ORIGINAL RESEARCH   **PEDIATRIC ANESTHESIA**

Dexmedetomidine compared to ketofol for sedation in pediatric patients undergoing dental procedures: a double-blind, randomized clinical trial

Rania Maher Hussien[1], Dalia Fahmy Emam[2], Aktham Adel Shoukry[3]

Author affiliation:

1. Rania Maher Hussien, Eladeeb Mohamed Elsbaee ST, ElNozha elgdida, Cairo, Egypt; E-mail: drrania_maamon@med.asu.edu.eg
2. Dalia Fahmy Emam, Mohamed Mandor Street, Nasr City, Cairo, Egypt; E-mail: daliafahmy78@gmail.com
3. Aktham Adel Shoukry; El Rehab City, New Cairo Block 129, Building 21, Cairo, Egypt; E-mail: aktham.shoukry1@gmail.com

Correspondence: Dr. Rania Maher Hussien; E-mail: drrania_maamon@med.asu.edu.eg; Phone: +20 1000544520

Abstract

Background & objective: Hospital phobia and anxiety are still prevalent issues in the pediatric patients. Various sedative regimes have been in dental practice, but the evidence for safe and effective sedative drugs in this population is scarce. We compared the safety and efficacy of intravenous combination of ketamine plus propofol (ketofol) with dexmedetomidine (Dex) as a sedative premedication in anxious children undergoing dental pulp therapy.

Methodology: This double-blind, randomized clinical study recruited 40 anxious children who were to undergo dental pulp therapy. The study participants were allocated into two groups (20 subjects each). Subjects in Group I received ketofol solution (ketamine/propofol mixture, each mL contains 2 mg of ketamine plus 4 mg of propofol). A loading dose of 0.3125 mL/kg was administered intravenously (IV) over 10 min, followed by maintenance infusion at a rate of 0.05-0.125 mL/kg/h. Subjects in Group II received the Dex solution (4 μg/mL). A loading dose of 2 μg/kg was administered IV over 10 min, followed by a maintenance infusion of 0.1-1 μg/kg/h. Non-invasive blood pressure, SpO_2, heart rate (HR), and respiratory rate (RR) were assessed at baseline, at 2 min, and then at 5 min intervals till 60 min. Ramsay sedation score was assessed before, during, and after the procedure and Aldrete's recovery rating score was assessed at the end of the procedure.

Results: Compared to the Dex group, the ketofol group showed a statistically significant shorter sedation onset (P = 0.017) but longer discharge time as well as higher rescue dose and a number of interruptions (P < 0.001). There was more stable respiration in Dex group, but with significantly more bradycardia. The mean arterial blood pressure showed some episodes of significant elevations with ketofol compared to Dex, while a biphasic response was observed in the Dex group.

Conclusion: The use of Dex induced successful sedation of children who underwent tooth pulp therapy in terms of minimizing the number of interruptions during the procedure, the frequency of rescue drugs administration as well as the total procedure and discharge times. Dexmedetomidine showed no adverse respiratory effects but was associated with bradycardia and biphasic mean blood pressure alterations that require careful titration.

Abbreviations: HR: heart rate; IV: Intravenous; RSS: NMDA: N-Methyl D-Aspartate PACU: Post Anesthesia Care Unit; Ramsay sedation score

Key words: Dexmedetomidine; Dental pulp procedures; Human; Hypnotics; Ketofol; Premedication; Pediatric; Sedatives; Sedation

1. Introduction

Fear and anxiety remain common problems in children presented for small dental procedures, and often need to be managed by the anesthetist. Behavioral management procedures often fail to control an anxious uncooperative child. In such conditions, pharmacologic sedation is indicated, so that a high-quality dental care can be accomplished.[1] Currently, a wide variety of drugs are available for sedation, while allowing independent control of the airway, ventilation, and cardiovascular stability throughout the procedure.[2] The challenges in dental pharmacologic sedation include the risk of losing consciousness, respiratory or cardiovascular depression, and airway obstruction. Additionally, intraoperative arrhythmias resulting from trigeminal nerve stimulation might occur.[3] Sedation can be performed orally, parenterally, or by inhalation. Intravenous (IV) sedation has the advantage of rapid action, and it is highly effective when applied properly.[4]

Propofol is a strong sedative-hypnotic drug that acts by positive modulation of the inhibitory function of the neurotransmitter gamma-aminobutyric acid. It is characterized by rapid onset and recovery besides its amnesic and anti-emetic properties. On the other hand, its respiratory depressant and dose-dependent hypotensive effects may restrict its use.[5] Ketamine is a phencyclidine derivative that blocks n-methyl d-aspartate (NMDA) receptors. It produces a dissociative state of complete anesthesia, analgesia, and amnesia with the preservation of vital brain stem functions.[6] The most serious disadvantage of ketamine is emergence phenomenon in up to 5% of children. It also has sympathomimetic effects on the heart rate and blood pressure, excessive salivation, and vomiting.[7] A combination of ketamine and propofol (ketofol) has shown many benefits. Ketamine reduces the consumption of propofol and maintains hemodynamic stability, while propofol relieves ketamine-associated hallucinations.[8] Using this combination has several advantages, such as quick recovery, keeping patent airways and spontaneous breathing, and stabilizing the hemodynamic parameters.[9]

Dexmedetomidine (Dex) is a highly selective α_2-adrenergic agonist, which reduces endogenous norepinephrine release in the brain and spinal cord.[10] It produces sedation, anxiolysis, and reduction in blood pressure and heart rate in a dose-dependent manner without inducing respiratory depression.[11,12] Considerable research has been conducted on different sedation methods in children; however, the current evidence for the safest and most effective drug is scarce.[13] Further, well-planned studies that compare the safety and effectiveness of different kinds of sedatives are relatively few.[14] Therefore, the main objective of this study was to compare ketofol and dexmedetomidine in terms of the sedative, respiratory, and hemodynamic effects in anxious children undergoing dental pulp therapy.

2. Methodology

As the standard deviation (SD) of the primary outcome is not known, the minimal detectable difference was defined in terms of that unknown SD.[15,16] Calculation of sample size using formula;

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

revealed that at least 15 subjects in each group were needed to detect a difference in the average number of interventions as small as one standard deviation (effect size = 1.0) with a power of 0.8 and a significance level (α) of 0.05. The sample size was increased by 30% (i.e., 20 patients in each group) as the distribution of the primary outcome variable was expected to be skewed (or generally not normally distributed).

This double-blind, parallel group, randomized, clinical study was conducted after receiving approval from the local research ethics committee (No. IRB 000-637 Date: 4/10/2020). The study was registered with ClovinicalTrials.gov with No. NCT04678050. Written informed consents were obtained from the children's parents or guardians. Both the dentist and the independent observer/data collector were blind to the type of intervention. The study drugs were prepared by an anesthesiologist who did not participate in the observation of the data. All the lines and syringes were wrapped to mask the colors of the sedative drugs, and the syringes were coded. Participants were randomly allocated into two groups (20 subjects each) by the envelope draw method.

We included ASA-I children, aged 5-10 y, requiring dental pulp therapy, whose dental treatment under local anesthesia failed or was not completed because of their anxiety and lack of cooperation. Exclusion criteria included children with ASA II or above, dental treatment expected to exceed 45 min, a history of allergy to drugs used, respiratory tract infections, high risk for airway adverse events (e.g. obesity, snoring, stridor, sleep apnea, maxillofacial malformations, or gastroesophageal reflux), cardiovascular disease, the history of head injury or seizures; hepatic or renal impairment, anemia (hemoglobin < 10 g/dL), diabetes, a thyroid disorder, psychosis, porphyria, and glaucoma. In addition, we excluded vulnerable children including orphans and those with mental disorders or learning disabilities.

In the preparation room and in the presence of at least one of the parents, personal, medical, and dental histories were recorded in detail, and the child was checked by the anesthesiologist for fasting, vital signs, and the routine

laboratory investigations. Then, prilocaine cream (Pridocaine® by Global NAPI Pharmaceuticals) was applied for 60 min before obtaining venous access using a 22G cannula. All the children in both groups were premedicated with atropine (0.01 mg/kg).

Subjects in Group I (n = 20) received ketofol solution (ketamine/propofol mixture prepared as 1:2 ratio i.e. 2 ml ketamine + 20 ml propofol in 28 ml of normal saline (NS) solution in a 50 ml syringe. This solution contained 2 mg/ml of ketamine and 4 mg/ml of propofol. A loading dose of 0.3125 ml/kg of this solution was infused over 10 min followed by maintenance infusion at the rate of 0.05-0.125 ml/kg/h. Subjects in Group II (n = 10) received the Dex solution (4 µg/mL) (2 ml of dexmedetomidine + 48 ml of NS). A loading dose of 2 µg/kg was administered IV over 10 min, followed by a maintenance infusion of 0.1-1 µg/kg/h.

Sedation level was assessed using Ramsay sedation score (RSS) and the dentist was allowed to start the procedure when the score was ≥ 4. Once the desired sedation level was reached and the child was cooperative, topical anesthetic gel (Opahl 20% Benzocaine gel, Dharma Research, Inc, FI, USA) was applied and local anesthesia was achieved by infiltration or by inferior alveolar nerve block using articaine 4% (ARTINIBSA 4%, Inibsa Dental, Barcelona, Spain). Then, a mouth gag was applied for stabilization of mouth opening. Dental treatment included pulpotomy (zincinol application) (Prevest Denpro Limited, Jammu, India), or pulpectomy (zinc oxide eugenol and zincinol application). Stainless steel crown (Shinhung Co., Ltd. Seoul, Korea) as a final restoration was then cemented by glass ionomer cement (Ningbo Gaoju Imp. & Exp. Co., Ltd., Zhejiang, China). During any unwanted movement or unfavorable sedation level during the surgical procedure, the dentist was instructed to stop the procedure momentarily and increments of propofol rescue doses (1-2 ml = 10-20 mg) were administered until the desired RSS ≥ 4 was restored.

In the operating room, standard monitoring, e.g., pulse oximeter, 5-lead electrocardiogram and non-invasive blood pressure cuff were applied to every child. Baseline vital signs were recorded. Continuous monitoring was done and recorded in a pre-printed sheet at 2 min, then at 5 min intervals till 60 min.

The overall response to the sedative drugs was assessed on the basis of RSS. Once the desired sedation level was reached (RSS ≥ 4), the onset of sedation was recorded (the time from IV injection of the loading dose till reaching RSS ≥ 4).

Treatment time (the time from starting injection of the local anesthesia to the end of the dental procedure) was recorded. Number of interruptions during the procedure; total amount of the rescue drug used; and any intraoperative complications were noted.

After the dental procedure was completed, the infusion of the drugs was stopped. The vital signs were continuously monitored. The recovery time - time from stoppage of sedation till reaching a Modified Aldrete's recovery rating score of 10 was noted. Any adverse event was also noted.

The children were then shifted to the post anesthesia care unit (PACU), where parents were allowed to attend, feel comfortable and secure. In the ward, the children were monitored until they fulfilled the discharge criteria then they were allowed to go home. The discharge criteria included appropriate age responses to verbal commands and the ability to walk and drink clear fluids without nausea, vomiting, or pain. The discharge time (from reaching a Modified Aldrete's recovery rating score of 10, till fulfilling the discharge criteria) was recorded.

Our primary outcome was the number of interruptions that occurred during the procedure; and the secondary outcomes were total dose of rescue drug, the onset of sedation, recovery time, discharge time, and vital signs.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Version 20 for Windows. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed data are presented as mean and standard deviation (SD) values. Categorical data are presented as frequency and percentage. T-test was used for comparison between ketofol and dexmedetomidine with continuous data. Fisher's exact test was used for comparison between groups with categorical data. ANOVA for repeated measures was used for comparison between follow up study periods in each group followed by planned contrast. The significance level was set at $P < 0.05$.

3. Results

This study enrolled 40 children who were randomly allocated to receive either ketofol or Dex. Both groups (20 subjects each) were comparable regarding demographic data (Table 1).

Table 1: Demographic data of the studied groups

Variable	Ketofol	Dexmedetomidine	t/ X²	P-value
Age	6.55 ± 1.76	6.80 ± 1.44	0.492	0.626
Weight	20.05 ± 4.16	21.75 ± 3.96	1.324	0.193
Gender				
Female	16 (80%)	17 (85%)	0.173	0.677
Male	4 (20%)	3 (15%)		

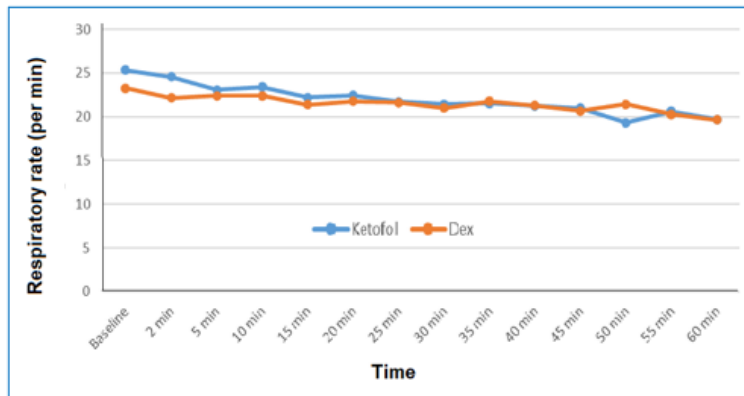*Values are expressed as mean ± SD or n (%), T = t-test, X² = Chi-square*

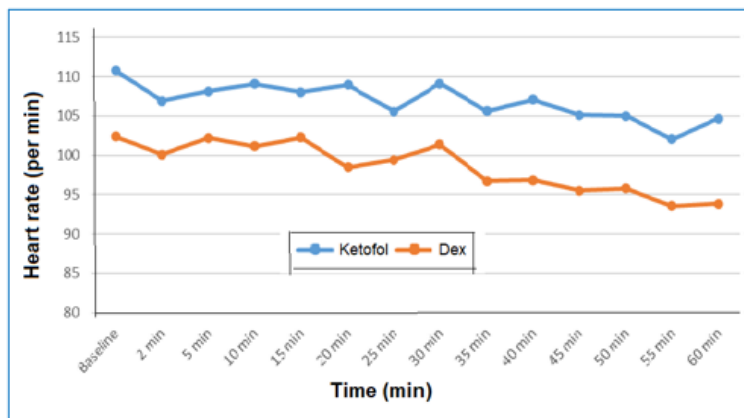**Figure 1: Comparative respiratory rates in two groups**

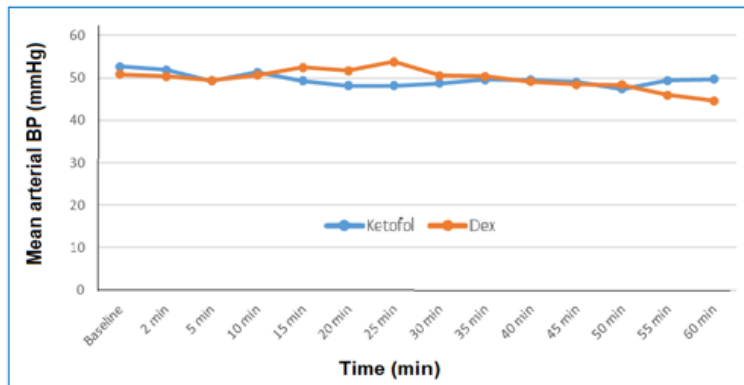**Figure 2: Comparative heart rates in two groups**

Figure 3: Comparative mean arterial blood pressure in two groups

Compared to the Dex group, the ketofol group showed a significantly higher respiratory rate at 2 min (P = 0.014) and a significantly lower respiratory rate at 50 min (P = 0.001) (Figure 1). The Dex group showed statistically significant lower heart rates than the ketofol group at 20, 30, 35, 40, 45, 50, 55, and 60 min (Figure 2). The mean arterial blood pressure was significantly higher in the ketofol group than Dex group at 55 and 60 min (P = 0.036, and 0.002, respectively), whereas the Dex group

showed a statistically significant higher mean arterial blood pressure at 15 to 25 min and a lower mean arterial blood pressure at 55 and 60 min when compared to baseline (Figure 3).

The ketofol group showed a statistically significant shorter onset of sedation (P = 0.017) than the Dex group. On the other hand, the ketofol group had a longer discharge time, higher rescue doses, and a number of interruptions than the Dex group with statistically significant differences (P < 0.001), Both groups had no significant differences regarding the treatment time (P = 0.541) or recovery time (P = 0.277) (Table 2).

4. Discussion

The development of a safe and effective anesthetic method for uncooperative children is highly warranted. Hence, there is continuous research for the appropriate sedative drugs that achieve such goals in different dental procedures.[19] We compared the safety and efficacy of IV ketofol vs. Dex in terms of sedative, respiratory, and hemodynamic effects in anxious children who underwent dental pulp therapy.

In this study, Ketofol induced a significantly more rapid onset of sedation associated with need of significantly higher doses of rescue drugs in comparison to Dex. On the other hand, Dex induced a more stable level of sedation of the children during the procedure which is reflected by a statistically significant less frequency of interruptions and rescue drugs administration, and the discharge time was significantly longer in the ketofol group. Furthermore, follow up of the vital signs in both groups revealed more stable respiration with Dex administration, but there was significant Dex-induced bradycardia. The mean arterial blood pressure showed some episodes of significant elevation with Ketofol than Dex, while the biphasic response was observed in the Dex group.

In this study, assessment of the level of sedation by RSS revealed significantly higher numbers of interruptions and rescue drugs administration as well as the discharge time in the ketofol group compared to the Dex group. In accordance with these findings, Kim et al. successfully managed a series of uncooperative children by the

Table 2: Comparison between groups regarding times, doses, and interruptions

Parameters	Ketofol	Dexmedetomidine	t	P-value
Sedation Onset (min)	5.20 ± 3.47	7.70 ± 2.81	2.502	0.017*
Treatment Time (min)	34.65 ± 2.66	35.20 ± 2.97	0.617	0.541
Recovery Time (min)	18.80 ± 2.44	17.95 ± 2.44	1.102	0.277
Discharge Time (min)	65.90 ± 4.29	38.85 ± 1.90	25.780	< 0.001*
Rescue Dose (mg)	122.95 ± 1.23	57.10 ± 1.55	148.471	< 0.001*
Interruption Number	6.65 ± 0.49	2.45 ± 0.51	26.563	< 0.001*

Significant at P < 0.05. Values are expressed as mean ± SD

administration of Dex at 1 µg/kg/h by continuous infusion over 10 min.[20] A comparable study compared the efficacy of IV Dex versus ketamine and atropine in uncooperative children during dental treatment. There was significantly better sedation and control of the child's behavior with Dex at a loading dose of 1 µg/kg, followed by IV infusion at a rate of 0.2 µg/kg/h. Comparison of IV ketamine/propofol combination versus ketamine/Dex combination in tooth extraction for uncooperative anxious children revealed similar sedation profiles.[21]

Dexmedetomidine produces a state of unconsciousness similar to natural sleep, with the unique feature that patients continue to be easily arousable and cooperative.[22] Ketofol has been used for procedural sedation in children. The addition of low-dose ketamine effectively provides adequate sedation and analgesia and minimizes the cardiorespiratory depression caused by propofol.[23] In this study, ketofol showed more rapid onset of sedation but failed to maintain a stable level of sedation. This observation might be attributed to the lipophilic nature of propofol and its short half-life, which produces uneven blood level and affects site concentrations of the drug.[24] The present study also demonstrated the absence of significant differences between ketofol and Dex regarding the time needed for fulfilling the recovery criteria. However, the discharge time was significantly more prolonged with ketofol use. This coincides with the findings of Ferguson et al. who stated that the added effects of ketamine and propofol prolonged PACU discharge time compared to the control group in patients undergoing orthopedic surgery.[25]

Generally, the use of sedative drugs is limited by their undesirable adverse effects.[26] The safety profile in terms of respiratory and hemodynamic effects of the investigated drugs was considered in this study. The Dex group showed stable respiration, while there was an episode of a significantly increased respiratory rate at 2 min and another one of significantly decreased respiratory rates at 50 min in the ketofol group. The complementary effects of ketamine/propofol

combination are supposed to result in lower adverse effects compared to the use of each drug alone due to the logical reduction of the required doses.[27] The use of ketofol mixture in a 1:2 ratio, which guarantees the lower ketamine dose, had a lower side effect profile.[28] Two meta-analyses concluded that sedation using a ketamine/propofol combination had been associated with a lower incidence of adverse respiratory events.[29,30] These studies agree with the observed occasional effects on the respiratory rate with ketofol use in this study. However, it seems that Dex is an attractive choice for sedation, because of the lack of respiratory depression.

Assessment of hemodynamic parameters in this study showed significant Dex-induced bradycardia, which started at 20 min after the drug infusion and continued till the end of the procedure at 60 min, whereas the Dex group showed a statistically significant higher mean arterial pressure at 15 to 25 min and lower values at 55 and 60 min in comparison with the baseline readings. Similarly, it has been reported that hemodynamic alterations in the form of bradycardia and biphasic blood pressure alterations were the main adverse effects of Dex that necessitated a safe and quick intervention.[31]

Dex infusion induces an initial transient increase in the blood pressure due to vasoconstriction resulting from activation of the peripheral postsynaptic α2B receptors in the vascular smooth muscles. This is followed by a decrease in blood pressure and heart rate through activation of α2A receptors in the central nervous system.[32] The dose-dependent negative effect of Dex on blood pressure has been reported by Potts et al.[33] They investigated different bolus doses of Dex (1 to 4 µg/kg) and suggested a small bolus of 0.5 µg/kg followed by continuous infusion to minimize this adverse effect.

Ketofol administration was associated with significantly higher mean arterial blood pressure at 55, and 60 min. In accordance with this finding, Sabertanha et al. concluded that the sympathomimetic effects of the added ketamine might overcome the cardiovascular depressant effects of propofol in patients undergoing orthopedic leg surgeries.[34]

5. Conclusion

The use of dexmedetomidine induced desirable sedation

in children who underwent tooth pulp therapy in terms of minimizing the procedural interference, frequency of rescue drugs administration, and the discharge times as compared to a combination of ketamine and propofol. Dexmedetomidine showed no adverse respiratory effects, but it was associated with bradycardia and biphasic blood pressure alterations that require careful titration.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Conflict of interest

The study utilized a grant by Faculty of Medicine, Universitas Indonesia, and no external or industry funding was involved.

8. Authors' contribution

RM: Concept, conduct the study, data collection, data analysis. manuscript writing, editing and correction, final approval

DF, AA: Searched the literature, data analysis. manuscript writing, editing and correction_ Final approval

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