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Clinical Use of Ketodex in Managing Dental Anxiety: A Systematic Review with Statistical Analysis Plan

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Systematic Review

ABSTRACT

This literature review examines the clinical efficacy, pharmacological profile, and safety of the combination of dexmedetomidine and ketamine (Ketodex) in dental procedures. A comprehensive search was conducted in the PubMed, Scopus, Web of Science, and Google Scholar databases, including studies published between 2000 and 2025. Articles were selected that investigated the use of Ketodex in dentistry and compared it with other sedation protocols such as midazolam-fentanyl and propofol-ketamine (Ketofol). The combination of dexmedetomidine and ketamine demonstrated effective sedation, hemodynamic stability, and a low incidence of adverse events. The intranasal route stood out for its practicality and good tolerability, particularly in pediatric patients. Compared to traditional sedation protocols, Ketodex showed notable advantages, including enhanced respiratory safety and more favorable post-sedation recovery. Ketodex emerges as a promising alternative for sedation in outpatient dental settings, especially among vulnerable populations. However, multicenter studies with larger sample sizes and cost-effectiveness analyses are still needed to support its widespread implementation in clinical practice.

Keywords: Intranasal ketodex; Pediatric closed reduction; Procedural sedation and analgesia; Dental anxiety; Dentistry.

Uso Clínico do Ketodex no Manejo da Ansiedade Odontológica: Uma Revisão Sistemática com um Plano de Análise Estatística

RESUMO

Esta revisão de literatura analisa a eficácia clínica, o perfil farmacológico e a segurança da combinação de dexmedetomidina e cetamina (Ketodex) em procedimentos odontológicos. A busca foi realizada nas bases de dados PubMed, Scopus, Web of Science e Google Scholar, incluindo estudos publicados entre 2000 e 2025. Foram selecionados artigos que abordavam o uso do Ketodex na odontologia, comparando-o a outros protocolos sedativos, como midazolam-fentanil e propofol-cetamina (Ketofol). A combinação de dexmedetomidina e cetamina demonstrou sedação eficaz, estabilidade hemodinâmica e baixa incidência de eventos adversos. A via intranasal destacou-se por sua praticidade e boa tolerabilidade, especialmente em pacientes pediátricos. Em comparação aos protocolos tradicionais, o Ketodex apresentou vantagens relevantes, como maior segurança respiratória e recuperação pós-sedação mais favorável. O Ketodex configura-se como uma alternativa promissora para a sedação em odontologia ambulatorial, especialmente em populações vulneráveis. No entanto, são necessários estudos multicêntricos, com amostras robustas e análises de custo-benefício, para subsidiar sua ampla adoção na prática clínica.

Palavras-chave: Cetodex intranasal; Redução fechada pediátrica; Sedação e analgesia para procedimentos; Ansiedade Odontológica; Odontologia.

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INTRODUCTION

Dental anxiety is a highly prevalent condition, affecting between 10% and 20% of the global population, with even higher incidence among children and individuals with special needs. [1,2] This scenario poses a significant barrier to the delivery of dental care, often leading to missed appointments, treatment refusal, and increased complexity of clinical procedures. [3,4] In this context, conscious sedation has emerged as a key strategy to enable dental interventions with greater comfort and safety. [4]

Among the various pharmacological protocols available, the use of Ketodex a combination of dexmedetomidine and ketamine stands out. Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that provides sedation and analgesia with minimal respiratory depression. [4] Ketamine, on the other hand, is an NMDA receptor antagonist with potent analgesic and dissociative properties that also preserves respiratory reflexes. When combined, these agents act synergistically, offering an optimal balance between effective sedation, hemodynamic stability, and rapid recovery.[5,6]

Ketodex presents notable advantages over traditional sedation protocols such as midazolam-fentanyl and propofol-ketamine (Ketofol), particularly in terms of lower incidence of respiratory adverse events, shorter recovery times, and improved cardiovascular stability. [6] These characteristics make it especially valuable in pediatric dentistry, where airway maintenance and patient comfort are clinical priorities.[7]

Furthermore, alternative routes of administration, such as intranasal delivery, have gained increasing attention for being less invasive and better tolerated, especially among children and individuals with needle phobia.[8] Recent evidence suggests that this route enables fast and effective induction, enhancing procedural acceptance and reducing the need for physical restraint.[9]

Given the growing demand for safe, effective, and easily administered sedation methods in dental practice particularly in outpatient settings this systematic review aims to explore the use of Ketodex in dentistry, analyzing its pharmacological properties, clinical applications, comparisons with other protocols, and safety profile.

METHODOLOGY

Protocol and Registration

This scoping review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. Although this review was not prospectively registered, future systematic reviews on this topic are encouraged to register protocols in PROSPERO to improve transparency and reproducibility.

Eligibility Criteria

The inclusion criteria were defined based on the PCC framework (Population, Concept, Context):

I. Population: Pediatric patients and individuals with special needs undergoing dental procedures.
II. Concept: Use of the combination of dexmedetomidine and ketamine (Ketodex) for conscious sedation.
III. Context: Outpatient dental settings.

Eligible studies included randomized controlled trials, observational studies, and systematic reviews published between 2000 and 2025, in English, Portuguese, or Spanish. Studies had to address the clinical use of Ketodex (via oral, intramuscular, intravenous, or intranasal routes) in dental procedures or compare it to other sedation protocols.

Exclusion criteria included

I. Duplicate publications.
II. Studies without full text availability.
III. Articles using ketamine or dexmedetomidine as monotherapy.

Studies involving non-dental procedures or hospital settings not comparable to ambulatory dental practice.

Information Sources and Search Strategy

A comprehensive search was conducted between January and May 2025 across the following electronic databases: PubMed, Scopus, Web of Science, Scholar Google. The following controlled descriptors and keywords were used in various combinations with Boolean operators:

I. "Ketodex" AND "dentistry"
II. "dexmedetomidine" AND "ketamine" AND "dental sedation"
III. "dexmedetomidine" AND "ketamine" AND "pediatric dentistry"
IV. "sedation" AND "dentistry" AND "intranasal"

Selection of Sources of Evidence

Two reviewers independently screened titles and abstracts of the retrieved articles. Full texts of potentially eligible studies were then assessed for inclusion. Disagreements were resolved through discussion and consensus.

Data Charting Process

A data extraction form was developed and piloted to collect the following information from each study: authors, year of publication, study design, population characteristics, route of administration, sedation protocol, outcomes measured, and main findings.

Synthesis of Results

Included studies were grouped based on sedation protocol comparisons, administration routes, and patient populations. Results were synthesized narratively and presented in tables and figures, highlighting patterns, benefits, and safety outcomes associated with Ketodex use in dentistry.

Steps of the Selection Process	**N (number of studies)**
Records identified through the databases:	
PubMed	145
Scope	132
Web of Science	117
Google Scholar	164
Total number of records identified	**558**
Records after removal of duplicates	392

Steps of the Selection Process	N (number of studies)
Records excluded after reading the title and abstract	320
Articles selected for full reading	72
Articles excluded after full reading (with reasons):	48
Use of only one of the drugs (n = 21)	
Non-dental procedures (n = 15)	
Articles with full text unavailable (n = 7)	
Hospital study without outpatient applicability (n = 5)	
Studies included in the final review	**24**

Table. 1 - PRISMA-ScR flow diagram based on the 24 studies.

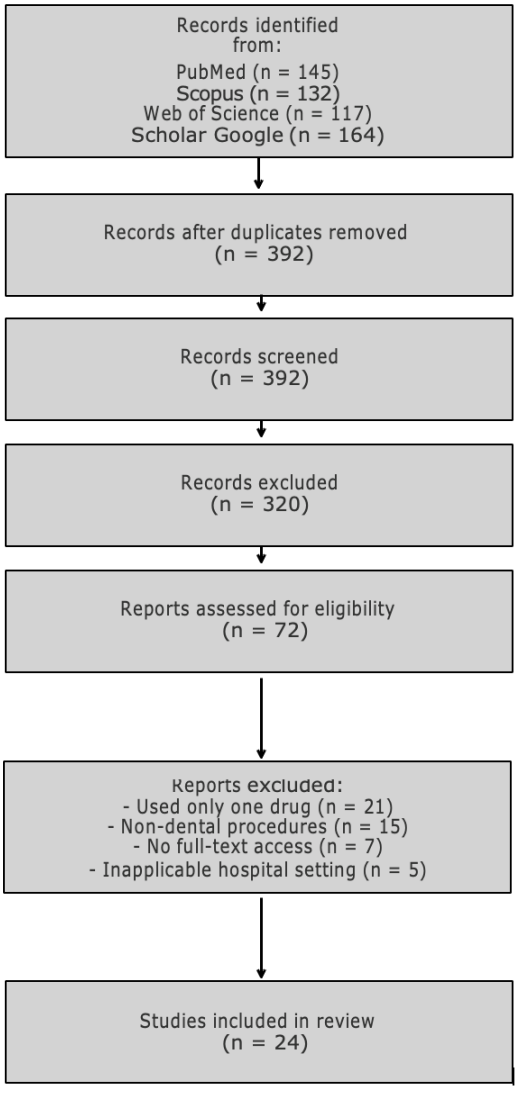

Figure. 1 - PRISMA-ScR flow diagram-based studies.

SCOPING REVIEW

Pharmacology of Dexmedetomidine and Ketamine

Dexmedetomidine is a selective agonist of alpha-2 adrenergic receptors, promoting sedation, analgesia, and mild anxiolysis without causing significant respiratory depression.[10] Ketamine acts as a non-competitive antagonist of NMDA receptors, inducing profound analgesia, amnesia, and dissociation, while preserving airway reflexes and respiratory function.[11]

When combined, these drugs exhibit synergistic effects: dexmedetomidine attenuates the psychotomimetic effects of ketamine, while ketamine contributes to a more stable and deeper sedation without causing severe bradycardia. This combination results in an ideal pharmacokinetic profile for short- and medium-duration dental procedures.[12]

Clinical Applications in Pediatric Dentistry and Special Needs Patients

In pediatric dentistry, conscious sedation with Ketodex has been widely studied for its ability to induce calmness and cooperation in anxious children, particularly during invasive procedures such as multiple extractions, scaling, or surgical interventions.[13]

The intranasal route, preferred in outpatient settings, allows rapid absorption with minimal discomfort, making it ideal for pediatric patients or those with needle phobia.[14] Furthermore, this combination has proven effective in patients with special needs, such as those with neurological disorders or severe phobias, enabling safe and compassionate care.[15]

Comparison with Other Sedative Protocols

Comparative studies demonstrate that Ketodex offers significant advantages over conventional protocols. Compared to midazolam-fentanyl, Ketodex shows reduced respiratory depression, better cardiovascular stability, and smoother recovery.[16] When compared to Ketofol (propofol + ketamine), Ketodex stands out for maintaining spontaneous ventilation and a lower incidence of nausea, vomiting, and emergence agitation.[17]

Adverse Effects and Safety

Ketodex's safety profile is one of its main advantages, the combination allows

dose reduction of each drug individually, minimizing adverse events such as delirium, excessive salivation, bradycardia, or hypertension.[18] The intranasal route has a low risk of local complications and excellent tolerance, making it a promising strategy, especially in children.[17,18]

Characteristics	Ketodex	Midazolam-Fentanyl	Ketofol (Propofol + Ketamine)
Route of administration	Intranasal, IV, IM	IV	IV
Onset of action	Rapid (3–10 min)	Moderate (5–15 min)	Rapid (1–5 min)
Hemodynamic stability	Excellent	Variable	Good
Respiratory depression	Minimal	Moderate to significant	Mild to moderate
Recovery	Mild, rapid	Slow, with increased agitation	Moderate
Common adverse effects	Mild bradycardia	Nausea, vomiting, respiratory depression	Agitation, delirium
Indicated for pediatric dentistry	Yes	With caution	Yes, with close monitoring

Table. 2 - Comparison table between Ketodex vs Midazolam-Fentanyl vs Ketofol.

Description of the Steps: Pre-assessment: intended for children aged 2 to 12 years, including medical history, prior exams, confirmation of adequate fasting, and ASA status evaluation (I or II).[19] Ketodex protocol selection: determine dosage based on the child's weight and age and select the most appropriate administration route (IV or IM).[20] Continuous monitoring: monitor oxygen saturation (SpO_2), heart rate (HR), respiratory rate (RR), and blood pressure (BP) using a pulse oximeter and, if possible, electrocardiogram (ECG).[21,22] Recovery and safe discharge: the child can be discharged after full recovery, stable vital signs, and alertness, with clear instructions provided to the caregivers.[23,24]

DISCUSSION

The use of the dexmedetomidine and ketamine combination (Ketodex) in dental settings has shown promising results, particularly in pediatric patients and individuals

with special health care needs.[4,7,9] The studies included in this review indicate that this pharmacological combination provides effective sedation while preserving spontaneous ventilation, maintaining hemodynamic stability, and presenting a low incidence of adverse events. These characteristics make Ketodex especially attractive for use in outpatient dental clinics, where structural limitations may hinder the implementation of advanced monitoring.[10-12]

However, the current literature presents several important limitations. Many of the available studies are small in scale, with limited sample sizes and heterogeneous methodological designs, which compromises the strength and generalizability of the evidence.[13,14,17] Furthermore, there is a lack of randomized controlled trials (RCTs) with sufficient statistical power and long-term follow-up. Another limitation is the inconsistent use of standardized sedation assessment criteria, which impairs comparability across studies.[12-15]

In addition to methodological issues, clinical barriers also hinder the broader adoption of Ketodex in dental practice.[10] Dexmedetomidine, while effective, is significantly more expensive than traditional sedatives, which may limit its accessibility in both public and private dental settings with limited financial resources.[15,16] Moreover, its pharmacological management requires more advanced clinical knowledge, demanding specific training for dental professionals, particularly when administered through alternative routes such as the intranasal route.[17,18]

From a regulatory standpoint, access to dexmedetomidine for use outside of hospital environments remains restricted in many countries, including Brazil.[19] This limitation underscores the need for regulatory updates to enable its safe use in outpatient dental care.[20] The lack of commercially available formulations adapted for alternative administration routes such as intranasal further hampers the widespread implementation of this sedation approach.[21]

Regarding scientific production, there is a notable lack of multicenter and national studies evaluating Ketodex in dental outpatient settings, particularly in the Brazilian context.[21,22] Additional investigations are needed to assess its effectiveness across different age groups, dental procedures, and patient risk profiles. Direct comparisons with other commonly used pharmacological combinations are also scarce

and necessary.[22]

Given these gaps, future research is strongly recommended to explore the use of Ketodex across diverse clinical settings, with large sample sizes, cost-benefit analyses, systematic monitoring of adverse effects, and strategies to ensure logistical feasibility.[23] Multicenter studies, prospectively registered in platforms such as PROSPERO and aligned with established methodological guidelines (e.g., PRISMA or CONSORT), would significantly contribute to consolidating Ketodex as a safe and effective alternative for dental sedation.[24]

FINAL CONSIDERATIONS

Ketodex emerges as an effective pharmacological alternative for dental sedation, particularly in pediatric patients and those with special needs. Its combination offers deep sedation while maintaining spontaneous ventilation and hemodynamic stability, addressing some of the limitations observed with traditional protocols such as midazolam-fentanyl and propofol-ketamine. Despite these observed benefits, the use of Ketodex remains limited by logistical and regulatory barriers, including high drug costs and restricted authorization for outpatient use. The integration of Ketodex into routine dental practice depends on the development of robust, well-designed clinical trials capable of evaluating its efficacy in various ambulatory contexts. Such evidence will be essential to support the formulation of evidence-based protocols and to guide clinical decision-making in dental sedation.

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DATA AVAILABILITY

All data analyzed during this study are available from the corresponding author upon reasonable request.

DISCLAIMER OF LIABILITY AND DISCLOSURE

All data analyzed during this study are available from the corresponding author upon reasonable request. The authors report no conflicts of interest regarding any of the products or companies discussed in this article.

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