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EDITORIAL

Is the combination of oral midazolam and ketamine as preanesthetic medication a safe and effective practice?

Preoperative anxiety is very common in subjects who will undergo surgery, mainly children. Preoperative anxiety in children may manifest in different ways: some will verbalize what they are feeling, while others will have specific stress related behavior. In general, stress associated anxiety is related to fear of separation from parents, fear of experiencing pain, fear of not surviving the procedure, among other sources of worries.[1]

Anxiety may have two different manifestations: state and trait anxiety. While state anxiety is a transitory and emotional behavior that fluctuates over time, varies in intensity and includes feelings of tension, apprehension, nervousness, and worry; trait anxiety refers to a personality trait that remains stable over time.[2,3] Reducing anxiety in children undergoing surgery is important both for compassionate reasons as well as to increase their cooperation during anesthesia induction. However, it may also reduce the risk of postoperative emergence delirium and behavioral changes, as we will discuss further.[4,5] Interestingly, patients with high levels of preoperative state anxiety are particularly vulnerable to severe pain after surgery.[2]

Children with a higher degree of preoperative anxiety are also at greater risk of presenting maladaptive behavior in the postoperative period. Among these behaviors we may observe irritability, separation anxiety, nightmares, feeding problems, night crying, disobedience, and nocturnal enuresis. These behavioral changes may persist for up to one year, while negative memories of the perioperative period may persist into adulthood.[1,6]

The hypothalamic-pituitary-adrenal axis is activated by the stress caused by anxiety. This activation determines an increase in the glucocorticoid plasma level and may contribute to changes to the immune system with increased risk of infections.[1] Anesthetic premedication is one of the most helpful tools for reducing stress in children. Various drugs and dosage forms may be used as premedication, including oral midazolam and ketamine.[7] Midazolam is currently one the most used premedication drugs in pediatric practice.[8]

Midazolam is a water-soluble drug that can be administered orally, intranasally, sublingually, rectally, intramuscularly, or intravenously. It has fast onset, with duration of action of approximately 30 min, generally not interfering with vital signs in doses below 0.5 mg.kg^{-1}.[8,9] These characteristics make midazolam suitable as premedication, in special for children. The bioavailability of midazolam is on average 36%, with a very broad range (971%).[10] Its use as a premedication drug is associated with 60 to 80% of good responses, while in dental surgery the success rates are even lower.[9] For this reason, and to improve its success rate, other drugs may be associated to midazolam as premedication.

Ketamine has been studied as an adjuvant drug added to midazolam in the perioperative period. The rationale for the coadministration of these two drugs as premedication is the assumption that midazolam anxiolysis is added to the sedative and analgesic properties of ketamine, not increasing side effects.[11] Ketamine is a dissociative general anesthetic that, when used and in a lower dose, can be an analgesic. It is a racemic mixture, although more recently S-ketamine is commercially available. The latter may be associated with fewer side effects, although it is a two to four times more potent analgesic than the original compound. The bioavailability of oral S-ketamine is estimated to be 11%, suggesting that the first hepatic passage plays an important role, while the racemic compound has an oral bioavailability of 17 to 24%.[12]

Oliveira Filho et al published an interesting systematic review and meta-analysis in the BJAN on the use of oral midazolam alone and in combination with ketamine in the preoperative period for children. Their studied primary outcomes were anxiety and sedation levels, child's behavior during separation from parents, face mask acceptance, and venipuncture. Twenty studies were included in the meta-analysis, with a total of 1540 patients. Oral midazolam associated to ketamine was administered in 834 subjects, while 706 received only midazolam.[11]

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Unexpectedly, adding oral ketamine to midazolam did not improve anxiolysis. However, the probabilities of obtaining a better outcome was higher among patients who received the combination of both drugs for sedation, including behavior during parental separation, facial mask acceptance and venipuncture outcomes. Treatments did not differ regarding the probabilities of occurrence of adverse effects, including perioperative nausea and vomiting, hallucinations, excessive salivation, diplopia/nystagmus, or oxygen desaturation. Only one included study evaluated excessive sedation, headache, tachycardia, bradycardia, involuntary movements, hiccoughs, and delayed recovery, without observing differences among groups.

It is noteworthy that the association of these drugs can produce different (or more pronounced) anxiolysis and analgesia effects depending on the administered doses of each drug, the pharmaceutical presentation, and the characteristics of the studied population. According to Oliveira Filho et al, there is a great variation in the doses used for both drugs, from 0.2 to 0.75 mg.kg^{-1} for midazolam, and from 1 to 6 mg.kg^{-1} for ketamine, as well as the use of different pharmaceutical formulations.[11] The oral midazolam solution has adequate bioavailability for administration by this route, but when the parenteral presentation is used orally, changes in the solution's pH may occur, causing medication bioavailability and absorption changes interfering in the effectiveness of midazolam.[13]

The authors of the study concluded that, due to the small effect sizes, high within-study risk of bias, high methodological and statistical heterogeneity, and high risk of publication bias found in meta-analyses, a weak level of recommendation is provided for replacing oral midazolam alone with oral combinations of midazolam and ketamine for the preanesthetic medication of pediatric surgical patients.[11]

It is important to note that some groups of patients benefit from more powerful sedation and analgesia in the preanesthetic period, especially those with high levels of anxiety, changes in behavior and sociability, cognitive deficits, or the need for awake venopuncture. In this scope, in another study presented in the BJAN, Penna et al demonstrated that patients with autism spectrum disorder (ASD) are a group with special needs in terms of anesthetic care, requiring individualized care from the preoperative period to hospital discharge, with the aim of making the hospital experience less traumatic and as comfortable as possible.[14]

In the past 20 years, there has been a significant increase in the prevalence of ASD, mainly due to greater knowledge and better diagnostic methods for this condition. ASD is a neurodevelopmental disorder, present from birth and persistent throughout life, which causes impaired social interaction, communication and isolation problems, behavioral disturbances, disorders of the sensory sphere, as well as altered motor skills. Sensory disorders are represented by inadequate responses to tactile and proprioceptive stimuli and by altered pain perception.[15]

In the study by Penna et al, the need to use effective preanesthetic medication for dental treatment under general anesthesia in patients with ASD is evident, mainly justified by the difficulties in approaching these patients in the conventional way, both for dental treatment and preanesthetic management. In this parallel, double-blind, controlled, randomized clinical trial, the authors included 64 persons with ASD aged 2—59 years scheduled for dental care under general anesthesia. The primary objective was to compare the degree of sedation, and the secondary outcomes were the need for physical stabilization to obtain intravenous access, time to wake up, and the occurrence of adverse events. The sample was randomized to receive preanesthetic medication with an oral solution of midazolam alone 0.5 mg.kg (maximum 15 mg) or receive oral midazolam 0.5 mg.kg^{-1} (maximum 15 mg) associated with oral S-ketamine 3 mg.kg^{-1} (maximum 300 mg).[14]

The results are consistent with those observed in the systematic review and meta-analysis by Oliveira Filho et al.,[11] in which the level of sedation achieved by the oral association of S-ketamine and midazolam promoted better sedation, with an increase in the probability of Ramsay $\geq$ 3, compared to midazolam alone. The association was also useful from an analgesic point of view, facilitating venous access without requiring physical restraint. The association of midazolam and S-ketamine did not cause an increase in the time of awakening or the occurrence of adverse events when compared to midazolam alone.[14]

Based on these results, from both studies presented in this edition of BJAN, the association of ketamine and midazolam is an interesting alternative in preanesthetic medication, when a powerful sedative and anxiolytic effect is desired, especially in patients who are not very cooperative or with disorders related to socialization or sensory changes, in which the benefit of analgesia provided by ketamine is welcome. However, larger and new studies are needed comparing similar drug doses and presentations (formulations) in larger populations, in healthy individuals, in order to conclude that this association is superior from the point of view of sedation and anxiolysis, as well as, devoid of adverse events and prolonged awakening time in other clinical settings.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Norma Sueli Pinheiro Módolo [a,*], Luciana Cavalcanti Lima [b], Débora de Oliveira Cumino [c], Paulo do Nascimento Júnior [a], Guilherme Antonio Moreira de Barros [a]

[a] *Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu (FMB), Departamento de Especialidades Cirúrgicas e Anestesiologia, Botucatu, SP, Brazil*
[b] *Instituto Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil*
[c] *Hospital Infantil Sabará, São Paulo, SP, Brazil*

[*] Corresponding author.
E-mail: norma.p.modolo@unesp.br (N.S. Módolo).