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ORIGINAL INVESTIGATION

Comparison between oral midazolam versus oral ketamine plus midazolam as preanesthetic medication in autism spectrum disorder: double-blind randomized clinical trial

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Abstract

Background: Conventional dental care is often impossible in patients with Autism Spectrum Disorder (ASD). Non-collaborative behaviors, sometimes associated with aggressiveness, are usual justifications for premedication in this population. Thereby, this research focuses on the effects of oral midazolam versus oral ketamine plus midazolam as preanesthetic medication in ASD.

Methods: The sample included 64 persons with ASD, aged 2-59 years, scheduled for dental care under general anesthesia. The primary objective of this study was to compare degrees of sedation between two parallel, double-blinded, equally proportional groups randomized to receive oral midazolam (0.5 mg.kg^{-1}, maximum 15 mg) or oral midazolam (0.5 mg.kg^{-1}) associated with oral *S*(+)-ketamine (3 mg.kg^{-1}, maximum 300 mg). The secondary outcomes were the need of physical stabilization to obtain intravenous line, awakening time, and occurrence of adverse events.

Results: According to the dichotomous analysis of sedation level (Ramsay score 1 and 2 *versus* Ramsay $\geq$ 3), oral association of *S*(+)-ketamine and midazolam improved sedation, with increased probability of Ramsay $\geq$ 3, Relative Risk (RR) = 3.2 (95% Confidence Interval [95% CI] = 1.32 to 7.76) compared to midazolam alone. Combined treatment also made it easier to obtain venous access without physical stabilization, RR = 2.05 (95% CI = 1.14 to 3.68). There were no differences between groups regarding awakening time and the occurrence of adverse events.

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Conclusion: The association of oral *S*(+)-ketamine with midazolam provides better preanesthetic sedation rates than midazolam alone and facilitates intravenous line access in patients with autism.

Introduction

In 2016, the United States Centers for Disease Control monitoring system estimated the prevalence of Autism Spectrum Disorder (ASD) at 18.5/1000 children by the age of eight.[1] This was 175% higher than the results from 2000 and 10% higher than the results from 2014 using the same database. In Northern Ireland, in 201920, the prevalence rate was 4.2% in school-age children.[2] This increased prevalence may be related to broader diagnostic criteria, public awareness of ASD and improved diagnostic tools. ASD is defined as persistent deficits in social communication and social interaction in multiple contexts.[3] Due to these traits, persons with ASD may not cooperate during regular dental care, whether children or adults. In a sample of individuals with neurological disabilities who required general anesthesia for dental treatment, 30% had ASD.[4]

Midazolam is the most commonly used drug as preanesthetic,[5] especially by the oral route, which is better tolerated than the nasal or intramuscular routes in non-cooperative patients. Although not available in oral formulation, parenteral formulation of *S*(+)-ketamine has been used as preanesthetic by oral or nasal route,[6,7] and more recently by fogging.[8] Despite an obvious and increasing demand, the literature provides little data on preanesthetic medications in the autistic population.[9] Premedication makes the experience less unpleasant for the patient and family members, decreases the possibility of physical stabilization, and facilitates multiprofessional management to the individual with ASD.[10]

We hypothesized that adding oral *S*(+)-ketamine to oral midazolam would lead to a better premedication state, compared to oral midazolam alone, when administered as preanesthetic in patients with ASD. Thus, the primary endpoint was to observe the degree of sedation in groups receiving oral midazolam alone *versus* oral midazolam plus oral *S*(+)-ketamine.

Methods

This study was approved by the ethics committee of Faculdade de Medicina da Universidade Estadual Paulista — Campus de Botucatu (CAAE 65117917.1.3001.5411). The trial was registered prior to patient enrollment in REBEC (ensaiosclinicos.gov.br, code RBR-8ttw3f). This parallel, double-blind, controlled, randomized clinical trial was conducted between September 2018 and January 2021 with individuals who had been previously diagnosed with ASD by a neuropsychiatrist and were referred for dental care under general anesthesia. At least 15 days before the procedure, the written informed consent to participate in the study was presented to the next of kin of potential participants during the preanesthetic consultation. Direct patient assent was waived due to their impaired verbal and non-verbal communication. The research was conducted according to the CONSORT statement.

The primary outcome was the degree of sedation in the oral midazolam *vs* the oral midazolam plus oral *S*(+)-ketamine groups. Reaction to peripheral venous access, interference in awakening time and occurrence of agitation, nystagmus, sialorrhea, and postoperative vomiting were secondary outcomes.

To calculate the sample size, a 50% sedation rate in the desired range (Ramsay sedation score $\geq$3) for midazolam alone was considered, with an absolute increase of 35% (h = 0.775) for midazolam plus *S*(+)-ketamine. A total of 27 participants were required in each group for detection power of 80% and 5% tolerance interval of error. We added five individuals to each group to compensate for any losses due attrition. The sample included males and females between two and 59 years of age, previously diagnosed with ASD, American Society of Anesthesiologists (ASA) physical status II, who required preanesthetic medication and were undergoing general anesthesia for dental assistance at the Hospital Geral de Goiânia Alberto Rassi, or at the Hospital Santa Terezinha in Goiânia, GO, Brazil. The non-inclusion criteria were prediction of difficult airway, renal dysfunction, heart disease, history of allergy or adverse reaction to the study drugs. Exclusion criteria after enrollment were inadequate intake and vomiting after drug administration, as well as major bleeding during surgery or any other significant surgical complication that could interfere in postoperative recovery. The degrees of autism were considered as stratified by the American Psychiatric Association: 1 = requires support, 2 = requires substantial support, 3 = requires very substantial support.[3] The analysis was performed per-protocol to assess the effect of treatment under ideal conditions.

On the day of the procedure, the head nurse in the inpatient ward received, in writing, the weight adjusted dose for one or both medications for each individual participant and administered the premedication according to group determination. Allocation was performed with opaque envelopes numbered from 1 to 64, each containing one of the proposed intervention options (32 envelopes for each group). The envelopes were then drawn in a random order determined by a simple randomization process with the aid of specific software (www.randomization.com). Neither the participants nor their tutors were aware of the intervention group.

The fasting period was 6 hours for light solid foods and 2 hours for clear liquids. If the participants routinely used psychotropic medications, their administration was scheduled to no less than two hours prior to the surgical procedure. The participants received the designated medication while in the inpatient ward. In the Midazolam group,

midazolam dose was 0.5 mg.kg^{-1} (maximum 15 mg), while in the Midazolam/Ketamine group, midazolam dose was 0.5 mg.kg^{-1} (maximum 15 mg) plus *S*(+)-ketamine dose 3 mg.kg^{-1} (maximum 300 mg), diluted in the oral midazolam solution. The formulation of midazolam was in original manufactured formulation syrup with sweet taste (2 mg.mL^{-1}) and *S*(+)-ketamine was in parenteral formulation (50 mg.mL^{-1}), both manufactured by Cristalia® pharmaceutical industry. The doses were calculated based on actual body weight within a limit of 15 mg for midazolam and 300 mg for *S*(+)-ketamine to avoid major collateral effects in accordance with previously published studies.[5,11]

Thirty minutes after ingestion, the anesthesiologist, who was blinded to the allocation group, assessed the degree of sedation using the Ramsay scale (1: anxious, agitated; 2: awake, cooperative, calm; 3: asleep, awakens to low auditory stimulus; 4: asleep, reacts briskly to light glabellar tap or loud auditory stimulus; 5: asleep, reacts slowly to vigorous painful stimulus or loud auditory stimulus; 6: asleep, unresponsive to vigorous painful stimulus or loud auditory stimulus).[12] The sedation level was dichotomized into Ramsay scores 1 and 2 vs. ≥3. The participants were separated from their parents or tutors at entering in the surgical theater.

In the operating room, the reaction prior to peripheral venous access was stratified into four degrees (1: pharmacological intervention; 2: protective physical stabilization; 3: minimal reaction; 4: no reaction). Pharmacological intervention involved protective physical stabilization plus inhalation of sevoflurane and 100% O_2 through a face mask, or intramuscular administration of ketamine (3 mg.kg^{-1}). Protective physical stabilization involved careful stabilization by nursing professionals. Minimal reaction consisted in minimal stabilization only of the limb to be punctured. No reaction represented immobility. The reaction to vascular access was dichotomized as either with stabilization (score 1 and 2) or without stabilization (score 3 and 4).

Intraoperative monitoring consisted of continuous electrocardiogram, noninvasive blood pressure, peripheral oxygen saturation, capnometry ($EtCO_2$), and axillary temperature. Preoxygenation was given for three minutes, and anesthesia was induced with propofol (3 mg.kg^{-1}), fentanyl (2 μg.kg^{-1}), and cisatracurium besylate (0.15 mg.kg^{-1}). Trachea was intubated through nasal route and after waiting for the maximum effect of the neuromuscular blocker. Mechanical ventilation was initiated according to the following parameters: tidal volume 6 mL.kg^{-1} (peak airway pressure limited in 30 cm H_2O) and age-appropriate respiratory rate for a target $EtCO_2$ between 35 to 45 mmHg with a FiO_2 of 80% and positive end-expiratory pressure of 5 cm H_2O. Anesthesia was maintained with sevoflurane, within the minimum alveolar concentration of 2%, with increments of 0.5% based on cardiovascular parameters. If the required dose of sevoflurane reached 4%, incremental boluses of fentanyl (1 μg.kg^{-1}) were administered up to a maximum dose of 5 μg.kg^{-1}. When endodontic treatment and/or tooth extraction were indicated, local anesthesia was performed by the surgical team with 2% lidocaine with vasoconstrictor. During the intraoperative period, the anesthesiologist was blinded to the participant's intervention group.

At the end of the procedure, metamizole (30 mg.kg^{-1}) and ondansetron (0.15 mg.kg^{-1}) were administered. Controlled ventilation was continued until there were signs of swallowing and respiratory movement, at which point neuromuscular blockade was reversed with atropine (0.02 mg.kg^{-1}) and neostigmine (0.04 mg.kg^{-1}). The tracheal tube was removed when the neuromuscular blocker had been completely reversed, with the patient showing signs of adequate spontaneous ventilation and attempts at self-extubation. The awakening time was measured in minutes from the moment that inhalation anesthetic was interrupted until removal of endotracheal tube. Participants remained in the postanesthetic care unit until they had returned to their usual neuropsychological condition with a score of seven or more on the Aldrete and Kroulik scale. They were still observed for the occurrence of agitation, nystagmus, sialorrhea, vomiting, and signs of postoperative pain. The hospitalization regime planned was ambulatorial.

In the statistical analysis, qualitative variables were expressed as sample proportions and 95% Confidence Intervals (95% CI) of the percentage differences and Relative Risks (RR). For comparison between groups, chi-square test with Yates correction and Fisher's exact test were used when applicable. For quantitative variables, the Shapiro-Wilk test and histogram analysis were performed to assess the normality of distribution. Since continuous variables were normally distributed, they were expressed as mean and standard deviation, and the groups were compared using an unpaired Student's *t*-test. Differences in awakening time was assessed using the Kaplan-Meier survival curve; *p*-values < 0.05 were considered statistically significant. The analyses were carried out in the R environment.[13]

Results

To evaluate and compare the degree of sedation between midazolam and the combination of midazolam plus *S*(+)-ketamine as oral premedication in patients with ASD, a total of 64 participants were recruited and randomly allocated in two equal groups. Four participants in the combined treatment group, 6.25% of the total sample, did not ingest the premedication and were excluded from the study (Fig. 1).

The groups were similar in terms of patient characteristics, preoperative conditions, and duration of the procedures (Table 1). All participants were considered ASA physical status II, mainly due to autism. In children and adolescents, obesity was considered a z-BMI score ≥ 2 according to World Health Organization score curves adjusted for sex and age group.[14,15] In adults, a BMI ≥ 30 was used to diagnose obesity.[16]

Regarding the primary outcome, the degree of sedation differed between the two groups, with Ramsay score 2 predominating in the Midazolam group. There was a significant difference between the groups overall, with *p*-value = 0.02 (Table 2). Dichotomous analysis of the degree of sedation (Ramsay score 1 and 2 vs. Ramsay score ≥ 3) showed a significant difference between groups, as well. In the Midazolam group, the occurrence of Ramsay score ≥ 3 was 15.6%, while in the Midazolam/Ketamine group this same score was observed in 50% of the participants, which bestows a

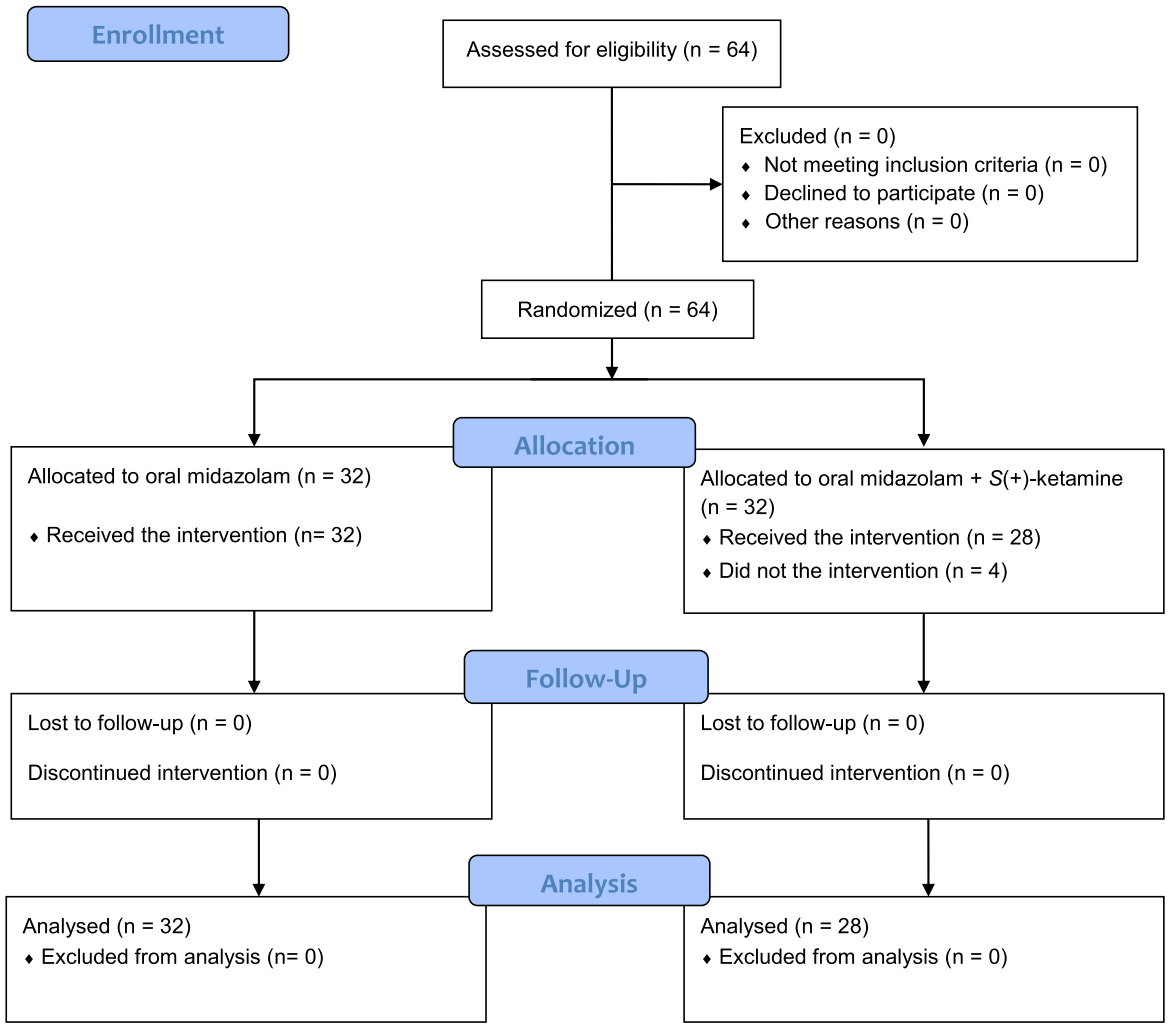

Figure 1 Clinical trial flow diagram (CONSORT).

RR = 3.2 (95% CI = 1.32 to 7.76 with *p*-value = 0.01) for this degree of sedation.

Venous access was significantly easier in the combined treatment group (*p*-value = 0.01), with a higher relative frequency of physical stabilization required in the Midazolam group (Table 3). Dichotomous evaluation of venous access revealed that adding *S*(+)-ketamine to midazolam facilitated venous access without resorting to restraint (64.2%) when compared with midazolam alone (31.2%) with a RR = 2.05 (95% CI = 1.14 to 3.68) and *p*-value = 0.02.

Regarding awakening time, the groups did not differ significantly in a time to event analysis as shown in the Kaplan-Meier curve (Fig. 2). None of the participants in both groups needed additional boluses of opioids, however about 30% in each group required minimum alveolar concentration of sevoflurane up to 3%, without significant differences between them (Table 1).

Concerning secondary outcomes in the Midazolam group and Midazolam/Ketamine group, the respective occurrences of adverse effects were as follows: agitation 9.3% vs. 7.1% (RR = 0.76 [95% CI = 0.13 to 4.23] *p*-value = 0.75), nystagmus 3.1% vs. 0% (RR = 0.37 [95% CI = 0.01 to 8.95] *p*-value = 0.54), sialorrhea 21.8% vs. 17.8% (RR = 0.81 [95% CI = 0.29 to 2.28] *p*-value = 0.69), and vomiting 0% vs. 3.5% (RR = 3.41 [95% CI = 0.14 to 80.58] *p*-value = 0.44). None of the participants required additional analgesia.

All patients from both groups had acquired conditions of being released from the postanesthetic care unit within 60 minutes, and of hospital discharge within two hours after leaving the surgical theater.

Discussion

Among the many challenges faced by autistic patients, difficulty in social communication and low adaptability to non-routine sensory experiences are particularly frequent. Non-collaborative behaviors and high occurrence of anxiety in the perioperative period are key justifications for preanesthetic medication in this specific population, especially in those individuals who exhibit aggressive behaviors. It not only helps all procedures related with anesthetic induction, but also facilitates amnesia, favoring non-memorization of triggering events that could lead to worse behaviors in

Table 1 Patients' characteristics, preoperative conditions, anesthesia duration and minimum alveolar concentration of sevoflurane in Midazolam group and Midazolam + Ketamine group (η = 60).

Variable	Midazolam group (η = 32)	Midazolam + ketamine group (η = 28)
Age (years)[a]		
< 12 years	16 (50%)	11 (39.3%)
12 to 19 years	5 (15.6%)	4 (14.3%)
> 19 years	11 (34.4%)	13 (46.4%)
Male[a]	25 (78.1%)	20 (71.4%)
Body mass index ($kg{\cdot}m^{-2}$)[b]	22.0 ±6.0	21.8 ±5.0
Degree of autism[a,c]		
1	4 (12.5%)	4 (14.3%)
2	12 (37.5%)	9 (32.1%)
3	16 (50%)	15 (53.6%)
Comorbidities[a]		
None	8 (25%)	6 (21.5%)
Epilepsy	10 (31.2%)	10 (35.6%)
Obesity	8 (25%)	8 (28.5%)
Other	7 (21.9%)	5 (17.9%)
Medications[a]	24 (75%)	22 (78.5%)
Anticonvulsants	11 (34.4%)	13 (46.4%)
Antipsychotics	20 (62.5%)	15 (53.6%)
Antidepressants	3 (9.4%)	3 (10.7%)
Benzodiazepines	6 (18.8%)	8 (28.6%)
Anesthesia duration (minutes)[b]	149.5 ± 66.0	143.3 ± 66.4
Minimum alveolar concentration of sevoflurane		
2%	22 (68.7%)	19 (67.8%)
2.5%	5 (15.6%)	3 (10.7%)
3%	5 (15.6%)	6 (21.4%)

[a] Values expressed in absolute numbers and relative frequency (in parentheses).
[b] Values expressed as mean and standard deviation.
[c] Degree of Autism: 1 = requires support; 2 = requires substantial support; 3 = requires very substantial support.

Table 2 Sedation levels in Midazolam group and Midazolam + Ketamine group according to Ramsay scale.

Variable	Midazolam group (η = 32)	Midazolam + ketamine group (η = 28)	Difference between percentages (95% CI of differences)	p[c]
Ramsay scale[a]				0.02
1	6 (18.8%)	5 (17.9%)	+0.9% (−18.7 to +20.7)	
2	21 (65.6%)	9 (32.1%)	+33.5% (+9.6 to +57.4)	
3	3 (9.4%)	8 (28.6%)	−19.2% (−38.7 to +0.3)	
4	2 (6.2%)	2 (7.1%)	−0.9% (−13.6 to +11.8)	
5	0	4 (14.3%)	−14.3%[b]	

[a] Values expressed in absolute numbers and relative frequency (in parentheses).
[b] Impossible to calculate the difference between percentages.
[c] Chi-square test for independence; significance level: $p < 0.05$

future interventions. Perioperative management should be individualized according to clinical manifestations, autism degree, and associated comorbidities.[10]

The oral route of premedication seems to be less invasive, nonetheless 6.25% of our sample did not accept the proposed preanesthetic and showed uncollaborative behaviors before even tasting the formula (original manufacturer's formulation syrup with sweet taste). Regarding the primary outcome, 81.2% of the participants in the Midazolam group and 82.1% in the Midazolam/Ketamine group had a Ramsay score ≥ 2, which can be interpreted as an anxiolysis state. The low oral bioavailability of S(+)-ketamine, estimated between 8% and 11%,[17,18] may have contributed to the fact that only 50% of participants in the Midazolam/Ketamine group presented a Ramsay score ≥3 (drowsy, asleep, or sedated). Nevertheless, this rate was three times higher than in the Midazolam group, whose rate was 15.6%.

Our sample characteristics were compatible with previous studies, which indicate that the incidence of ASD is approximately three times higher in males than in females.[19] Neuropsychologic behaviors in ASD are similar despite age and merging different age groups in studies with this

Table 3 Comparison of difficulty in obtaining intravenous access between Midazolam group and Midazolam + Ketamine group.

Variable	Midazolam group (η = 32)	Midazolam + ketamine group (η = 28)	Difference between percentages (95% CI of differences)	p^b
Ease of obtaining[a]				0.01
No reaction	1 (3.1%)	7 (25%)	−21.9% (−39.0 to +4.7)	
Minimal reaction	9 (28.1%)	11 (39.2%)	+11.2% (−35.0 to +12.7)	
Physical stabilization	19 (59.4%)	5 (17.9%)	+41.5% (+19.4 to +63.7)	
Pharmacological intervention	3 (9.4%)	5 (17.9%)	−8.5% (−25.9 to +8.9)	

[a] Values expressed in absolute numbers and relative frequency (in parentheses).
[b] Chi-Square test for independence; significance level: $p < 0.05$

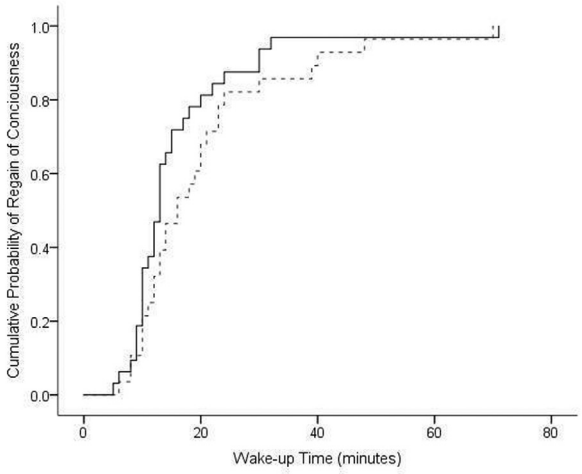

Figure 2 Kaplan-Meier survival analysis for wake-up time in minutes. Midazolam group: continuous line, Midazolam + Ketamine group: dashed line. Log rank test with p = 0.221.

population is not uncommon among published papers related to the matter, since in the real-world scenario a large age range can be observed in referral services for this condition. Regarding comorbidities associated with ASD, epilepsy was present in 33.4% of the participants, which was higher than the proportion found in a systematic review (12.1%).[20] The prevalence of obesity in the general Brazilian population is approximately 14% in children and adolescents and 26% in adults.[21] The prevalence in our sample, which included children, adolescents and adults, was 26.7%. A meta-analysis on the association between ASD and obesity showed an Odds Ratio of 1.84 for the prevalence of obesity in persons with ASD compared to non-autistic individuals.[22]

Almost four-fifths of our sample (76.6%) used psychotropic medications, which is higher than the 63.6% reported in a United States study.[23] The ASD severity distribution of our participants, according to the American Psychiatric Association, showed a predominance of level 3 (requires very substantial support), which comprised more than half of the participants, followed by level 2 (requires substantial support) in more than a third. This is to be expected since those patients are more likely to be referred to a specialized service. A previous study comparing the necessity of premedication in children with ASD, found an odds ratio of 2.70 and of 5.50 for this intervention when ASD level one was compared to level two and to level three respectively, which was similar to our findings.[24]

A clinical trial in non-autistic children that compared midazolam alone and midazolam plus ketamine at the same doses used in our study found an anxiolysis rate of 90% in the combined group and 75% with the midazolam group. This study reported a Ramsay score ≥3 in 70% of the combined group and less than 60% in the midazolam group.[11] Another clinical trial comparing different doses of midazolam in non-autistic children found that a dose of 0.5 $mg.kg^{-1}$ resulted in a sedation level comparable to Ramsay ≥3 in 15% of the sample.[25]

The chronic use of psychotropic medications among our sample, which can alter the functioning of the hepatic cytochrome P450 system,[26] as well as the genetic variability of cytochrome P450,[27] specifically CYP2B6 (involved in the metabolization of ketamine),[28] may have influenced the lower rates of anxiolysis and drowsy or sleeping status in our study. The difference in rates may be attributed to the use of racemic ketamine in previous studies, which has greater bioavailability than oral *S*(+)-ketamine.[17,18,29]

Venous access was a relevant aspect of our trial; in 64.2% of the combined treatment group and 30.3% of the midazolam group, peripheral venous access did not require physical stabilization. This difference could be due to the analgesic properties of ketamine, which acts on NMDA and opioid receptors.[30] A previous publication by Funk et al. used a scale identical to ours to assess the reaction to venous access[11] and showed better venipuncture scores with midazolam/ketamine association in pediatric anesthesia among non-autistic children, however, topical anesthetic at the puncture site was used, which may muddle analogies to our study.

The awakening time analysis with the Kaplan-Meier curve showed no difference between the groups in the present study. Previous studies using the same dosages also found no significant differences between groups.[11,31]

There was a low incidence of agitation, nystagmus, and sialorrhea in both intervention groups and the rates did not differ significantly between them in our research. These results are of an exploratory nature and must be analyzed with due caution, since the sample size was calculated as a function of the primary objective; our detection power for other events is underestimated. We chose to compare only midazolam and the association of midazolam and ketamine due to the lower sedation rates reported with ketamine alone seen in a previous paper,[11] which also found higher rates of

nausea, vomiting, and psychomimetic effects in children that received ketamine alone at a higher dosage (6 $mg.kg^{-1}$).[11]

Since no randomized clinical trials have been conducted on the use of oral midazolam and oral ketamine as preanesthetic in autistic persons, our study is both relevant and unprecedented. Our results can contribute to improve perioperative management in this population. Certain limitations are inherent to this study, such as the per-protocol analysis itself. This type of assessment was used to register the effectiveness of combined treatment in an ideal situation due to the scarcity of clinical data in the literature. Potential exclusion biases could compromise the effectiveness of the intervention, for which an intention-to-treat analysis would be more appropriate. Since it is assumed that ketamine can compromise the individual's sociobehavioral aspects beyond the hospitalization period, the lack of data in this topic could be considered as another limitation, as well as the non-evaluation of parent's anxiety, age difference between groups, non-monitoring of neuromuscular blockade and anesthesia depth. Also, the occurrence of adverse events must be seen with caution due to its inherent exploratory nature, which could lead to type 2 error related to insufficient detection power.

We conclude that the association of oral *S*(+)-ketamine and midazolam provides higher rates of a satisfactory preanesthetic sedation state than oral midazolam alone in patients with ASD. Combined treatment facilitates peripheral venous access without increasing awakening time or the incidence of adverse events.

Conflicts of interest

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

References

1. Maenner MJ, Shaw KA, Baio J, et al. Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2016. MMWR Surveillance Summaries. 2020;69:1—12.
2. Rodgers H, McCluney J. Prevalence of autism (including Asperger's syndrome) in school age children in Northern Ireland 2021. [Internet]. Prevalence of autism (including Asperger's syndrome) in school age children in Northern Ireland 2021. 2021: 1—25. Available from https://www.health-ni.gov.uk/sites/default/files/publications/health/asd-children-ni-2021.pdf.
3. American Psychiatric Association. American Psychiatric Association. DSM-5 Task Force. p 1, 5th ed. Diagnostic and statistical manual of mental disorders: DSM-5, 1; 2013. p. 20131—991.
4. Ouchi K, Sugiyama K. Required propofol dose for anesthesia and time to emerge are affected by the use of antiepileptics: prospective cohort study. BMC Anesthesiology. 2015;15:34.
5. Manso MA, Guittet C, Vandenhende F, Granier L. Efficacy of oral midazolam for minimal and moderate sedation in pediatric patients: A systematic review. Pediatric Anesthesia. 2019;29:1094—106.
6. Sado-Filho J, Viana KA, Corrêa-Faria P, Costa LR, Costa PS. Randomized clinical trial on the efficacy of intranasal or oral ketamine-midazolam combinations compared to oral midazolam for outpatient pediatric sedation. PLOS ONE. 2019;14. e0213074-e0213074.
7. Poonai N, Canton K, Ali S, et al. Intranasal ketamine for procedural sedation and analgesia in children: A systematic review. PLOS ONE. 2017;12:e0173253.
8. Chen C, Cheng X, Lin L, Fu F. Preanesthetic nebulized ketamine vs preanesthetic oral ketamine for sedation and postoperative pain management in children for elective surgery. Medicine. 2021;100. e24605-e24605.
9. Taghizadeh N, Davidson A, Williams K, Story D. Autism spectrum disorder (ASD) and its perioperative management. Pediatric Anesthesia. 2015;25:1076—84.
10. Taghizadeh N, Heard G, Davidson A, Williams K, Story D. The experiences of children with autism spectrum disorder, their caregivers and health care providers during day procedure: A mixed methods study. Paediatric Anaesthesia. 2019;29:927—37.
11. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. British Journal of Anaesthesia. 2000;84:335—40.
12. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with Alphaxalone-Alphadolone. BMJ. 1974;2:656—9.
13. R Core Team. R: A language and environment for statistical computing [Internet]. R: A language and environment for statistical computing; 2018. Available from https://www.r-project.org/.
14. de Onis M. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85:660—7.
15. Organization WH. Child growth standards /Standards / Body mass index-for-age (BMI-for-age) [Internet]. 2006. Available from: https://www.who.int/tools/child-growth-standards.
16. World Health Organization. Obesity and overweight [Internet]. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
17. Peltoniemi MA, Saari TI, Hagelberg NM, Laine K, Kurkinen KJ, Neuvonen PJ, et al. Rifampicin has a profound effect on the pharmacokinetics of oral S-ketamine and less on intravenous S-ketamine. Basic Clin Pharmacol Toxicol. 2012;111:325—32.
18. Fanta S, Kinnunen M, Backman JT, Kalso E. Population pharmacokinetics of S-ketamine and norketamine in healthy volunteers after intravenous and oral dosing. Euro J Clin Pharmacol. 2015;71:441—7.
19. Arnold B, Elliott A, Laohamroonvorapongse D, Hanna J, Norvell D, Koh J. Autistic children and anesthesia: is their perioperative experience different? Pediatric Anesthesia. 2015;25:1103—10.
20. Lukmanji S, Manji SA, Kadhim S, et al. The co-occurrence of epilepsy and autism: A systematic review. Epilepsy Behavior. 2019;98:238—48.
21. Ministério da Saúde. Pesquisa nacional de saúde: 2019: percepção do estado de saúde, estilos de vida, doenças crônicas e saúde bucal: Brasil e grandes regiões/IBGE. Coordenação de Trabalho e Rendimento. 2020. [Internet]Available from https://biblioteca.ibge.gov.br/visualizacao/livros/liv101764.pdf.
22. Zheng Z, Zhang L, Li S, Zhao F, Wang Y, Huang L, et al. Association among obesity, overweight and autism spectrum disorder: a systematic review and meta-analysis. Scientific Reports. 2017;7:11697.
23. Houghton R, Ong RC, Bolognani F. Psychiatric comorbidities and use of psychotropic medications in people with autism spectrum disorder in the United States. Autism Research. 2017;10(12):2037—47.
24. Swartz JS, Amos KE, Brindas M, Girling LG, Ruth, Graham M. Benefits of an individualized perioperative plan for children with autism spectrum disorder. Pediatric Anesthesia. 2017;27:856—62.
25. Sheta SA, AlSarheed M. Oral midazolam premedication for children undergoing general anaesthesia for dental care. Inter J Pediatrics. 2009: 1—7. 2009.

26. Hedrich WD, Hassan HE, Wang H. Insights into CYP2B6-mediated drug—drug interactions. Acta Pharmaceutica Sinica B. 2016;6:413—25.
27. Zanger UM, Klein K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. Frontiers in Genetics. 2013;4.
28. Wang PF, Neiner A, Kharasch ED. Stereoselective ketamine metabolism by genetic variants of cytochrome P450 CYP2B6 and cytochrome P450 oxidoreductase. Anesthesiology. 2018; 129:756—68.
29. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of I.M. and oral ketamine. Br J Anaesth. 1981;53:805—10.
30. Mion G, Villevieille T. Ketamine pharmacology: An update (Pharmacodynamics and molecular aspects, recent findings). CNS Neuro Therap. 2013;19:370—80.
31. Trabold B, Rzepecki A, Sauer K, Hobbhahn J. A comparison of two different doses of ketamine with midazolam and midazolam alone as oral preanaesthetic medication on recovery after sevoflurane anaesthesia in children. Pediatric Anesthesia. 2002;12:690—3.