

# A Double-Blind, Randomized Clinical Trial Comparing Sedation Outcomes of Dexmedetomidine and Ketofol in Pediatric Dental Interventions

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## ABSTRACT

**Background and Objective:** Fear and anxiety in pediatric patients undergoing dental procedures remain significant challenges in clinical practice. Despite the availability of various sedation protocols, evidence regarding their comparative safety and efficacy in children is limited. This study aimed to evaluate the sedation efficacy and safety of intravenous ketofol (a ketamine-propofol combination) versus dexmedetomidine (Dex) as premedications for anxious children undergoing endodontic treatment. **Methodology:** A double-blind, randomized clinical trial was conducted with 40 anxious pediatric patients scheduled for endodontic treatment. The participants were randomized into two groups (20 patients each). Group I received ketofol (2 mg/mL ketamine and 4 mg/mL propofol) with a loading dose of 0.3125 mL/kg intravenously (IV) over 10 minutes, followed by a maintenance infusion of 0.05–0.125 mL/kg/h. Group II received Dex (4 µg/mL) with a loading dose of 2 µg/kg IV over 10 minutes, followed by a maintenance infusion of 0.1–1 µg/kg/h. Vital parameters, including non-invasive blood pressure (BP), oxygen saturation (SpO<sub>2</sub>), heart rate (HR), and respiratory rate (RR), were monitored at baseline, every 2 minutes initially, and every 5 minutes for up to 1 hour. Ramsay sedation scores were assessed pre- and postoperatively, and Aldrete's recovery scores were recorded postoperatively. **Results:** Group I (ketofol) demonstrated a significantly shorter sedation onset time ( $P = 0.017$ ) compared to Group II (Dex). However, Group I exhibited longer discharge times and required more frequent rescue doses and procedure interruptions ( $P < 0.001$ ). Dex provided more stable respiratory parameters but was associated with a higher incidence of bradycardia compared to ketofol. Group I showed significant increases in mean arterial blood pressure (ABP), while Group II displayed a biphasic BP response. **Conclusion:** Dexmedetomidine is an effective sedative for pediatric patients undergoing endodontic treatment, characterized by minimal interruptions, lower rescue medication requirements, and shorter procedure and discharge durations. Although Dex has no adverse effects on respiration, it is associated with bradycardia and biphasic BP changes, necessitating careful dosing and monitoring. These findings highlight the importance of tailoring sedation protocols to individual patient needs for optimal outcomes.

**Keywords:** Dexmedetomidine; Endodontic Treatment; Human; Hypnotics; Ketofol; Premedication; Pediatric; Sedatives; Sedation

## INTRODUCTION

Fear and anxiety are common difficulties in kids undergoing simple dental treatments, and they are commonly managed by an anesthetist. Behavioral management approaches are frequently ineffective in settling disobedient and nervous children. In these cases, pharmacologic sedation is required to ensure the provision of excellent dental treatment [1, 2]. Numerous types of sedative medicines are presently accessible, allowing for independent control of the airway, breathing, and cardiac function throughout operations [3, 4]. Unfortunately, dental pharmacologic sedation has various drawbacks, such as the possibility of unconsciousness, airway obstruction, and cardiovascular depression. Furthermore, trigeminal nerve stimulation might cause intraoperative arrhythmia [5]. Sedation is given in many ways including orally, parenterally, and via inhalation, with intravenous (IV) sedation providing the advantages of quick onset and high effectiveness when delivered correctly [6, 7]. Propofol is a powerful sedative-hypnotic medication that acts by increasing the blocking effect of the gamma-aminobutyric acid neurotransmitter. It is renowned for its quick onset and recovery times, in addition to its amnesic and anti-emetic effects. However, its ability to produce respiratory depression and dose-dependent hypotension may limit its utilization [8, 9]. Ketamine, a phencyclidine derivative,

inhibits receptors of N-methyl-D-aspartate, causing a dissociative state that delivers total analgesia, anesthesia, and amnesia while preserving crucial brainstem processes [10]. Despite its advantages, ketamine's main problem is the emergence phenomenon, which affects up to 5% of pediatric patients. Ketamine can also have sympathomimetic effects on the heart rate (HR) and blood pressure (BP), as well as increased incidence of vomiting and salivation [11, 12]. The use of a ketamine and propofol combination, known as ketofol, has several advantages. Ketamine reduces the consumption of propofol while maintaining hemodynamic stability, whereas propofol reduces the hallucinogenic symptoms associated with ketamine treatment [13]. This combination method has several advantages, including rapid recovery and preservation of open airways, hemodynamic variables, and spontaneous breathing [14]. Dexmedetomidine (Dex) is an  $\alpha_2$ -adrenergic agonist known for its high selectivity; it inhibits the release of endogenous norepinephrine in the spinal cord and brain [15]. Its pharmacological effects include inducing sedation, reducing anxiety, and modifying BP and HR in a dose-dependent manner, all while avoiding respiratory depression [16]. Despite extensive studies into various sedation strategies for pediatric patients, clear information on the safest and most effective sedative drugs is lacking [17]. Moreover,

the total amount of well-designed comparative studies evaluating the safety and efficacy of various sedation methods is limited [18]. Thus, the major goal of this work was to compare the sedative, respiratory, and hemodynamic impacts of ketofol and Dex in anxious children receiving endodontic treatment.

## Methods

Given the unknown standard deviation (SD) of the principal result, the minimal detectable variation was established relative to this unspecified SD [19, 20]. Sample size calculation was performed utilizing the following formula:

$$n \geq \frac{2sp^2}{\delta^2} (t_{\alpha(1),v} + t_{\beta(1),v})^2$$

A minimum of 15 participants in every group was required to identify a variance in the mean frequency of interventions, corresponding to one SD (impact size = 1.0) with a power of 0.8 and a significance ( $\alpha$ ) of 0.05. To account for a skewed or generally non-normal distribution of the key outcome variable, we raised the sample size by 30%, with 20 participants assigned to each group. This clinical trial, which was intended as a double-blind, parallel-group, randomized study, began after being approved by the local research ethics committee. It was formally registered on ClinicalTrials.gov under the number NCT04678050. Prior to enrollment, participating minors' parents or legal guardians provided informed consent. To preserve blindness, neither the administering dentist nor the data collector were aware of the intervention being delivered. An anesthesiologist who was not involved in data collection prepared the study drugs, with all syringes and lines carefully disguised to avoid the colors of the sedatives from being identified. The envelope draw method was used to randomly allocate individuals into two groups (each of which included 20 subjects). We chose ASA-I children aged 5–10 years who required endodontic treatment and whose previous dental treatment under local anesthetic had been unsatisfactory or incomplete due to fear and uncooperativeness. Exclusion criteria included an ASA II or higher classification, expected dental procedures lasting more than 45 min, documented drug allergies, respiratory infections, and an increased risk of airway complications. Exclusion criteria included cardiovascular illness, previous head trauma or seizures, hepatic or renal failure, anemia, diabetes, thyroid problems, psychosis, porphyria, or glaucoma. The research also omitted vulnerable populations, such as orphans and those with mental health or learning problems. With at least either parent present, detailed histories were meticulously taken, and the pediatric patient was evaluated by the anesthesiologist to ensure that fasting guidelines were followed, evaluate vital signs, and carry out laboratory tests. Prilocaine cream (Pridocaine®) was applied topically, allowing for an absorption interval of 60 min before establishing venous access with a 22G cannula. All participants in the two groups were premedicated with atropine at a dosage of 0.01 mg/kg. Participants in group I ( $n = 20$ ) were administered ketofol, which was made by mixing ketamine and propofol in a 1:2 ratio (20 mL of propofol + 2 mL of ketamine in 28 mL of normal saline [NS]). The mixture contained 4 mg/mL propofol and 2 mg/mL ketamine. A loading dosage of 0.3125 mL/kg of this mixture was administered during a 10-minute period, followed by a maintenance infusion at a rate ranging from 0.05 mL/kg/h to 0.125 mL/kg/h. Participants in group II ( $n = 10$ ) were given Dex (4 µg/mL) containing 2 mL of Dex and 48 mL of NS. An initial loading dosage of 2 µg/kg was given IV for 10 min, followed by a maintenance

infusion of 0.1–1 µg/kg/h. Ramsay sedation score (RSS) was used to evaluate the depth of sedation, which guided the start of dental treatments after the score reached or surpassed 4. After reaching the intended degree of sedation and ensuring the child's cooperation, a topical anesthetic agent (Opahl 20% benzocaine gel) was utilized, followed by infiltration of local anesthesia and/or blockage of inferior alveolar nerve with 4% articaine (ARTINIBSA 4%). The mouth was kept open by a mouth gag. Dental procedures included pulpotomy (using zincinol) and pulpectomy (using zinc oxide eugenol and zincinol). Subsequently, a stainless-steel crown (Shinhung Co., Ltd., Seoul, Korea) was affixed as the final restoration by utilizing glass ionomer cement (Ningbo Gaoju Imp. & Exp. Co., Ltd., Zhejiang, China). In case of unintended movement or insufficient sedation during the surgery, the dentist temporarily interrupted the treatment and delivered further rescue doses of propofol (10–20 mg) until the necessary RSS of  $\geq 4$  was achieved again. Each child was monitored in the surgery theater using conventional methods such as pulse oximetry, 5-lead ECG, and non-invasive BP cuff. Prior to starting the operations, the vital signs of the baseline were registered. Persistent monitoring was carried out and documented methodically on a pre-designed sheet at 2 min intervals, with successive recordings at 5 min intervals lasting up to 1 h. The comprehensive evaluation of the sedative drugs' effectiveness was based on the RSS. Upon achieving the target sedation level (RSS  $\geq 4$ ), the start of sedation was documented, indicating the duration from the intravenous administration of the loading dose until the RSS reached or exceeded 4. The duration of treatment, defined as the duration from the initiation of local anesthesia injection until the completion of the dental intervention, was documented. Additionally, the frequency of interruptions during the intervention, the overall quantity of rescue medication administered, and any intra-procedural complications were recorded. Upon completion of the dental procedure, the administration of sedative drugs was discontinued, and continuous monitoring of vital signs was maintained. The duration of recovery, defined as the duration from end of sedation until achieving a modified Aldrete's recovery rating score of 10, was recorded. Additionally, any adverse events were documented. Subsequently, the children were transferred to the post-anesthesia care unit (PACU), as parents may be present to give support and reassurance. The children were observed at the unit until they satisfied the prescribed discharge requirements, at which point they were permitted to go home. These discharge requirements included age-appropriate responses to spoken orders, as well as the capacity to walk and drink fluids with no vomiting, nausea, or discomfort. Discharging was determined by the time it took to achieve a modified Aldrete's recovery rating score of 10 and fulfill the discharge criteria. The principal outcome of the study was to quantify the interruption frequency during the operation, with secondary outcomes including the overall dosage of rescue drugs administered, sedation initiation, discharge and recovery times, and vital signs.

## Statistical Analysis

SPSS software (V 23) was used to process the recorded data. The numerical variables were expressed as mean  $\pm$  SD. Frequency and proportions represented qualitative parameters. Normality of data was explored using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparison between two means was performed by T-test. ANOVA was used to compare follow-up durations in each category. Chi-square test was used for the comparison of qualitative parameters between groups, and Fisher's exact test was used when the expected count in any cell

<5. The accepted marginal error was set at 5%, and confidence interval was set at 95%.  $P < 0.05$  was significant.

## Results

A total of 40 children were randomly chosen to be given either ketofol or Dex. Demographic data were the same in both groups (20 kids each) Participants in group I had considerably higher and lower

respiratory rates at 2 ( $P = 0.012$ ) and 50 min ( $P = 0.001$ ), respectively (Figure 1), than those in group II. Group II displayed remarkably lower heart rates compared with group I at different times (Figure 2). Group I suffered from significantly higher mean arterial BP (ABP) than group II at 55 ( $P = 0.037$ ) and 60 min ( $P = 0.003$ ). Group II suffered from significantly higher mean ABP compared with group I at 15 and 25 min and lower values at 55 and 60 min in comparison with baseline (Figure 3).

**Table 1:** Characteristics of the Categories.

| Features | Ketofol          | Dexmedetomidine  | T/ $\chi^2$ | P-Value |
|----------|------------------|------------------|-------------|---------|
| Age      | 6.88 $\pm$ 1.85  | 7.14 $\pm$ 1.51  | 0.487       | 0.629   |
| Weight   | 21.05 $\pm$ 4.37 | 22.84 $\pm$ 4.16 | 1.327       | 0.192   |
|          | Gender           |                  |             |         |
| Female   | 15 (75.0%)       | 16 (80.0%)       | 0.186       | 0.896   |
| Male     | 5 (25.0%)        | 4 (20.0%)        |             |         |

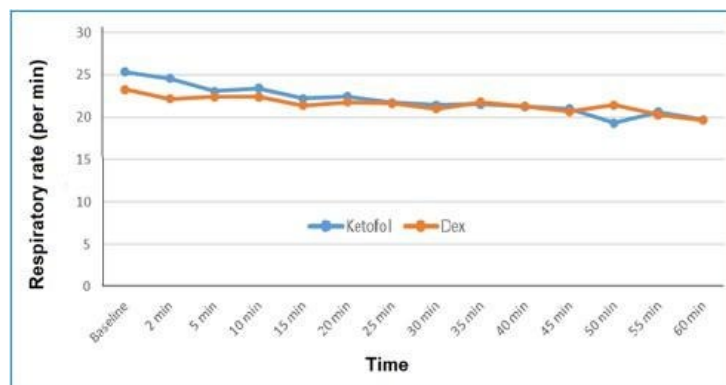


**Figure 1:** Comparative Respiratory Rates in Two Groups

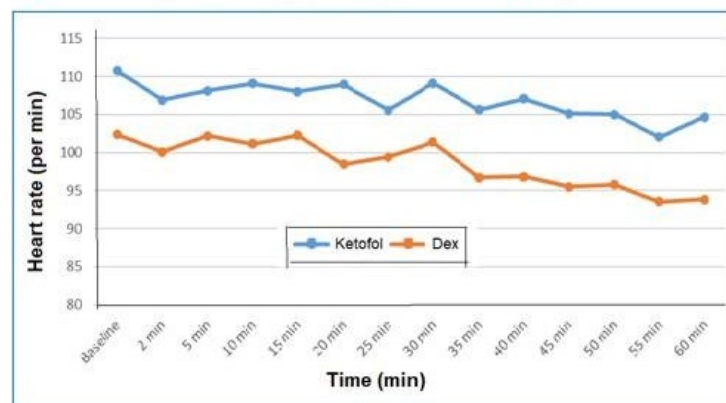


**Figure 2:** Comparative Heart Rates in Two Groups

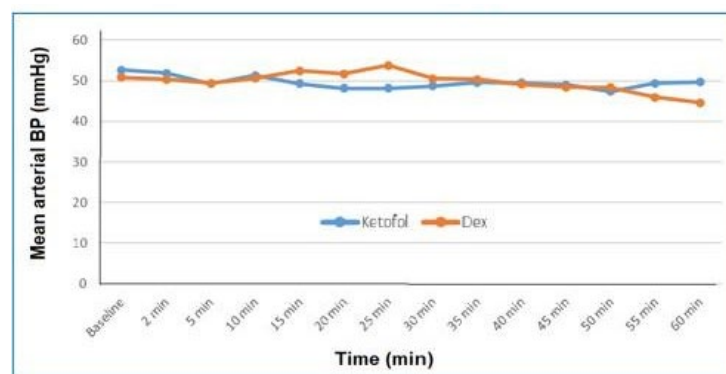


**Figure 3:** Comparative Mean Arterial Blood Pressure in Two Groups

Onset of sedation was significantly shorter in group I than in group II ( $P = 0.016$ ). However, the discharge time was longer and rescue doses and interruption frequency were higher in group I than

in group II, showing remarkable variation ( $P < 0.001$ ). Both categories had no considerable variance regarding the treatment ( $P = 0.538$ ) or recovery duration ( $P = 0.279$ ), as shown in Table 2.

**Table 2:** Comparison Between the Groups

|                      | Ketofol     | Dexmedetomidine | Test Value | P-Value |
|----------------------|-------------|-----------------|------------|---------|
| Sedation Onset (min) | 5.36±3.57   | 7.93±2.89       | 2.502      | 0.016*  |
| Treatment Time (min) | 35.69±2.74  | 36.26±3.06      | 0.621      | 0.538   |
| Recovery Time (min)  | 19.36±2.51  | 18.49±2.51      | -1.096     | 0.279   |
| Discharge Time (min) | 67.88±4.42  | 40.02±1.96      | -25.769    | <0.001* |
| Rescue Dose (mg)     | 126.64±1.27 | 58.81±1.60      | -148.497   | <0.001* |
| Interruption Number  | 6.85±0.50   | 2.52±0.53       | -26.576    | <0.001* |

## Discussion

The search for effective and safe anesthetic techniques for fearful kids, who are scheduled to receive dental treatment, continues to be a priority, driving continuous research into appropriate sedative drugs for a variety of dental operations [21]. This study compared and contrasted the effectiveness and safety of IV ketofol and Dex on anxious kids receiving endodontic treatment, assessing their sedative, respiratory, and hemodynamic effects. In our study, ketofol demonstrated a significantly quicker onset of sedation but required notably higher doses of rescue medications compared with Dex. Conversely, Dex maintained a more constant level of sedation throughout the process, as seen by much fewer interruptions and a lower requirement for rescue medicine, compared with ketofol. However, the ketofol group had considerably longer discharge times than the Dex group. Vital sign monitoring demonstrated that Dex offered more consistent respiratory function, despite a high incidence of Dex-induced bradycardia, than ketofol. Furthermore, ketofol was linked to considerable increases in mean ABP, whereas the Dex group exhibited a biphasic BP response. In this study, the RSS assessment showed that group I had significantly more interruptions, required more frequent rescue drug administration, and had longer discharge times compared with group II. Such outcomes were consistent with the findings of Kim et al., who successfully treated a group of uncooperative children using Dex at a rate of 1 µg/kg/h via continuous infusion for 10 min [22]. Similar research evaluated the effectiveness of IV Dex versus a combination of ketamine and atropine in uncooperative pediatric patients during dental procedures, demonstrating that Dex, given as a loading dose of 1 µg/kg followed by an infusion at 0.2 µg/kg/h, achieved significantly better sedation and behavior control than ketamine plus atropine. Furthermore, a comparison of IV ketamine/propofol with ketamine/Dex combinations in tooth extraction for anxious and uncooperative pediatric patients showed comparable sedation profiles [23].

Dex causes a level of unconsciousness similar to normal sleep, with the additional characteristics that patients feel safe about their kids [24]. Ketofol, a mixture of ketamine and propofol, was initially utilized for sedation in kids. Additional low-dose ketamine ensures sufficient sedation and analgesia while decreasing the cardiorespiratory depression commonly seen with propofol [25]. In the current research, ketofol resulted in a rapid sedation onset but was unable to maintain a stable sedation level. This instability may be related to propofol's lipophilic characteristics and short half-life, causing variable blood levels and uneven drug concentration at the target site [26]. The study found no considerable variation between ketofol and Dex in the time required to meet recovery criteria. Nonetheless, discharge time was notably longer with ketofol than with

Dex. This outcome was consistent with Ferguson et al.'s findings, which indicated that the combination of ketamine and propofol extended PACU discharge times compared with the controls in orthopedic surgery cases [27]. The use of sedative drugs is often restricted due to its side effects [28]. This study assessed the respiratory and hemodynamic safety characteristics of the drugs being investigated. Group II had stable respiration, but group I had a significant rise in respiratory rate at 2 min and then a significant drop at 50 min. The combination of ketamine and propofol is thought to have fewer side effects than either medication alone, most likely because of the low dosages necessary when administered together [29]. Utilizing a ketofol combination in a 1:2 ratio, which ensured a low dose of ketamine, resulted in a reduced side impact profile [30]. Two meta-analyses reported that sedation with ketamine/propofol is related to minimal respiratory side effects [31, 32]. The results of these studies were consistent with the side effects observed in the respiratory rate of group I. However, Dex can be considered an alternative as it causes much less respiratory depression compared with ketofol [33]. The evaluation of hemodynamic parameters in the present study demonstrated considerable bradycardia in group II, which began 20 min following drug infusion and lasted until the end of the 1 h intervention. Furthermore, group II suffered from significantly higher mean ABP compared with group I at 15 and 25 min and a lower mean ABP at 55 and 60 min in comparison with baseline. Similarly, previous studies have identified hemodynamic changes, notably bradycardia and biphasic BP changes, as the predominant adverse impacts of Dex, demanding immediate and cautious management [34]. Dex causes vasoconstriction by activating  $\alpha_2B$  receptors in vascular smooth muscles, resulting in a temporary increase in BP. The central nervous system's stimulation of  $\alpha_2A$  receptors leads to a reduction in BP and HR [35]. Potts et al. found a dose-dependent detrimental influence of Dex on BP [36]. The study tested bolus dosages of Dex ranging from 1 µg/kg to 4 µg/kg, and they found that administering a modest bolus of 0.5 µg/kg followed by continuous infusion can reduce side effects [37]. The injection of ketofol caused a considerable elevation in mean ABP at 55 and 60 min. Consistent with the above results, ketamine's sympathomimetic qualities might counterbalance the cardiovascular depressive impacts of propofol in cases involving orthopedic leg surgery [38].

## Conclusion

Compared with ketamine and propofol, the use of Dex contributed to better sedation results for children receiving endodontic treatment, including less procedural interference, less frequent rescue drug administration, and shorter discharge durations. Although Dex had no adverse respiratory impacts, it was correlated with bradycardia and biphasic BP variations, requiring precise titration.

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