

Evaluation of the Efficacy and Safety of Multimodal Sedation with Dexmedetomidine and Ketamine (Ketodex) at Different Ratios: A Randomized Clinical Trial

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Abstract

Objectives: To evaluate the efficacy and safety of sedation with dexmedetomidine and ketamine (Ketodex) at 1:1, 1:2, 1:3 ratios in children with autism spectrum disorder undergoing dental procedures.

Materials and Methods: A randomized, parallel-group, triple-blind clinical trial included 63 children with ASD randomly assigned to three groups (n = 21 each). Physiological parameters, sedation efficacy using the Houpt Scale, and adverse events were evaluated at a 5% significance level.

Results: Sedation success differed significantly among groups ($p < 0.001$) and increased progressively with higher ketamine proportions, with the 1:3 ratio showing the highest clinical efficacy. Compared with 1:1, the odds of successful sedation were over tenfold higher with 1:2 and 85-fold higher with 1:3. The relative risk of sedation failure decreased by 64.7% and 94.1%, respectively, corresponding to numbers needed to treat of 1.91 and 1.31. Physiological parameters remained clinically stable, with no serious adverse events. Vomiting was more frequent with the 1:3 ratio, but all episodes were self-limited, required no intervention, and did not prevent completion of dental treatment.

Conclusions: The Ketodex combination was effective and safe for sedating children with ASD undergoing dental treatment. The 1:3 ratio demonstrated the best overall clinical performance, with the highest sedation success rate and an acceptable safety profile, making it a promising option for the dental management of this population. **Clinical Relevance:** Ketodex at 1:2 and 1:3 ratios may provide effective intramuscular sedation for dental treatment in children with ASD while maintaining cardiorespiratory stability.

Trial registration

Brazilian Registry of Clinical Trials (ReBEC), RBR108hw8xt, registered on June 18, 2026. Universal Trial Number (UTN) U111113405747.

What is Known - What is New

This study evaluated three proportions of Ketodex (dexmedetomidine and ketamine combined at 1:1, 1:2, and 1:3 ratios via intramuscular administration) for sedation in children with Autism Spectrum Disorder (ASD) during dental care. As the first triple-blind clinical trial to directly compare increasing proportions of ketamine with a fixed dose of dexmedetomidine in this specific population, it demonstrates that behavioral success directly depends on the chosen ratio. Clinical efficacy was significantly highest in the 1:3 protocol, achieving a 95.2% success rate compared to 71.4% in the 1:2 group and 19.0% in the 1:1 group ($p < 0.001$), while increasing the odds of local anesthesia success by 85 times compared to the 1:1 ratio. Regarding safety, all proportions maintained cardiorespiratory stability without serious adverse events. Vomiting episodes were self-limiting and occurred more frequently in the 1:3 group (28.6%), suggesting the preventive administration of antiemetics. Ultimately, Ketodex 1:3 emerges as the optimal clinical choice by combining maximum behavioral efficacy with a high physiological safety profile.

Introduction

Patients with Autism Spectrum Disorder (ASD) frequently exhibit a high prevalence of dental caries and periodontal disease, requiring both preventive and restorative dental care[1, 2]. However, the success of dental treatment depends largely on behavioral management, which remains one of the greatest challenges in the outpatient setting.[3, 4] This complexity stems from impairments in verbal and non-verbal communication, limited eye contact, and ASD-specific characteristics such as sensory hypersensitivity, heightened anxiety, and reduced behavioral predictability[3, 5]. Given these challenges, the pharmacological management, often involving multimodal sedation strategies, is frequently essential to ensure successful treatment and patient safety[6, 7].

Dexmedetomidine, an α_2 -adrenergic agonist that acts on the locus coeruleus, has gained prominence because it provides sedation while preserving spontaneous ventilation and producing anxiolytic effects. It acts by inhibiting norepinephrine release, thereby partially suppressing the arousal system and inducing sedation. Ketamine, in contrast, produces dissociative sedation and potent analgesia while maintaining hemodynamic stability. Its mechanism of action involves antagonism of N-methyl-D-aspartate (NMDA) receptors within the glutamate system[8, 9]. By blocking these receptors in the synaptic cleft, ketamine prevents calcium influx into neurons and interrupts the transmission of pain signals and sensory stimuli to the cerebral cortex. As a result, patients experience dissociation: although they may appear awake, they are unable to process or respond to pain or the surrounding environment.[8, 10] The combination of dexmedetomidine and ketamine, commonly referred to as Ketodex, represents a safe pharmacological strategy because the pharmacological profile of each drug offsets the adverse effects of the other. Dexmedetomidine attenuates the increases in heart rate and blood pressure associated with ketamine, whereas ketamine reduces the bradycardia and hypotension induced by dexmedetomidine[6, 11].

Furthermore, children with ASD exhibit distinct neurobiological characteristics, including an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission systems, sensory processing dysfunction, and autonomic nervous system hyperreactivity, all of which directly influence the pharmacodynamics of anesthetic and sedative agents[12, 13]. This unique neurophysiological profile makes the direct application of sedation protocols developed for the general pediatric population inappropriate. Consequently, it cannot be assumed that the drug ratio considered optimal for neurotypical children also represents the most effective and safe approach for patients with ASD[14, 15]. Investigating different dexmedetomidine-ketamine ratios is therefore justified by the need to identify the optimal balance among sedative efficacy, physiological stability, and clinical safety in this specific population.

Accordingly, the objective of this study was to evaluate the efficacy and safety of sedation with dexmedetomidine and ketamine (Ketodex) at dexmedetomidine-ketamine ratios of 1:1, 1:2, and 1:3 in children with ASD undergoing dental procedures. The study hypothesis was that increasing the

proportion of ketamine would increase the sedation success rate without compromising clinical safety or increasing the incidence of serious adverse events.

Material and methods

This study was a randomized, controlled, parallel-group, triple-blind, three-arm superiority clinical trial conducted in accordance with the CONSORT 2025 Statement guidelines for randomized clinical trials. The study was approved by the Research Ethics Committee of the Federal University of Alagoas (UFAL) (Approval No. 7.988.731) and complied with the ethical principles established by Brazilian National Health Council (CNS) Resolution No. 466/2012. The trial was registered in the Brazilian Clinical Trials Registry (ReBEC) under number RBR-108hw8xt (available at: <https://ensaiosclinicos.gov.br/rg/RBR-108hw8xt>).

This study was conducted during the first semester of 2026 in Maceió, Alagoas, northeastern Brazil, and enrolled children with ASD. The study population consisted of children aged 6 to 10 years with ASD who required level 2 or level 3 support according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The diagnosis, level of severity, and support needs were confirmed through a medical report issued by a specialist. Participants were screened and treated at the Pediatric Dentistry Clinic of the School of Dentistry at the Federal University of Alagoas.

The pilot phase included an initial sample of 45 participants (15 per group), who were randomly assigned in a 1:1:1 ratio to assess the logistical feasibility of the intramuscular pharmacological protocol and to train the clinical team. After preliminary data on the variability of Ketodex efficacy had been obtained from the pilot study, the sample size for the definitive clinical trial was calculated using G*Power software (version 3.1.9.7). No modifications to the study design were made between the pilot and the definitive trial. The sample size calculation was based on a superiority design, assuming 95% statistical power and a two-sided significance level of 5%. A minimum of 21 participants per group was required. Therefore, the final sample comprised 63 patients.

The study included children of both sexes, aged 6 to 10 years, clinically classified as ASA I (healthy) and diagnosed with ASD (requiring level 2 or 3 support). Participants had a level of cooperation that precluded conventional dental care without pharmacological support, as determined using the Frankl Behavior Scale (classified as Definitely Negative [F1] or Negative [F2]). Participation required the signing of an Informed Consent Form by the parents or legal guardians and, where applicable, an Informed Assent Form by the child. Parents, caregivers, and participants were not involved in the design or conduct of the clinical trial. Neurotypical children, including those with behavior classified within the parameters established by the Frankl scale, were excluded, as were children with ASD who had had a known allergy or hypersensitivity to ketamine or dexmedetomidine, a history of cardiac arrhythmia or uncorrected congenital heart disease, sleep apnea, other concomitant psychiatric or neurological disorders, a general health status unsuitable for outpatient sedation, or behavioral severity beyond the indications for multimodal sedation.

Participants were randomly assigned to three groups in a 1:1:1 ratio according to sedation protocol. Group 1 received dexmedetomidine and ketamine (Ketodex) at a dexmedetomidine-to-ketamine dose ratio of 1 mcg/kg:1 mg/kg; Group 2 received dexmedetomidine and ketamine at a ratio of 1 mcg/kg:2 mg/kg; and Group 3 received dexmedetomidine and ketamine at a ratio of 1 mcg/kg:3 mg/kg. All medications were administered 15 minutes before the procedure. Randomization was stratified by ASD support level using IBM® SPSS statistical software (version 23.0), ensuring a balanced distribution of participants and support levels across the groups.

To minimize response bias related to treatment allocation, a triple-blind design was used. The person administering the medication, the child, the parent or caregiver, and the outcome assessor were unaware of treatment assignment. Only the study supervisor was aware of the group assignments, which were disclosed only after completion of all data collection. Given the wide range of dental procedures required by children with ASD and the need to avoid the final procedure as a potential confounding variable, assessment of sedation efficacy was focused exclusively on the administration of local anesthesia. Only children whose clinical treatment required local anesthesia were included. The administration of local anesthesia was performed strictly on the basis of therapeutic indication and not solely for research purposes.

A brief medical history was obtained from the guardian prior to the dental procedure. Eligible patients were examined to assess their suitability for sedation, and guardians were instructed regarding pre-sedation fasting requirements: 2, 4, and 6 hours for clear liquids, milk, and light meals, respectively. On the day of the appointment, vital signs, including systolic and diastolic blood pressure (SBP and DBP), measured using a digital sphygmomanometer, and heart rate and oxygen saturation, measured using a pulse oximeter, were monitored before and during treatment, and at discharge.

Each participant's body weight was recorded at the beginning of the appointment to ensure accurate drug dosing. The medications were prepared from commercially available parenteral formulations without dilution or the addition of a vehicle: dexmedetomidine hydrochloride (Precedex 100 µg/mL) and ketamine hydrochloride (Ketamine 50 mg/mL). For the intervention, the exact doses of both drugs were sequentially drawn into a single syringe and combined without dilution. To maintain blinding and ensure allocation concealment, the syringes for all groups were prepared by an independent researcher and presented in identical, opaque, coded containers, preventing the administering clinician and outcome assessor from visually identifying the treatment ratio.

The medications were administered intramuscularly into the vastus lateralis muscle of the thigh. Following skin antisepsis with 70% alcohol, the sedative was injected perpendicular to the skin surface (90° angle) using disposable hypodermic needles appropriate for the child's muscle mass (25 x 0.7 mm). Aspiration was performed before injection to confirm the absence of blood reflux and ensure strictly intramuscular administration, followed by slow and continuous administration of the solution.

The dental procedure began once the child reached the drowsiness stage on the Houpt Scale, which was considered the target level of sedation. For this study, a Houpt score of 4 or higher was defined as

successful sedation, whereas a score of 3 or lower was defined as sedation failure. Immediately before administration of local anesthesia, topical anesthesia with 20% benzocaine gel was applied using a cotton swab for 60 seconds. Local infiltration anesthesia was then administered in the maxilla or mandible using 2% lidocaine with 1:100,000 epinephrine (DFL® brand). This anesthetic was selected based on its safety profile and good bone diffusibility. Behavioral and physiological data were collected at three specific time points: before administration of local anesthesia, during its administration, and immediately after its completion. The subsequent dental procedure was continuously monitored for safety purposes but was not considered a primary efficacy outcome.

The initial assessment of sedation efficacy was based on the successful administration of local anesthesia. Primary behavioral outcomes were assessed using the Houpt Scale, developed by Houpt et al. (1985), which evaluates consciousness, movement, vocalization, and overall behavior to provide a sedation and cooperation score. Continuous monitoring was performed using pulse oximetry to measure peripheral oxygen saturation (SpO₂), heart rate (HR), and noninvasive blood pressure (BP) using a multiparameter monitor connected to the patient. Assessments were performed during local anesthesia administration and every 15 minutes thereafter. Secondary outcomes included the identification and frequency of adverse events and clinical complications observed during and after sedation, including prolonged drowsiness, paradoxical reactions (agitation and irritability), anterograde amnesia, hallucinations, hiccups, emetic episodes (nausea and vomiting), and general malaise.

The assumption of normality was assessed using the Shapiro-Wilk test. The Kruskal-Wallis test was used to compare the three independent experimental groups with respect to physiological parameters, including systolic blood pressure, diastolic blood pressure, heart rate, and peripheral oxygen saturation. When the overall test indicated a statistically significant difference, post hoc pairwise comparisons were performed using the Mann-Whitney U test, with Bonferroni correction applied to adjust the significance level. Associations between categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, with the latter used when the expected frequencies did not meet the assumptions of the chi-square test. All efficacy analyses were conducted according to the intention-to-treat (ITT) principle, with participants analyzed according to the groups to which they were originally randomized. A significance level of 5% ($p < 0.05$) was adopted for all inferential analyses.

Results

The sample consisted of 63 participants, of whom 46 (73.0%) were male and 17 (27.0%) were female, with no significant difference in sex distribution across the groups ($p = 0.923$). Participants were equally distributed across the three parallel experimental arms ($n = 21$ per group). The detailed flow of recruitment, screening, eligibility, randomization, allocation, and participant analysis is summarized in Fig. 1.

Baseline demographic characteristics were comparable across the three experimental groups ($p > 0.05$). The median age was 8 years (range: 6–10 years) in all groups ($p = 0.985$). Mean body weight was 25.56

± 8.14 kg in Group 1, 28.26 ± 9.03 kg in Group 2, and 28.07 ± 11.11 kg in Group 3, with no statistically significant difference between the groups ($p = 0.612$).

As shown in Table 1, the sedation success rate differed significantly across the experimental groups ($p < 0.001$). Sedation success rates were 19.0% in Group 1, 71.4% in Group 2, and 95.2% in Group 3. Pairwise comparisons with Bonferroni adjustment showed statistically significant differences between Group 1 and Group 2 ($p = 0.001$) and between Group 1 and Group 3 ($p < 0.001$), whereas no statistically significant difference was observed between Group 2 and Group 3 ($p = 0.093$). Compared with Group 1, the odds of successful sedation were significantly higher in Group 2 (OR = 10.62; 95% CI: 2.44–46.23; $p = 0.001$) and Group 3 (OR = 85.00; 95% CI: 7.42–973.63; $p < 0.001$). The relative risk reduction (RRR) for sedation failure was 64.7% in Group 2 and 94.1% in Group 3. The corresponding NNTs were 1.91 and 1.31, respectively.

Table 1
Analysis of sedation success and failure according to experimental group (N = 63)

Group	Sedation success, n (%)	Sedation failure, n (%)	OR for successful sedation (95% CI)	RRR for sedation failure	NNT	p-value
G1 (1:1)	4 (19.0%)	17 (81.0%)	1.00	—	—	—
G2 (1:2)	15 (71.4%)	6 (28.6%)	10.62 (2.44–46.23)	64.7%	1.91	0.001
G3 (1:3)	20 (95.2%)	1 (4.8%)	85.00 (7.42–973.63)	94.1%	1.31	< 0.001
Note: RRR= Relative Risk Reduction; NNT = number needed to treat; OR = odds ratio; CI = confidence interval. RRR for sedation failure was calculated relative to the control group (G1). Pairwise p-values are based on comparisons with G1. Overall chi-square: $\chi^2 = 27.06$; $p < 0.001$.						

Behavioral outcomes assessed using the Houpt Scale are presented in Table 2. Statistically significant differences were observed among the experimental groups for crying ($p = 0.001$), movement ($p < 0.001$), consciousness ($p = 0.021$), and overall behavior ($p < 0.001$). Adequate crying behavior was observed in 71.4% ($n = 15$) of participants in Group 1 and in 100.0% ($n = 21$) of participants in both Groups 2 and 3. Adequate movement control was observed in 38.1% ($n = 8$), 66.7% ($n = 14$), and 100.0% ($n = 21$) of participants in Groups 1, 2, and 3, respectively. Adequate consciousness was observed in 76.2% ($n = 16$) of participants in Group 1, 95.2% ($n = 20$) in Group 2, and 100.0% ($n = 21$) in Group 3. Overall successful behavior according to the Houpt Scale was observed in 19.0% ($n = 4$) of participants in Group 1, 71.4% ($n = 15$) in Group 2, and 95.2% ($n = 20$) in Group 3.

Table 2

Distribution of behavioral outcomes according to the Houpt Scale and experimental group (N = 63).

Variable	G1, n (%)	G2, n (%)	G3, n (%)	χ^2	p-value
Adequate crying behavior	15 (71.4)	21 (100.0)	21 (100.0)	13.26	0.001
Adequate movement control	8 (38.1)	14 (66.7)	21 (100.0)	18.61	< 0.001
Adequate consciousness	16 (76.2)	20 (95.2)	21 (100.0)	7.74	0.021
Successful sedation	4 (19%)	15 (71.4)	20 (95.2)	23.97	< 0.001
Note: Pearson's chi-square test. Values are presented as absolute frequencies and percentages.					

No statistically significant differences were observed in heart rate (HR) either at the pre-sedation stage (G1: 110.2 ± 27.26 bpm; G2: 112.4 ± 22.89 bpm; G3: 108.4 ± 17.66 bpm) or during sedation (G1: 107.0 ± 20.30 bpm; G2: 106.3 ± 14.75 bpm; G3: 99.90 ± 10.21 bpm) ($p > 0.05$). A similar pattern of stability was observed for peripheral oxygen saturation (SpO_2), both pre-sedation (G1: $97.71 \pm 2.55\%$; G2: $94.10 \pm 9.48\%$; G3: $98.29 \pm 1.23\%$) and during sedation (G1: $98.19 \pm 1.32\%$; G2: $97.10 \pm 4.14\%$; G3: $98.33 \pm 1.01\%$) ($p > 0.05$).

No adverse reactions were observed in 95.2% ($n = 20$) of participants in Group 1, 76.2% ($n = 16$) in Group 2, and 71.4% ($n = 15$) in Group 3. Vomiting occurred in one participant (4.8%) in Group 1, two participants (9.5%) in Group 2, and six participants (28.6%) in Group 3. Three transient episodes of hiccups (14.3%) were observed exclusively in Group 2.

The distribution of adverse reactions differed significantly among the experimental groups ($p = 0.022$). Despite this difference, the overall safety profile of the protocols was satisfactory, with the majority of participants (81.0%; $n = 51/63$) undergoing the dental procedures without adverse effects.

Discussion

The present randomized clinical trial evaluated the efficacy and safety of intramuscular dexmedetomidine–ketamine (Ketodex) administered at 1:1, 1:2, and 1:3 ratios in children with ASD undergoing dental treatment. The findings supported the study hypothesis, demonstrating that increasing the proportion of ketamine while maintaining a fixed dexmedetomidine dose progressively increased the sedation success rate. The 1:3 Ketodex protocol showed the highest sedation success rate while maintaining physiological stability throughout the procedure. These findings suggest that optimizing the ketamine component of the Ketodex combination may enhance behavioral control during dental treatment without compromising the overall safety profile[11, 15].

Dental treatment in children with ASD is particularly challenging because behavioral dysregulation is often exacerbated by sensory hypersensitivity, communication deficits, restricted and repetitive behaviors, and heightened responses to environmental and nociceptive stimuli[2, 4, 15, 16]. These characteristics frequently compromise cooperation during highly aversive procedures, particularly the

administration of local anesthesia, making effective behavioral control a critical determinant of sedation success[2, 4, 17, 18]. In the present study, the 1:1 Ketodex protocol was insufficient to consistently control movement and crying during local anesthesia administration, whereas progressively increasing the ketamine proportion resulted in marked improvements in behavioral outcomes, with the 1:3 protocol achieving the greatest clinical success. These findings are consistent with previous randomized clinical trials and systematic reviews demonstrating that the combination of dexmedetomidine and ketamine provides superior behavioral management compared with dexmedetomidine alone during pediatric dental sedation[15, 19].

The superior efficacy observed with the 1:3 Ketodex protocol is biologically plausible and can be attributed to the complementary pharmacodynamic actions of dexmedetomidine and ketamine. Dexmedetomidine produces cooperative sedation, anxiolysis, and analgesia through selective α_2 -adrenergic receptor agonism, whereas ketamine induces dissociative sedation and potent analgesia primarily through antagonism of N-methyl-D-aspartate (NMDA) receptors[8, 20]. Increasing the ketamine proportion while maintaining a fixed dexmedetomidine dose may have enhanced tolerance to nociceptive stimulation during local anesthesia without compromising spontaneous ventilation or protective airway reflexes[10]. This complementary pharmacological profile is consistent with the progressive improvements in movement control, crying, and overall behavioral performance observed as the ketamine proportion increased[14, 15, 19].

The clinical relevance of these findings is further supported by the effect size estimates. Compared with the 1:1 Ketodex protocol, both the 1:2 and 1:3 protocols demonstrated greater clinical efficacy, as evidenced by higher odds of successful sedation, greater relative risk reduction, and lower NNT values. These findings indicate that increasing the ketamine proportion not only enhanced the likelihood of successful sedation but also substantially reduced the risk of sedation failure. Furthermore, the low NNT values suggest that treating only a small number of patients with the 1:2 or 1:3 Ketodex protocols instead of the 1:1 regimen would result in one additional successful sedation, reinforcing the clinical relevance of these protocols. Among the evaluated regimens, the 1:3 protocol showed the greatest magnitude of effect across all measures, indicating the highest clinical efficacy. Overall, these findings suggest that increasing the ketamine proportion within the Ketodex protocol may provide meaningful clinical benefits while maintaining a favorable safety profile. Collectively, these results support the use of individualized sedation strategies according to the behavioral demands of the patient and the procedure, rather than relying on a universal pharmacological regimen[3, 21].

Unlike previous randomized clinical trials, the present study exclusively enrolled children with ASD classified as DSM-5 Levels 2 and 3 and directly compared three intramuscular Ketodex dose ratios while maintaining a fixed dexmedetomidine dose[15, 19]. In addition, behavioral outcomes were systematically assessed during local anesthesia administration, the most aversive stage of dental treatment for children with ASD[2, 18]. To the authors' knowledge, this is the first randomized clinical trial to specifically investigate the effect of increasing ketamine proportions within an intramuscular Ketodex protocol in this population. These methodological characteristics enhance the clinical applicability of the

findings and provide novel evidence supporting individualized sedation strategies for children with ASD undergoing dental treatment[3, 11].

An important finding of the present study was that an apparently adequate level of sedation alone was insufficient to ensure procedural success. Although most participants in the 1:1 protocol appeared clinically sedated, this did not consistently translate into adequate movement control or reduction of disruptive crying during local anesthesia administration. In contrast, increasing the ketamine proportion resulted in progressive improvements across all behavioral domains of the Houpt Scale, particularly movement control and overall behavior[15, 19]. These findings reinforce that procedural success in children with ASD depends not only on achieving adequate sedation but also on maintaining effective behavioral control during the most aversive stage of dental treatment[11, 21].

Despite statistically significant differences in systolic blood pressure before sedation and diastolic blood pressure during the procedure, these findings should be interpreted with caution[8, 20]. The higher pre-sedation systolic blood pressure observed in the 1:3 Ketodex group most likely reflected baseline variability rather than an effect of the intervention, as these measurements were obtained before drug administration. During the procedure, the modest increase in diastolic blood pressure observed with the highest ketamine dose is consistent with the sympathomimetic properties of ketamine[20]. Importantly, all physiological parameters remained within clinically acceptable ranges, and no participant required therapeutic intervention, supporting the clinical safety of all three Ketodex protocols[11, 14]. Heart rate and peripheral oxygen saturation also remained stable throughout the study period, further supporting the absence of clinically relevant cardiorespiratory compromise despite the increasing ketamine proportion.

The overall physiological stability observed in this study can be explained by the complementary pharmacodynamic actions of dexmedetomidine and ketamine. Dexmedetomidine provides cooperative sedation, anxiolysis, and analgesia while attenuating sympathetic activity, whereas ketamine preserves airway reflexes and cardiovascular stability through sympathetic stimulation[21, 22]. The combination of these agents may improve their individual hemodynamic effects, contributing to the absence of clinically relevant cardiorespiratory instability despite increasing ketamine proportion. These findings support the use of Ketodex as a balanced multimodal sedation strategy that may improve procedural efficacy while preserving physiological stability.

Although cardiorespiratory stability was maintained across all groups, gastrointestinal adverse events, particularly vomiting, were more frequent with the higher ketamine proportions, with the highest incidence observed in the 1:3 Ketodex group. This finding is consistent with previous studies identifying nausea and vomiting as common adverse effects associated with ketamine-containing sedation regimens[11, 14, 22]. Transient hiccups were observed only in the 1:2 group, resolved spontaneously, and did not interfere with treatment or recovery. Notably, more than 80% of participants completed the procedure without any adverse event, reinforcing the favorable overall safety profile of the protocols. Furthermore, all reported adverse events were transient, self-limited, and did not interfere with

completion of the dental procedures or patient recovery. Therefore, prophylactic antiemetic therapy may be considered when higher ketamine proportions are incorporated into Ketodex protocols, particularly in patients with a known history or increased risk of postoperative nausea and vomiting[14, 23, 24].

The strengths of the present study include its randomized, triple-blind design, the absence of participant attrition, and the direct comparison of three intramuscular Ketodex dose ratios in a homogeneous population of children with ASD requiring Level 2 or Level 3 support according to DSM-5 criteria[25]. Moreover, behavioral outcomes were evaluated during local anesthesia administration, representing the most challenging stage of dental treatment[2, 18]. These methodological characteristics strengthen the internal validity and clinical applicability of the findings[3, 11].

A limitation of the study is the restriction of the sample to a specific age range (6 to 10 years), which limits immediate generalizability of the findings to younger children and adolescents with ASD. Further studies are therefore needed to assess the effectiveness of different Ketodex ratios across different age groups. Additionally, the single-center design, conducted in a university clinic, reflects a specific institutional setting and may limit the immediate generalizability of the findings to other clinical settings. Nevertheless, the rigorous triple-blind randomized design and the absence of participant attrition strengthen the internal validity of the study.

Conclusions

The multimodal combination of dexmedetomidine and ketamine (Ketodex) proved to be an effective and clinically safe strategy for sedating children with Autism Spectrum Disorder (ASD) during dental procedures. The 1:3 ratio demonstrated the highest sedation success rate and superior behavioral control while maintaining cardiorespiratory stability. Although it was associated with a higher frequency of self-limited vomiting episodes, no serious adverse events were observed. This protocol represents a promising option for the dental management of children with ASD. Future studies should investigate whether prophylactic antiemetic therapy can reduce these minor adverse events while preserving clinical efficacy.

Declarations

Ethics approval

This study was performed in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Research Ethics Committee of the Federal University of Alagoas (UFAL) (Approval No. 7.988.731).

Consent to participate

Written informed consent was obtained from the parents or legal guardians of all participants. Assent was also obtained from the children in accordance with their age and level of understanding.

Competing interests

The authors declare no competing interests.

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Author Contribution

L.A.M.T. contributed to conceptualization, methodology, investigation, data curation, and writing of the original manuscript. M.V.H. contributed to data analysis and manuscript review. T.F.M. contributed to data collection and manuscript review. K.R.M. contributed to data collection, data analysis, and manuscript review. V.B.F. provided resources and reviewed the manuscript. G.A.M.T. contributed to methodology, data analysis, and manuscript review. V.E.S.J. contributed to conceptualization, methodology, supervision, project administration, and manuscript review. All authors read and approved the final manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to participant privacy and confidentiality considerations but are available from the corresponding author on reasonable request.

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Figures

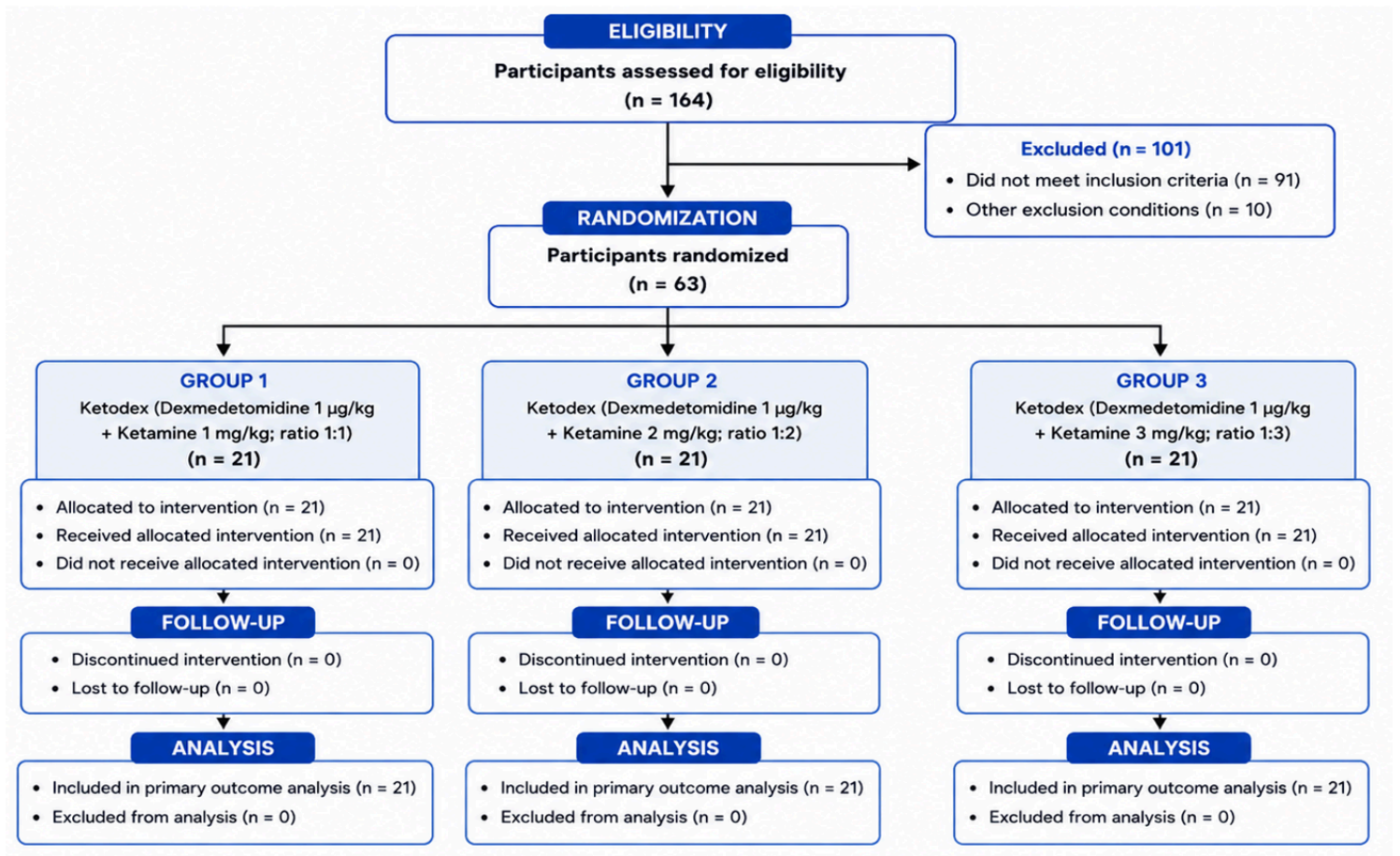


Figure 1

The consolidated standards of reporting trials flow diagram