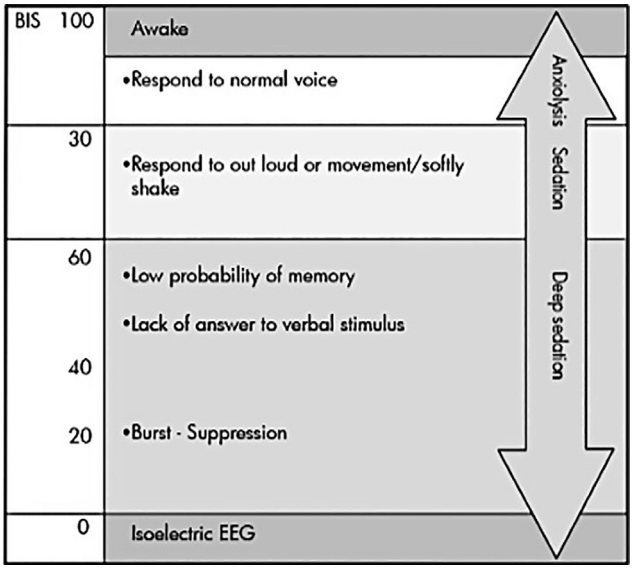

Fig. 3. This scale reflects the association between the patient clinical status and BIS™ values. Intervals are based on multicentric monitoring of BIS™ study results according to the administration of anesthetic agents. Regarding BIS™ values and intervals, it can be assumed that EEG is free of interference that could affect its measurement (Data from Aspect Medical Systems™).

4. Discussion

As evidenced in this article, it is highly important to assess adequate sedation levels in patients to whom MDZ is administered and in the pediatric population in general. The administration of the optimal drug dosage and the use of scales for sedation evaluation are considered necessary for patient monitoring, both with the aim of maintaining effective concentrations that reflect desired effects for patients undergoing diverse surgical procedures in clinical practice.

For adequate MDZ use, each patient's characteristics, base disease state, comorbidities, full complement of drug treatments and other factors related to their condition must be considered because possible pharmacokinetic and pharmacodynamic alterations must be considered.

It is worth mentioning that the clinical effect intensity is related not only to the degree of affinity of the drug for its receptors but also to the administered dose. This must be considered when administering MDZ, as a dosage adjustment may be required to obtain the desired effect while limiting the overdose risk and other adverse reactions in the CNS and immune system.

Some studies have used diverse approaches; however, there is still little information about sedation in pediatric patients. Thus, it would be advisable to perform more controlled clinical trials in this population for adequate control of the sedation effect in children. Therefore, performing pharmacology and biosecurity studies to develop evidence-based dosage regimens and minimize the risk of side effects is currently a priority.

Finally, it is important to emphasize that the main objectives of adequate sedation in children are to reduce adverse effects and complication risks, to avoid protraction of sedative effects, to decrease the length of hospitalization, to achieve an appropriate individualized dosage for the desired effect and to keep each patient stable.

5. Conclusions

In this systematic review, we found a few studies concerning MDZ-induced sedation for a pediatric surgery approach. This drug is widely used before surgical procedures due to its multiple effects, and its sedative effect seems to be the most important in the hospital environment. Although there are several clinical scales to assess MDZ sedative effects, such as the COMFORT and Ramsay scales, they remain subjective and may not assess sedation depth in all cases. Some other tools have been used, including the BIS™

and auditory evoked potentials, which can assess the degree of sedation more objectively; however, these tools are not always accessible.

To use MDZ accurately, individual patient characteristics, the base disease state, comorbidities, the treatment burden and other drugs with possible pharmacological interactions or adverse reactions must be considered to avoid direct alterations in the pharmacokinetics and pharmacodynamics of MDZ to obtain the desired effects and avoid overdosing in the pediatric population. Thus, performing controlled clinical trials in a pediatric population to determine the adequate sedation level with midazolam is recommended.

Ethics approval

Ethics approval not required.

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CFP, LAMR, JLCP and NANM, designed the study and performed the data search; CFP, JFP, MFAM, LCV and LSA analyzed the data and CFP wrote the manuscript.

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