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Combined Dexmedetomidine and Ketamine in Pediatric Anesthesia: A Brief Review

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ABSTRACT

Objectives: This review aims to evaluate the efficacy of the combination of dexmedetomidine and ketamine (KD) and focuses on pediatric perioperative and periprocedural applications of KD as well as its limitations e adverse events. Despite the concomitant use of these two drugs is well described in adult population, there are few studies on its administration in pediatric anesthesia.

Discussion: Drug combination proves to be an attractive regimen when adverse effects of one agent counteract the effects of another. When used together, dexmedetomidine can prevent ketamine's tachycardia, hypertension, sialorrhea and emergency agitation, while accelerating the onset of sedation, thus excluding prolonged dexmedetomidine latency as a single agent. Such profile may be favorable for pediatric patients in order to conceive adequate anxiolysis, prevention of emergency delirium, also allowing its use for procedures with significant algic stimulus. A literature search was conducted in PubMed, Lilacs and Embase to identify 21 articles from 2015 to 2019 that address the use of ketamine and dexmedetomidine simultaneously during anesthetic procedures in population between birth and18 years old.

Conclusion: The literature is favorable to the use of KD for invasive and noninvasive procedures, inside and outside of the operating room, presenting an attractive profile for pediatric patients.

Keywords

Dexmedetomidine, Ketamine, Pediatric anaesthesia.

Abbreviations

KD: concomitant use of ketamine and dexmedetominde; KET: ketamine; DEX: dexmedetomidine; FDA: Food and Drug Administration; ED: emergency *delirium*; PONV: postoperative náusea and vomiting; MAP: mean arterial pressure; Echo: echocardiogram; BMI: body mass index; HR: heart rate; NMDA: N-methyl-D-aspartate.

Introduction

The ideal anesthetic drug consists of rapid onset, short duration,

with limited lipossolubility, predictable response, easy titration, reliable in achieving a desired level of sedation, capable of preserving airway protection and not causing respiratory depression. This agent is also neuroprotective and exhibit minimal cardiovascular response.

Unfortunately, there is no such anesthetic, but some drugs have favorable characteristics and the association of some allows a greater range of desirable effects, but it can also favor the occurrence of adverse effects. Therefore it would be desirable if the adverse effect of one could be abolished by the adverse effect of another.

The adequate use of sedative-hypnotic agents is an integral part

of the patient's comfort and safety and the anatomic, physiologic, pharmacologic and psychological differences between children and adults must be understood when choosing the anesthetic technique. Some peculiarities of this age range make it challenging for the anesthesiologist.

The preoperative period is a stressful event for the majority of individuals undergoing surgery. It is especially true in the pediatric patient and is related to a limited understanding of the nature of the illness and the need of procedure by young children. Pharmacological and behavioral interventions are used to treat preoperative anxiety in children and their parents. The major objectives of premedication are to decrease the stress response with preservation of hemodynamic parameters, facilitate anesthesia induction, enable smooth awakening and produce amnesia [1].

Some commonly used drugs for the anesthetic procedures are at the risk of causing unwanted effects, occasionally promoting complications such as respiratory depression, paradoxical effect, emergence agitation, absence of analgesia and postoperative cognitive impairment. It is imperative the need of more studies available to ensure the use of new techniques. This article aims to study the association of two drugs with an attractive profile for children: ketamine and dexmedetomidine (KD).

Therefore, we accessed PubMed, Lilacs and Embase databases between 2014 and 2019, regarding the use of KD in anesthesia for pediatric patient (birth-18yo), using the keywords "ketamine", "dexmedetomidine" and "pediatric anesthesia".

Review
Sedoanalgesic drugs are commonly used for several medical procedures and the combination KD seems to have favorable characteristics in pediatric population. Ketamine is a phencyclidine derivative that antagonizes the N-methyl-D-aspartate receptor and its action is due to the central dissociation of the cortex from the limbic system, providing both sedative and analgesic properties while preserving upper airway muscular tone and respiratory drive [2], but an unpleasant psychomimetic effects. Dexmedetomidine is a specific central alpha 2-adrenergic agonist that decreases central presynaptic catecholamine release and also has properties of sedation, anxiolysis and analgesia, but as sole agent has not been uniformly successful for painful procedures [3].

When used together, DEX may prevent tachycardia, hypertension, salivation and emergence phenomena from KET, whereas KET may prevent bradycardia and hypotension witch has been reported with DEX. An additional benefit consists in the addition of KET to accelerate onset of sedation.

The use of its combination to perform different diagnostic and surgical pediatric procedures has increased: premedication with low doses of both drugs, allowing anxiolysis, analgesia, dissociative general anesthesia with airway patency [4,5], reducing morbidity related to airway handling, emergency delirium and shivering.

This review aims to demonstrate examples of this association in literature, providing data on doses, routes of administration (oral – PO, intranasal – IN, intramuscular – IM, intravenous – IV) efficacy, procedures and patient profiles eligible for the technique, as advantages and disadvantages over the techniques most commonly used.

Premedication
The preoperative period can be stressful due to the anxiety that accompanies this phase. Children can become uncooperative in separation from their parents, during venoclysis or facial mask application. Such anxiety, when disdained, can lead to hinder anesthetic induction, increase postoperative pain with greater need for analgesics in the period, emergence delirium and even later psychological and behavioral effects.

The most used drug for this purpose is midazolam, which promotes rapid onset sedation, anxiolysis and amnesia. However, it presents disadvantages, including the possibility of paradoxical reactions, postoperative cognitive-behavioral impairment and respiratory depression, demonstrating that there is an urgent need to increase the range of anesthetic techniques in order to achieve an ideal association of efficacy with minimal side effects.

A randomized clinical trial compared the combined or isolated use of DEX and KET in 135 children, between 2 and 5 years old, ASA I and II, who underwent eye surgery, allocated to receive DEX IN $2.5mcg.kg^{-1}$ (group D), KET PO $6mg.kg^{-1}$ (group K) or DEX IN $2mcg.kg^{-1}$ associated with KET PO $3mg.kg^{-1}$ (group KD) thirty minutes before surgery to check the success rate of venous cannulation. Qiao H et al. observed 47% success in group D, 68% in group K and 80% in group KD. Parental separation was similar in the 3 groups, but the incidence of adverse effects was higher in group K (postoperative vomiting, $P = 0.0041$; perioperative respiratory complications, $P = 0.0032$ and psychological / psychiatric adverse events, $P = 0.0152$) [6].

An unusual route of administration, nebulization (NBZ), was the subject of study by Zanaty and El Metainy who compared the use of DEX, KET or both as premedication for children undergoing dental procedures. This prospective, double-blind study evaluated sixty children aged 3 to 6 years, ASA I and II, randomized into three groups that would receive drugs under NBZ (group K: ketamine $2mg.kg^{-1}$; group D: DEX $2mcg.kg^{-1}$; group KD: DEX $1mcg.kg^{-1}$ + KET $1mg.kg^{-1}$). The level of sedation 30 minutes after drug administration was significantly higher in the KD group, also presenting better analgesia and shorter recovery time, in the absences of major adverse effects [7].

Oriby compares DEX IN $2mcg.kg^{-1}$ associated with KET PO $3mg.kg^{-1}$ (KD group) versus midazolam IN $0.2mg.kg^{-1}$ (group M) in 77 children thirty minutes before anesthetic induction undergoing dental procedures. Group M presented better sedation after 20 and 30 min ($P <0.05$), but greater need of analgesia ($P = 0.012$) and no difference observed during parental separation [8] (Figure 1).

Author and Design	Subject	KD doses	Comparison	Outcome	Observations
Qiao et al Randomized trial (RT) N 135	Ophtalmologic procedure 30 min before venous line placement	DEX IN 2mcg.kg^{-1} KET PO 3mg.kg^{-1}	-KD -DEX IN 2.5mcg.kg^{-1} -KET PO 6mg.kg^{-1}	Success rate KD 80% DEX 47% K 68%	-Parental separation: similar -KET: PONV, psychomimetic effects
Zanaty and Metainy Double-blinded RT N 60	Dental procedures Sedation after 30 min	NBZ DEX 1mcg.kg^{-1} KET 1mg.kg^{-1}	-KD -DEX 2mc.kg^{-1} -KET 2mg.kg^{-1}	DK presented better sedation level	-Better analgesia -Shorter recovery time -No adverse events
Oriby RT N77	Dental procedures Sedation after 30 min	DEX IN 2mcg.kg^{-1} KET PO 3mg.kg^{-1}	-DK -MDZ IN 0.2mg.kg^{-1}	M presented better sedation level	-Parental separation: similar -Better analgesia with KD

Figure 1: KD and Premedication.

Author and Design	Subject	KD: Doses and Administration Routes	Comparison	Primary Outcome	Observations
Goyal and Islam Case report	Xeroderma pigmentosa	Atack: KET 2mg.kg + DEX 1mcg.kg Maintenance: KET 0.6mg/kg/h + DEX 0.6mcg/kg/h IV	No comparison	Success in local excision with flap recovery	- Spontaneous breathing - No adverse events
Esra et al Case report	Maxilomandibullar synechia	KET 1mg kg^{-1} DEX 0.7 kg h^{-1} IV	No comparison	Success in synechia treatment and tracheostomy	- Spontaneous breathing - No adverse events
Ganigara A Case report	Carnitine deficiency	Maintenance DEX 0.5 mcg kg h^{-1} KET 0.5 mg kg h^{-1} IV	No comparison	Successful anesthesia	- Spontaneous breathing - No adverse events
Ibacache et al. DB-RT N 25	Sacral blockade Abdominal and pelvic surgeries	DEX 1mcg kg^{-1} KET variable IV	KET 1 to 2mg kg^{-1}	ED95: 2mg kg^{-1}	Need for inhalational anesthesia in 3 cases. Need for rescue with new doses in cases of blockade failure

Figure 2: KD and Anesthesia in the operating room.

Emergence Delirium

Emergence delirium (ED) is a complex disorder with psychomotor agitation that commonly occurs in pre-school children in the recent post-anesthetic period. The incidence of ED ranges from 10 to 80% and, although it sometimes presents itself as a short-term event, it increases the risk of self-injury and prolonged hospital stay. The prevalence has been increasing along with the increased use of sevoflurane and desflurane, two inhalational agents of low solubility, which promote early post-anesthetic excitation. The use of adjuvants can reduce the incidence of ED, from greater to less effective: DEX [9], fentanyl, KET, clonidine and propofol bolus at the end of an anesthesia based on sevoflurane [10].

In order to assess the effectiveness of KD, 92 children were randomized to receive KET 0.15mg.kg^{-1} followed by DEX 0.3mcg.kg^{-1} IV or saline about ten minutes before undergoing adenotonsillectomy, whose anesthesia was maintained with sevoflurane. Not only have they concluded ED reduction, but superior analgesia has also been demonstrated. Despite a longer time for interaction in the recovery room, extubation was smoother in the absence of tachycardia [11].

Anesthesia in the operating room

The KD combination is beneficial not only for patients with difficult airway management, emergence delirium risk as previously demonstrated, but also for those who have an altered drug metabolism, which could make the usual general anesthesia turn into a challenge.

Goyal R and Islam MS et al. report a case of a 16-year-old girl with xeroderma pigmentosa, a disease known for presenting lesions and contractures in the skin of face and neck and altered sensivity for inhaled and neuromuscular blockers, scheduled for wide local excision with flap cover for excision of basal cell carcinoma on the scalp, previously anesthetized with delayed recovery, managed successfully with IV KD (IV bolus KET 2mg.kg^{-1} + DEX 1mcg.kg^{-1}, followed by continuous infusion of KET 0.6mg.k.h-1 and DEX 0.6mcg.kg.h^{-1}), maintaining airway patency under spontaneous ventilation throughout the preceding period, without occurrence of adverse events [12].

Another example of difficult airway predictor is the limited mouth opening such as Congenital Maxillomandibular Synechiae in a 1-day-old newborn [13]. Esra did not observe adverse events in surgical treatment of the synechiae with the use of KET IV 1mg.kg^{-1} and DEX IV 0.7 – 1 mcg.kg.h^{-1}, maintaining spontaneous breathing with nasopharyngeal cannula providing O2 4L.min^{-1}.

Anesthesia in patients with mitochondrial defects is challenging. Ganigara A. et al. [14] describes a patient with congenital carnitine deficiency that underwent phacoemulsification surgery and insertion of intraocular lenses for cataract correction. The

choice of KD for maintenance of anesthesia was due to the risk of malignant hyperthermia under inhaled anesthetics and to the propofol inhibition of fatty acid transport to the mitochondria. Anesthetic induction was performed with thiopental, fentanyl and atracurium, maintained with DEX 0.5mcg.kg.h^{-1} and KET 0.5 mcg.kg.min-1, with no complications observed.

The combination can also be used as an alternative technique for usual procedures such as superficial surgeries in inferior abdomen and pelvis. A double-blinded study aimed to find ketamine ED95 associated with IV bolus of DEX 1mcg.kg^{-1}. For sacral blockade, it was found that 2 mg.kg^{-1} can ensure an adequate anesthesia [15]. Previous research showed the same success, including high-risk children [16 -19] (Figure 2).

Anesthesia for non-operating room procedures

Diagnostic tests are routine for conduction for acute and chronic diseases requiring patient cooperation and, sometimes, cardiovascular relation closer to the physiologic to affect the final result as little as possible.

Cardiologic exams are among theses cases. Joshi et al. randomized 60 children with congenital heart diseases and compared, during catheterization, efficacy of ketamine-propofol and KD. There was no difference in oximetry and cardiac or respiratory rates, but the recovery time was longer in KD group [20].

Another usual exam is the echocardiogram witch appropriate sedation is needed to obtain clear images. Liu J et al. studied 2304 children receiving DEX 2mcg.kg plus KET 1mg/kg IN and presented 96% success to perform the test, in the absence of adverse events such as desaturation, apnea, hypotension, bradycardia, aspiration or nausea and vomit [21].

In a recent retrospective study, Yang F. et al. analyzed 17.948 children undergoing sedation for diagnostic examination.

Electroencephalogram (EEG), magnetic resonance imaging (MRI), electrocardiogram (ECG), computed tomography (CT), and transthoracic echocardiography were performed. Patients received a combination of DEX 2mcg.kg and KET 1mg.kg IN. Sedation success was defined as successful completed the diagnostic examination and obtained adequate diagnostic-quality images and reports. Intranasal sedation success, rescue and failure were respectively defined as sedation success with intranasal a single dose, additional bolus dose and the need for EV medications/inhalation agents. The level of sedation and recovery was assessed and the rate sedation success was 93%, intranasal sedation rescue was 1.8% and intranasal sedation failure was 5.2%. Median sedation time, onset and sedation recovery was respectively 62min, 15 min and 45 min.

Incidence of adverse events was low 0.58%, with major and minor adverse event being reported in 0.02% and 0.56% patients, respectively. Postoperative nausea and vomiting was the most common 0.3% minor adverse event. Major events occurred in 4 children: airway was accessed in 3 children with difficult airway predictors (a patient with Down syndrome, another with adenoid and tonsils hypertrophy and an obese child) and one case of atrial tachycardia without sequelae [22].

Even for a simple test, the presence of comorbidities as alfa maninosis can be a challenge. Trevisan et al. describes the case of a five-year-old child affected by alpha-mannosidosis who required procedural sedation for an MRI scan and a lumbar puncture. It was administered DEX IN 4 μg.kg^{-1}, 45 min before intravenous cannulation, followed by one bolus of KET 1 mg.kg^{-1} for each procedure. The patient maintained spontaneous breathing and no desaturation or any complication occurred [23].

Handling adverse events outside the operating room, including nausea and vomiting in the postoperative period (PONV) can be challenging. A study compared KD to the KET-propofol (KP)

Author and study design	Subject	KD: Doses and administration route	Comparison	Primary outcome	Observations
Joshi et al RT N 60	-Congenital heart disease -Cardiac catheterization	Attack: DEX 1mcg kg^{-1} + KET 1mg kg^{-1} Maintenance DEX 0.5 mcg kg h^{-1} + KET 1mg kg h^{-1} IV	PK Attack: P 1mg kg^{-1} + KET 1mg kg^{-1}	Similar	KD: longer recovery time No hemodynamic difference
Liu J et al Retrospective study N 2.304	Transthoracic echocardiogram	DEX 2mcg kg^{-1} KET 1mg kg^{-1} IN	No comparison	Success in 96%	Sedation time: 15,7 min Recovery time 25 min No adverse events
Yang et al Retrospective N 17.948	Diagnostic testes	DEX 2 mcg kg^{-1} KET 1mg kg^{-1}	No comparison	Success: 93% Rescue 1.8% Failure 5.2%	Airway management in children with difficult airway predictors One case of tachycardia
Trevisan et al. Case report	-alpha manidosis	DEX 4mcg kg^{-1} before venoclisis KET 1mg kg^{-1} IV	No comparison	Successful MRI and lumbar puncture	Spontaneeous breathing
Canpolat et al. RT N 60	Exodonty	DEX 0.5mcg kg^{-1} KET 1 mg kg^{-1} IV	PK P 1mgkg^{-1} KET 1mg kg^{-1} IV	PK: surgeon satisfaction	DK PONV No hemodynamic difference

Figure 3: KD and Anesthesia for non-operating room procedures.

association, randomizing 60 children who underwent extractio. The KP group received 1mg.kg⁻¹ of ketamine and propofol, and the KD group received 1mg kg⁻¹ of ketamine + 0.5 μg kg⁻¹ of dexmedetomidine. It was demonstrated a higher incidence of PONV in the KD group (20%) compared to KP (3.3%), also providing a higher degree of satisfaction of the patient surgeon (KD 46.7% vs. KP 86.6%), but with the occurrence of hypoxia observed in 6.6% in the KP group. There was no difference between groups in terms of blood pressure (BP), heart rate (HR) and anxiolysis [24] (Figure 3).

Discussion

DEX was initially approved in 1999 by the FDA for use in adult patients on mechanical ventilation with therapy lasting less than 24 hours in an intensive care unit, with its perioperative use for sedation being later only authorized in patients adults [25]. Despite the exclusion of children in this group, as off-label medication, DEX has been administered as an adjunct to anesthesia (general and regional), as well as inside and outside the ICU [26]

It is a highly selective α2 agonist drug capable of providing sedation that resembles natural sleep, anxiolysis, analgesia, sympatholysis and an anesthetic-sparing effect with minimal respiratory depression [27,28]. As it leads to sympatholysis, it attenuates the cardiovascular and metabolic response in response to surgical trauma [26]. In addition, its use in the prevention and treatment of delirium and shivering [29-31], as well as during airway management, is established. Possible neuroprotection has also been observed in some studies, with apparent prevention of apoptosis commonly seen after administration of other anesthetics.

Responses from other organs containing α-2 receptors include: reduced salivation, secretion and gastric motility; inhibition of the release of renin and insulin; increased glomerular filtration rate; increased renal sodium and water secretion. Stimulation of α-2 receptors decreases the entry of calcium into the nerve terminals, which may contribute to its inhibitory effect on the release of the neurotransmitter [32,33]. However, attention should be paid to the hemodynamic effects of the drug, among which, depending on the dose administered and age group, bradycardia, hypertension (use of high doses that activate postsynaptic α2-b receptors generating vasoconstriction) and hypotension (low doses with effect on presynaptic α2-a that generate vasodilation) [34].

DEX has a rapid distribution phase. Its stable volume distribution phase is 118 L and its distribution half-life is six minutes. In children under 2 years of age, the volume of distribution in the stable phase is high, indicating that higher doses are required to obtain the stable phase; but its elimination half-life is prolonged, which can lead to high drug accumulation over time [35].

Its metabolism occurs in the liver through the conjugation of glucuronic acid and biotransformation by the cytochrome P450 enzyme system. There are no known active or toxic metabolites. However, liver release can be decreased by up to 50% of normal with severe liver disease. No difference was seen between healthy patients and those with renal impairment. Metabolites are

eliminated by up to 95% in urine and 4% in faeces. Considering that most metabolites are excreted in the urine, there is a theoretical risk of accumulation in these patients.

In relation to its expanding clinical applicability, in addition to its wide use in sedation for radiological procedures, among many other uses, are its pre-anesthetic, intra and postoperative administration as an adjuvant, in order to mitigate awakening complications such as pain, delirium and shivering, as well as during airway management.

KET was synthesized in 1962 and approved for use in 1970, has already been considered an ideal and complete agent because it was believed to provide all the requirements of anesthesia: analgesia, immobility, amnesia and hypnosis. However, due to important side effects, it did not achieve wide clinical acceptance until the appearance of the S (+) isomer, whose cognitive side effects were less intense and with greater analgesic potential [36]. Its popularity is due, in addition to its ability to provide the anesthetic requirements mentioned above, also to its beneficial secondary qualities. These include bronchodilation, the ability to maintain airway reflexes [37] and the sympathetic nervous system tone [38]. Studies still point to the existence of neuroprotective and anti-inflammatory properties [39].

It is a non-competitive antagonist of the N-methyl-D-aspartate glutamate (NMDA) receptor, providing dissociative anesthesia. It has a short distribution and elimination half-life, being metabolized by the cytochrome P450 system, deriving its main metabolite, norcetamine, with one third to one fifth of the potency of the original drug, and may be related to prolonged analgesic effects. Its elimination is renal.

The drug interacts with multiple binding areas, including NMDA and non-NMDA glutamate receptors; nicotinic, muscarinic, cholinergic, adrenergic and opioid receptors [40-42]. Due to the adrenergic effect, it leads to tachycardia, increasing cardiac output and blood pressure, except in cases of catecholamine depletion (eg critically ill patients), when it can cause a negative inotropic effect. Other potentially worrying effects are sialorrhea, nausea and its potential to cause neuronal apoptosis as well as other agents (eg benzodiazepines, volatile anesthetics) [43], thus determining a risk for neurodevelopment. Paradoxically, in studies with rats, despite the risk of apoptosis, neuronal protection against ischemia induced injury is observed [44]. Regarding its psychomimetic effects (eg dysphoria and hallucinations), a similar incidence was observed when using fentanyl, midazolam or general anesthesia during the recovery period [45].

Among its frequent clinical applications are the induction of anesthetic plan in emergency situations, especially patients in shock or hypotension, in patients with congenital heart disease and right-left shunt; patients with bronchospasm, anesthesia in burn victims, prevention of hyperalgesia caused by opioids, application as a pre-anesthetic drug through several routes, in order to reduce anxiety stress and reducing the emergency agitation, also preventing postoperative tremor [46-48].

When used together, DEX can limit tachycardia, hypertension, salivation and restlessness on KET awakening, while the latter can prevent DEX hypotension and bradycardia, in addition to speeding up the onset of sedation, maintaining airway patency. Given the considerable rate of outpatient anesthesia that pediatric patients are subjected to and the tendency to shorten the fasting period with the need for airway protection, the combination seems to be an appropriate option, still allowing providing good analgesic quality.

As undesirable effects, Yang F. et al. points out that the failure of sedation requiring the administration of a new dose of KD was attributed to the performance of prolonged procedures, the presence of fever, congenital heart disease and a history of previous sedations. In addition, adverse events considered major occurred in three patients with criteria for difficult airway and need for access to the airway (one patient with Down's Syndrome, frequently with macroglossia and difficulty in ventilation, during TTE, another with hypertrophy of adenoids and tonsils and the third presenting BMI 30.5, both for pulmonary testing, that is, commonly with variable degrees of airway obstruction) and one case of atrial tachycardia (FR: 250-300bpm, without subsequent sequela). Despite showing low incidence, it should not be discarded when choosing this technique [22].

Conclusion
Given the limited analgesic effects, DEX has not established itself as an ideal agent for performing invasive and painful procedures. However, the literature demonstrates that the association with KET is effective for this purpose, and can be used in several ways, including mixed in the same syringe.

The ability of one drug to neutralize the adverse effects of the other makes the combination profile attractive for several uses: procedures that benefit from spontaneous ventilation, but with the need for immobility, hypnosis and analgesia; patients with difficult ventilatory management, with contraindications for other anesthetic techniques.

There are several routes of administration, with the most recurrent IN dose in this review being between DEX 2-2.5mcg. kg^{-1}, despite a study administering 4mcg.kg^{-1}, and KET 1mg.kg^{-1}, with satisfactory results. There was one study that was successful with KD via NBZ DEX1mcg.kg^{-1} + KET 1mg.kg^{-1}. EV doses are between DEX 1-2mcg.kg^{-1} and KET 1-2mg.kg^{-1}, followed by continuous infusion of DEX 0.7-1mcg.kg.h^{-1} and supplementary doses of KET 0.5-1mg.kg^{-1} when necessary.

It is still necessary to obtain studies with data on the cost comparison of the different possible drug combinations and regimens and also on their potential treatment for acute and chronic pain, given its increasing use in the adult population with encouraging results.

References
1. Abdallah C, Hannallah R. Premedication of the child undergoing surgery. Middle East J Anaesthesiol. 2011; 21: 165-176.
2. Eikermann M, Grosse-Sundrup M, Zaremba S, et al. Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. Anesthesiology. 2012; 116: 35-46.
3. Yuen VM. Dexmedetomidine: perioperative applications in children. Paediatr Anaesth. 2010; 20: 256- 264.
4. Kandil A, Subramanyam R, Hossain MM, et al. Comparison of the combination of dexmedetomidine and ketamine to propofol or propofol/sevoflurane for drug-induced sleep endoscopy in children. Paediatr Anaesth. 2016; 26: 742-751.
5. Goutham Mylavarapu, Robert Fleck, Rajeev Subramanyam, et al. Effect Of A Combination Of Dexmedetomidine And Ketamine Anesthesia On The Upper Airway Caliber In Normal Children. Am J Respir Crit Med. 2020; 201: 4121.
6. Qiao H, Xie Z, Jia J. Pediatric premedication: a double-blind randomized trial of dexmedetomidine or ketamine alone versus a combination of dexmedetomidine and ketamine. BMC Anesth. 2017; 17: 158.
7. Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg. 2015; 121: 167-171.
8. Oriby ME. Comparison of Intranasal Dexmedetomidine and Oral Ketamine Versus Intranasal Midazolam Premedication for Children Undergoing Dental Rehabilitation. Anesth Pain Med. 2019; 9: 85227.
9. Fang XZ, Gao J, Ge YL, et al. Network meta-analysis on the efficacy of dexmedetomidine, midazolam, ketamine, propofol, and fentanyl for the prevention of sevoflurane-related emergence agitation in children. Am J Ther. 2016; 23: 1032-1042.
10. Moore AD, Anghelescu DL. Emergence delirium in pediatric anesthesia. Paediatr Drugs. 2017; 19: 11-20.
11. Hadi SM, Saleh AJ, Tang YZ, et al. The effect of KETODEX on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane based-anesthesia. Int J Pediatr Otorhinolaryngol. 2015; 79: 671-676.
12. Goyal R, Islam MS. Dexmedetomidine and ketamine combination for a patient with xeroderma pigmentosa. J Anesth. 2015; 29: 457-458.
13. Caliskan E. Congenital Maxillomandibular Synechiae: Anesthetic Approach with Ketamine and Dexmedetomidine Sedation for Surgical Division of Synechiae and Tracheostomy. Iran J Pediatr. 2017; 27: 59266.
14. Anuradha Ganigara, Madhavi Nishtala, Manasa Morubagal, et al. A combination of dexmedetomidine and ketamine for a child with primary carnitine deficiency posted for cataract extraction. Trends in Anaesthesia and Critical Care. 2017; 13: 13-15.

15. Ibacache ME, Muñoz HR, Fuentes R, et al. Dexmedetomidine-ketamine combination and caudal block for superficial lower abdominal and genital surgery in children. Paediatr Anaesth. 2015; 25: 499-505.

16. Bozdogan N, Sener M, Caliskan E, et al. A combination of ketamine and dexmedetomidine sedation with caudal anesthesia during incarcerated inguinal hernia repair in three high-risk infants. Pediatr Anesth. 2008; 18: 1009-1011.

17. Bozdoğan Özyılkan N, Yalçın Çok O, Eker HE, et al. Supplementing caudal anesthesia with sedative combination of ketamine and dexmedetomidine during incarcerated inguinal hernia repair in a high risk infant. Regional Anesthesia and pain medicine. 2016; 41: 162.

18. Tobias JD. Dexmedetomidine and ketamine: an effective alternative for procedural sedation? Pediatr Crit Care Med. 2012; 13: 423-427.

19. McVey JD, Tobias JD. Dexmedetomidine and ketamine for sedation during spinal anesthesia in children. J Clin Anesth. 2010; 22: 538-545.

20. Joshi V, Kollu S, Sharma R. Comparison of dexmedetomidine and ketamine versus propofol and ketamine for procedural sedation in children undergoing minor cardiac procedures in cardiac catheterization laboratory. Annals of cardiac anaesthesia. 2017; 20: 422-426.

21. Liu J, Du M, Liu L, et al. Sedation effects of intranasal dexmedetomidine combined with ketamine and risk factors for sedation failure in young children during transthoracic echocardiography. Paediatr Anaesth. 2019; 29: 77-84.

22. Fei Yang, Yang Liu, Qing Yu, et al. Analysis of 17 948 pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine. Pediatr Anesth. 2019; 29: 85-91.

23. Trevisan M, Romano S, Barbi E, et al. Intranasal dexmedetomidine and intravenous ketamine for procedural sedation in a child with alpha-mannosidosis: a magic bullet?. Ital J Pediatr. 2019; 45: 119.

24. Dilek Gunay Canpolat, Mustafa Denizhan Yildirim, Nukhet Kutuk, et al. Comparison of ketamine-propofol and ketamine-dexmedetomidine combinations in children for sedation during tooth extraction. Journal of the Pakistan Medical Association. 2017; 67: 693-697.

25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021038s021lbl.pdf Acesso em 04 nov. 2019.

26. Mason KP, Lerman J. Dexmedetomidine in children: current knowledge and future applications. Anesth Analg. 2011; 113: 1129-1142.

27. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015; 115: 171-182.

28. Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: Part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology. 2004; 101: 1066-1076.

29. Blaine Easley R, Brady KM, Tobias JD. Dexmedetomidine for the treatment of postanesthesia shivering in children. Paediatr Anaesth. 2007; 17: 341-346.

30. Mason KP. Paediatric emergence delirium: a comprehensive review and interpretation of the literature. British Journal of Anaesthesia. 2017; 118: 335-343.

31. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017; 34: 192-214.

32. Vutskits L, Sall JW. Reproducibility of science and developmental anaesthesia neurotoxicity: a tale of two cities. Br J Anaesth. 2017; 119: 451-452.

33. Duan X, Li Y, Zhou C, et al. Dexmedeto- midine provides neuroprotection: impact on ketamine-induced neuroapoptosis in the developing rat brain. Acta Anaesthesiol Scand. 2014; 58: 1121-1126.

34. Hammer GB, Drover DR, Cao H, et al. The effects of dexmedetomidine on cardiac elec- trophysiology in children. Anesth Analg. 2008; 106: 79-83.

35. Vilo S, Rautiainen P, Kaisti K, et al. Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. Br J Anaesth. 2008; 100: 697-700.

36. Pfenninger EG, Durieux ME, Himmelseher S. Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. Anesthesiology. 2002; 96: 357-366.

37. Jaume Canet, Jorge Castillo. Ketamine: A Familiar Drug We Trust. Anesthesiology. 2012; 116: 6-8.

38. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain and critical care. Anesth Essays Res. 2014; 8: 283-290.

39. Kawasaki T, Ogata M, Kawasaki C, et al. Ketamine suppresses pro-inflammatory cytokine production in human whole blood in vitro. Anesth Analg. 1999; 89: 665-669.

40. Hustveit O, Maurset A, Oye I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacol Toxicol. 1995; 77: 355-359.

41. Aronstam RS, Narayanan L, Wenger DA. Ketamine inhibition of ligand binding to cholinergic receptors and ion channels. Eur J Pharmacol. 1982; 78: 367-370.

42. Kress HG. Actions of ketamine not related to NMDA and opiate receptors. Anaesthesist. 1994; 43: 15-24.

43. Fredriksson A, Archer T, Gorth T, et al. Neurofunctionnal deficits and poten- tiated apoptosis by neonatal NMDA antagonist administration. Behav Brain Res. 2004; 153: 367-376.

44. Engelhard K, Werner C, Eberspächer E, et al. The effect of the a2-agonist dexmedetomidine and the NMDA antagonist S(þ)-ketamine on the expres- sion of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats. Anesth Analg. 2003; 96: 524-531.

45. Roback MG, Carlson DW, Babl FE, et al. Update on pharmacologicalmanagement of procedural sedation for children. Curr Opin Anaesthesiol. 2016; 29: 21-35.

46. Kurdi M, Theerth K, Deva R. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014; 8: 283-290.

47. Gangopadhyaya S, Gupta K, Acharjee S, et al. Ketamine, tramadol and pethidine in prophylaxis of shivering during spinal anaesthesia. J Anaesthesiol Clin Pharmacol. 2010; 26: 59-63.

48. Tabbert K, Virginia A. Low dose intraoperative ketamine for prevention of post-operative shivering: A systemic review protocol. JBI Database Syst Rev Implement Rep. 2013; 11: 38-47.