Original Article

pISSN 2383-9309 ▮ eISSN 2383-9317
J Dent Anesth Pain Med 2023;23(2):69-81 ▮ https://doi.org/10.17245/jdapm.2023.23.2.69

Comparative evaluation of intranasal midazolam-ketamine, dexmedetomidine-ketamine, midazolam-fentanyl, and dexmedetomidine-fentanyl combinations for procedural sedation and analgesia in pediatric dental patients: a randomized controlled trial

Abhilasha Agarwal[1], Afroz Alam Ansari[1], Rajendra Nath[2], Rakesh Kumar Chak[1], Rajeev Kumar Singh[1], Richa Khanna[1], Prem Raj Singh[3]

[1]Department of Pediatric and Preventive dentistry, Faculty of Dental Sciences, King George Medical University, U.P., Lucknow, India
[2]Department of Pharmacology & Therapeutics, King George Medical University, U.P., Lucknow, India
[3]Department of Department of Anesthesiology and Critical Care, King George Medical University, U.P., Lucknow, India

Background: In order to assess the effectiveness of various analgesio-sedative combinations for pain relief and sedation in pediatric dental patients, a thorough evaluation of clinical studies and patient outcomes is necessary.
Methods: A total of 128 healthy, uncooperative pediatric dental patients were randomly allocated to receive one of the four combinations of drugs via the intranasal (IN) route: Group I received midazolam-ketamine (MK), Group II received dexmedetomidine-ketamine (DK), Group III received midazolam-fentanyl (MF), and Group IV received dexmedetomidine-fentanyl (DF) in a parallel-arm study design. The efficacy and safety of the combinations were evaluated using different parameters.
Results: The onset of sedation was significantly faster in the DF group than in the DK, MF, and MK groups ($P < 0.001$). The depth of sedation was significantly higher in the DK and DF groups than in the MK and MF groups ($P < 0.01$). DK and DF produced significant intra- and postoperative analgesia when compared with combinations of MK and MF. No significant adverse events were observed for any of the combinations.
Conclusions: The DK and DF groups showed potential as analgesio-sedatives in view of their anxiolytic and analgesic effects.

Keywords: Analgesio-sedation; Dental anxiety; Dexmedetomidine; Fentanyl; Ketamine; Midazolam.

INTRODUCTION

Dental pain and anxiety are common in pediatric patients. However, both these symptoms have been underestimated and undertreated in pediatric settings due to the inability of children to express their fears and ignorance regarding the procedures that will be performed [1]. The value of a pediatric dentist always depends on how carefully the child has been managed at a young

Received: September 20, 2022 • Revised: February 7, 2023 • Accepted: February 27, 2023
Corresponding Author: Afroz Alam Ansari, Professor, Department of Pediatric and Preventive Dentistry, Faculty of Dental Sciences, King George Medical University U.P., Lucknow, India
Phoner: +919335166662 E-mail: afrozalamansari@rediffmail.com

age and how pediatric dentists instill a positive dental attitude so that the child obtains lifelong trust with the dentist and dentistry [2]. Different behavior modification techniques are dictated in modern pediatric dentistry to manage patients in the operatory settings according to different characteristics and levels of anxiety and fear [3]. Pharmacological agents are usually sedatives or analgesio-sedatives that simply enhance patient acceptance by reducing arousal and altering the anticipated danger without eliminating anxiety [4].

The American Academy of Pediatric Dentistry (AAPD) has recommended mild and moderate types of sedation for in-office dental procedures. Procedural Sedation and Analgesia, previously known as conscious sedation, is a minimally invasive technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function [5]. Different available agents can be administered alone or in combination, including chloral hydrate, promethazine, hydroxyzine, midazolam, ketamine, nitrous oxide, sevoflurane, propofol, and opioids [4].

Midazolam is a benzodiazepine that causes anxiolysis and amnesia, along with sedation. It is water-soluble and has a short half-life and recovery time compared with other benzodiazepine agents. It is generally administered in combination with opioids for painful procedures as it does not have any analgesic properties [6]. Ketamine is a versatile drug and a dissociative anesthetic. It has dose-dependent effects, causing analgesic and anxiolytic effects at lower doses, and sedation, analgesia, and amnesia at higher doses. Fentanyl is an opioid agonist and a potent analgesic with rapid onset and short duration of action. In combination with a sedative, it can provide mild sedative and anxiolytic effects [7]. Dexmedetomidine has recently been used in the pediatric population for sedation procedures after its efficient use in adult patients [4]. It is an alpha2-adrenergic agonist with dose-dependent effects, inducing different levels of sedation and anxiolysis. It causes a reduction in the sympathetic tone, leading to its analgesic potential [8].

There are various routes that can be used for the administration of these drugs, such as oral, inhalational, nasal, intramuscular, subcutaneous, and intravenous. Among these the intranasal (IN) route is highly popular, especially in pediatric patients because of its many advantages, and because it can bypass the need for invasive routes such as intravenous (IV) injection and the non-invasive oral route (bitter tasting) [9]. The use of different sedation methods and agents has been proposed in children; however, a nearly ideal method or agent is yet to be discovered. Various routes have been documented as safe and effective in children, such as the enteral [10], parenteral [11] and IN [12] routes, inducing moderate sedation. However, there is limited evidence regarding the role of these combinations via oral and IN routes for procedural sedation in children [13,14]. Moreover, no previous study has compared and evaluated all four combinations delivered intranasally. Thus, this study evaluated analgesio-sedative combinations for procedural sedation in children for dental treatment.

We hypothesized that there is no difference among the four combinations regarding their efficacy, safety, time to reach adequate sedation, anxiety level, analgesic effects, post-operative sedation effects, and recovery time.

METHODS

1. Study design

The study was initiated after the research protocol was reviewed and approved by the Institutional Ethics Committee of King George Medical University, U.P., Lucknow, India (Registration no: ECR/262/Inst/UP 2013/RR-19). The prospective registration of this clinical trial was performed using the Clinical Trials Registry, India (CTRI Reg no: CTRI/2021/02/030932) (ICMR-NIMS). This study was designed and reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [15]. Patient recruitment and data collection were conducted from February 2021 to November 2021. The possible risks and benefits of

the study protocol were explained to the parents and informed consent was signed by them before commencement of patient enrollment. Patients were also given full freedom to withdraw at any time during the study without citing any reason.

2. Sample size estimation

In the study by Jaikaria et al. the sample size was calculated based on the variation in sedation score at the end of dental treatment in two of the four study groups [16]. The authors of this study considered an equivalence test for sample size calculations. The sample size was estimated based on the following assumptions: alpha error of 5% and study power of 90%. Assuming a 10% loss to follow-up, the final sample size was calculated to be a minimum of 31 per group. However, in this study, we enrolled more than the calculated sample size; therefore, the experimental sample size consisted of 128 pediatric patients (n = 32).

3. Study sample

The study was conducted on 128 children with an age of 4–9 years (score 2 of Frankl's Behavior Rating Scale) [17], who visited the outpatient wing of the Pediatric and Preventive Dentistry Department, Faculty of Dental Sciences, King George Medical University, U.P., Lucknow, and met the inclusion criteria. Patients categorized as normal healthy children (class I: a normal healthy patient) or mild systemic controlled disease (class II: a patient with mild systemic disease) according to the American Society of Anesthesiologists (ASA) were included in the study [18]. All included participants had at least one decayed tooth with pulpal involvement. Patients with acute upper respiratory illness, intranasal pathology, nasal obstruction (obstructive sleep apnea), allergy to any of the drugs, or those requiring surgery under general anesthesia were excluded from the study. The study was conducted in collaboration with the Department of Anesthesiology and Critical Care and the Department of Pharmacology and Therapeutics of King George Medical University, Uttar Pradesh, Lucknow.

4. Randomization technique and allocation concealment

A computer-generated block randomization allocation technique was used in this study. The randomization sequence was generated by a researcher who was not involved in the study, using online software. The identity of the group was mentioned and placed in opaque envelopes that were sequentially numbered and sealed to maintain concealment. Only anesthesiologists knew the intervention group for each patient to allow immediate action in case of any inadvertent reactions to the drugs.

5. Grouping

Participants were enrolled into four groups according to the randomization sequence:

Group I: (n = 32) Midazolam-Ketamine (MK),
Group II: (n = 32) Dexmedetomidine-Ketamine (DK),
Group III: (n = 32) Midazolam-Fentanyl (MF),
Group IV: (n = 32) Dexmedetomidine-Fentanyl (DF).

6. Blinding

The patient, the observer, and the statistician were blinded to the intervention group.

7. Intra examiner reliability

To minimize intra-examiner bias, calibration was performed by enrolling 20 patients for a pilot study that was further evaluated by the researcher and statistician to assess the intra-examiner reliability. The sample in this pilot study was not included in the main study.

8. Patient preparation

The parents were well informed regarding the pre-sedation fasting guidelines according to the AAPD before the day of the procedure, that is, 2, 4, and 6 h of fasting for clear liquids, milk, and light meals, respectively [18]. Vital parameters, such as heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP) were measured and monitored for all patients using a digital sphygmomanometer (Morepen Laboratories

Limited) and pediatric pulse oximeter (Dr. Odin Human Accurate Bio-Medical Technology Co, Ltd.) before commencement of the procedure until discharge. The child's body weight was recorded at the start of the appointment. All intranasal regimens were prepared from parenteral preparations, and 0.9% saline was added to all regimens to produce an equal final volume to avoid bias during administration [9]. The MK group received 0.2 mg/kg (max 5.0 mg) midazolam and 4.0 mg/kg (max 100 mg) ketamine [19]. The DK group received 1 μg/kg (max 100 μg) dexmedetomidine and 1 mg/kg (max 100 mg) ketamine [20]. The MF group received 0.2 mg/kg (max 10 mg) midazolam and 2 μg/kg (max 100 μg) fentanyl [21]. The DF group received 1 μg/kg (max 100 μg) dexmedetomidine and 1.5 μg/kg (max 100 μg) fentanyl [16]. The parenteral formulations were midazolam hydrochloride injectable solution at a concentration of 1 mg/ml (Mezolam - Neon Laboratories Ltd); ketamine hydrochloride, 50 mg/ml (Aneket-Neon Laboratories Ltd); dexmedetomidine, 100 μg/ml (Dextomid – Neon Laboratories Ltd); and fentanyl, 50 μg/ml (Fent - Neon Laboratories Ltd). The drugs were administered in a systematic manner through the IN route: at minute "zero" — midazolam, after 5 min—ketamine and fentanyl in the MK and MF groups, respectively; similarly, at minute "zero"— dexmedetomidine, after 20 min— ketamine and fentanyl in groups DK and DF, respectively. In all groups, the second drug was administered at the mentioned interval to favor the peak plasma concentration of both drugs in the combination to coincide.

The drugs were administered using LMA MAD NasalTM: "Mucosal Atomization Device" (MAD) (Teleflex) connected to a 2 ml/ 5 ml syringe via Luer-Lock to convert an intravenous drug solution into a fine mist for intranasal administration, which also permits uniform application of the drug throughout the nasal mucosa. The drugs were administered into both nostrils with the child in a semi-recumbent position, with the head of the bed elevated at 30–45 degrees, and the tip of the LMA MAD Nasal snugly placed against the nostril, aiming upward and outward towards the lateral nasal wall (the inferior and middle turbine mucosa to increase the surface area of absorption and to maximize dispersion) [9]. Dental treatment was started once an adequate sedation level was reached (score 1) according to the UMSS sedation scale [22]. Sedation onset was measured as time (minutes) after both drugs in each group were administered until a satisfactory sedation level was achieved.

9. Operative procedure

Topical anesthesia (lidocaine, 15%; Nummit-ICPA, Mumbai) was applied for 60 s to decrease discomfort during needle insertion. The amount of local anesthesia (lignocaine HCL 2%, 1:200,000 Adrenaline; CELON LABORATORIES PVT. LTD. Medchal District, Telangana State, India) was calculated based on the weights of the patients. The treatment procedures for each patient were standardized such that the average duration of treatment was 45–60 min for all patients enrolled in the study. Local anesthesia (LA) was delivered in all sedation sessions in the form of a nerve block. Vital signs (SBP, DBP, HR, and oxygen saturation [SpO_2]) were recorded at regular intervals during the procedure [23]. The caregiver accompanied the child near the dental chair during the procedure. Augmented behavioral management techniques, such as voice control, tell-show-do, and mouth-prop, were used during the treatment based on the child's behavior. The observer continuously monitored the child to register the outcome parameters from the administration of sedatives until discharge. At completion of the procedure, the operator scored the ease of treatment completion on a rating scale. The patient and caregiver were transferred to the recovery clinic and the patient was under continuous observation until all discharge basics were achieved according to the AAPD and American Academy of Pediatrics (AAP) guidelines [i.e. cardiovascular function and airway patency are satisfactory and stable; the patient is easily arousable, and protective airway reflexes are intact; the patient can talk (if age appropriate); the patient can sit up unaided (if age appropriate); for a very young child or a child with a

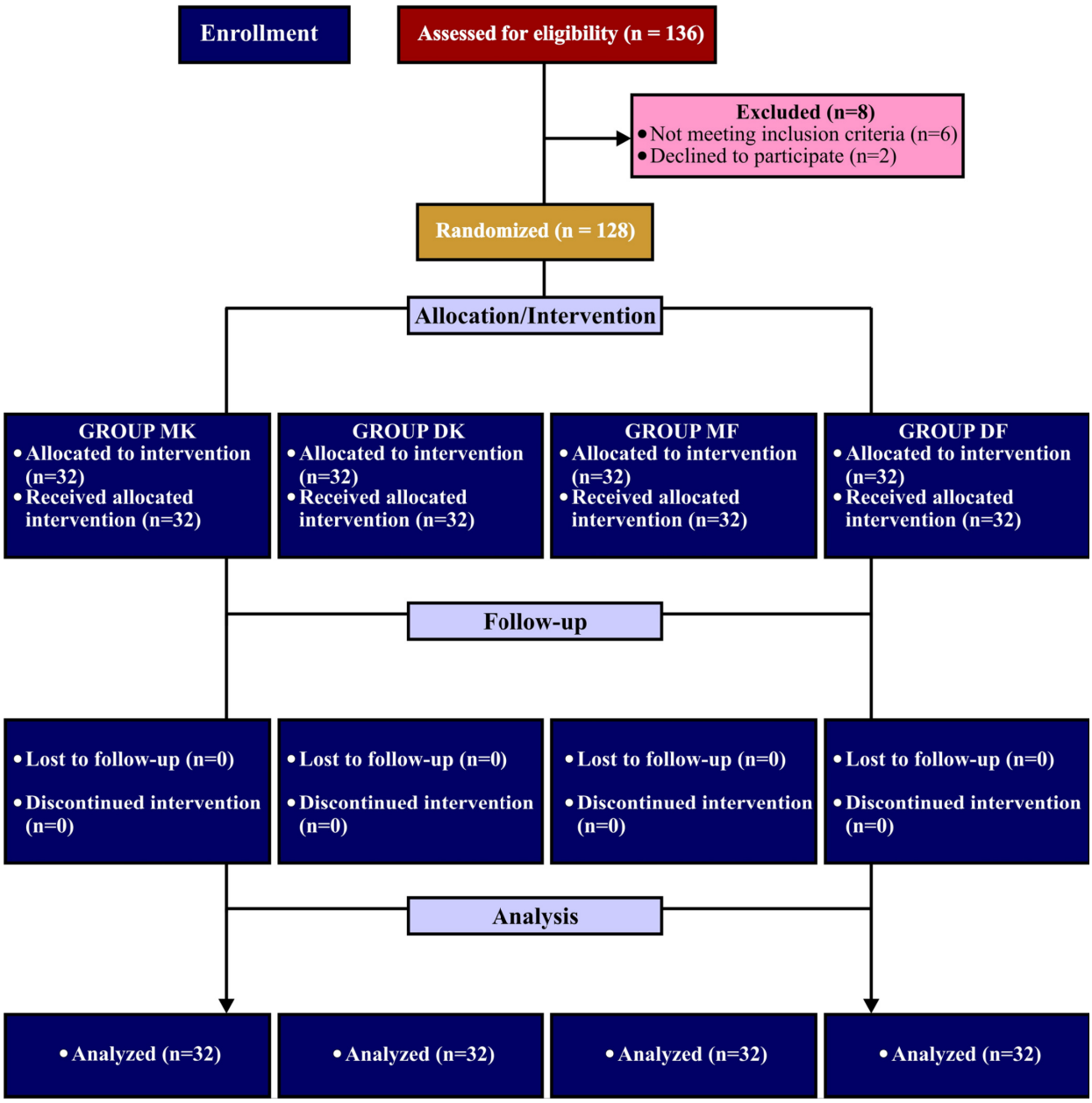

Fig. 1. A CONSORT diagram showing the study protocol. CONSORT, consolidated standards of reporting trials; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number.

disability who is incapable of the usually expected responses, the pre-sedation level of responsiveness or a level as close as possible to the normal level for that child should be achieved; the state of hydration is adequate] [18]. The parent/guardian accompanying the patient was informed about the postoperative instructions and was contacted after 24 h via phone and asked to score their experience of the sedation session on a rating scale and to probe any prolonged side effects such as vomiting, sleep disturbances, and hallucinations.

10. Statistical analysis

Intention-to-treat analysis was used to analyze the results of this study. Normality was checked for quantitative variables by using descriptive statistics, plots, and tests of normality. Means and standard deviations (SD) were

Table 1. Demographic and clinical data of the participants according to the intervention groups

VARIABLES	MK (n = 32)	DK (n = 32)	MF (n = 32)	DF (n = 32)	P Value
Sex: n (%)					
Female	16 (50.0)	17 (53.1)	17 (53.1)	18 (56.3)	0.969
Male	16 (50.0)	15 (46.9)	15 (46.9)	14 (43.8)	
Weight (kg) Mean ± SD	21.09 ± 2.81	20.72 ± 2.82	20.63 ± 2.71	19.81 ± 2.89	0.320
Age (yrs) Mean ± SD	5.99 ± 1.02	6.22 ± 1.08	6.45 ± 1.27	6.28 ± 1.11	0.444
ASA grade: n (%)					
I	31 (96.9)	31 (96.9)	30 (93.8)	31 (96.9)	0.891
II	1 (3.1)	1 (3.1)	2 (6.3)	1 (3.1)	
Sedation Onset Time (mins) Mean ± SD	9.60 ± 1.65	17.10 ± 2.18	10.79 ± 1.53	18.24 ± 2.07	< 0.001***
Duration of session under sedation (mins) Mean ± SD	48.44 ± 14.10	44.00 ± 12.28	46.78 ± 14.05	40.69 ± 12.71	0.106
Recovery Time (mins) Mean ± SD	45.71 ± 5.54	80.36 ± 5.71	40.19 ± 4.93	70.43 ± 6.19	< 0.001***
Adverse Effects: n (%) Emesis (vomiting)	2 (6.3)	1 (3.1)	1 (3.1)	0 (0.0)	0.559

*Statistically significant at P value < 0.05
ASA, American Society of Anesthesiologists; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number; SD, standard deviation.

calculated for all quantitative variables, whereas frequencies and percentages were calculated for qualitative variables. Continuous groups were compared by one factor (groups) analysis of variance (ANOVA) test or two factor (groups × periods) repeated measures of ANOVA test, and the significance of the mean difference between (inter) the groups was determined by Tukey's honestly significant difference (HSD) post hoc test after ascertaining normality by Shapiro-Wilk's test and homogeneity of variance between groups by Levene's test. Discrete (categorical) data were summarized as numbers (n) and percentages (%) and compared using the chi-square (χ^2) test. Two-tailed ($\alpha = 2$) statistical significance was set at $P < 0.05$. Data were analyzed using Social Sciences (SPSS) statistical software (Windows version 22.0).

11. Outcomes

Other than hemodynamic parameters and onset of sedation, the primary outcomes for this study were "depth of sedation" evaluated by (UMSS) [22], child's behavior during dental sedation evaluated according to the Modified Observer Assessment and Alertness/Sedation (MOAA/S) behavior rating scale [24], and "ease of treatment completion" evaluated according to the Houpt scale [25]. The secondary outcomes were "analgesic effect" recorded through the FLACC scale [26], parental satisfaction of the sedation session [27], recovery time, and incidence of adverse events.

RESULTS

A total of 128 children aged 4–9 years participated in this clinical trial (Fig. 1). The basic characteristics of the participants at baseline, duration of dental treatment, recovery time, and adverse events are presented in Table 1. The patients of the four groups were demographically (age, sex, and weight) matched and compared; hence, these may not influence other outcome measures of the study. After the first drug was administered, the time to achieve satisfactory sedation, defined by the UMSS sedation score, was significantly shorter in the MK and MF groups than that in the other groups (Table 1). In addition to the onset, the duration of the dental procedure

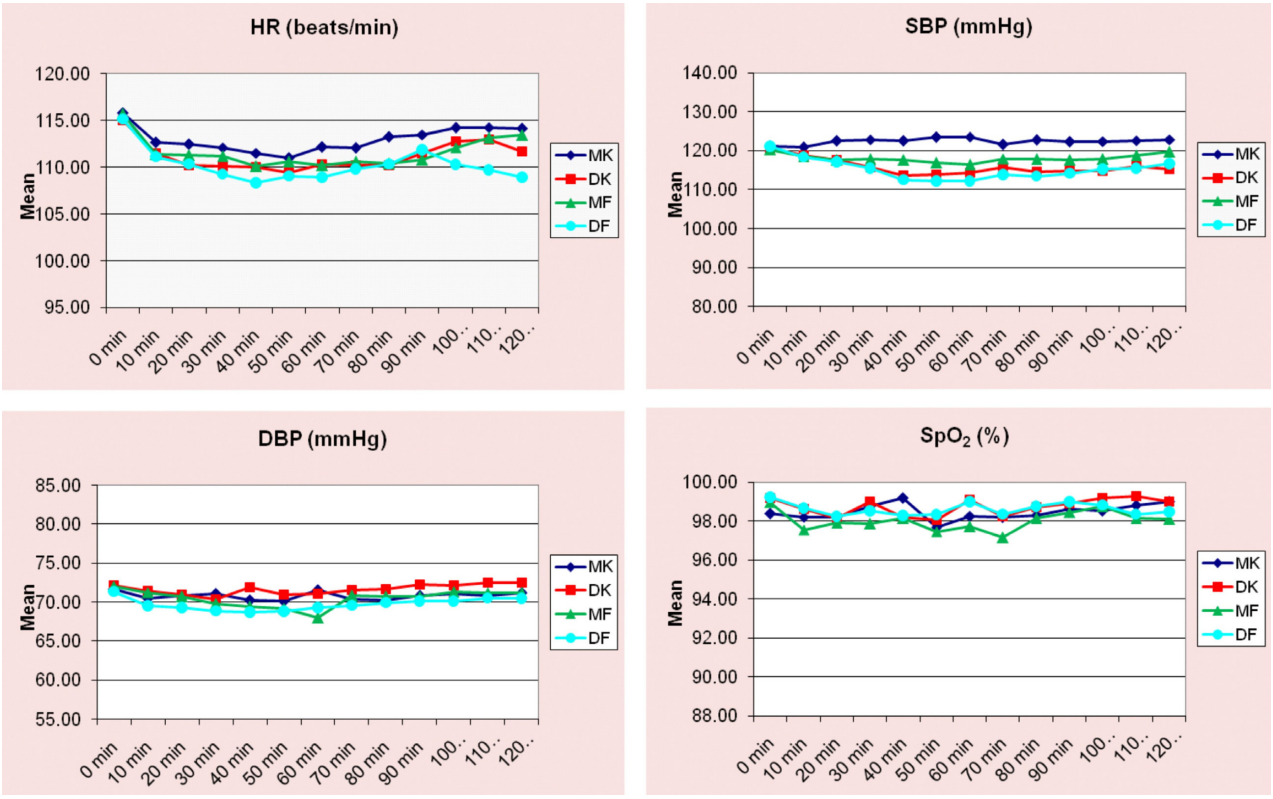

Fig. 2. Heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation values for the four treatment groups. Data are presented as the mean value. Data points were horizontally shifted to avoid overlapping. DBP, diastolic blood pressure; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; HR, heart rate; MF, midazolam-fentanyl; MK, midazolam-ketamine; SBP, systolic blood pressure; SpO_2, oxygen saturation.

Table 2. Depth of sedation according to University of Michigan (UMSS)

UMSS score	MK (n = 32) n (%)	DK (n = 32) n (%)	MF (n = 32) n (%)	DF (n = 32) n (%)	χ^2 value	P value
Awake and alert	8 (25.0)	0 (0.0)	9 (28.1)	2 (6.3)		
Minimally sedated	21 (65.6)	24 (75.0)	23 (71.9)	25 (78.1)	21.25	0.002**
Moderately sedated	3 (9.4)	8 (25.0)	0 (0.0)	5 (15.6)		

*statistically significant at P value < 0.05. χ^2 value, Chi square test; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number; UMSS, University of Michigan sedation scale.

and postanesthetic recovery time are listed in Table 1. Hemodynamic parameters were within 10% of the baseline values; hence, the changes observed were considered statistically and clinically insignificant and required no intervention (Fig. 2).

1. Depth of sedation - University of Michigan Sedation Scale (UMSS)

The frequency (%) of the UMSS score was compared among the four groups. There was a significant difference in the UMSS score (χ^2 = 21.25, P = 0.002) among the groups and the frequency of "awake and alert" score was significantly higher in both the MK and MF groups compared to that in the other groups (Table 2).

2. Child behavior/anxiety - Modified Observer Assessment and Alertness/Sedation Scale (MOAA/S) (behavior scores)

Concerning anxiety level, no significant difference was observed among the groups at baseline, at the start of treatment, and during treatment. However, at the end of the treatment, the difference was significant among the

Table 3. Anxiety level at different periods according to Modified Observer Assessment and Alertness (MOAA/S) - Behaviour rating scale

Period	Group	1 (Calm and Cooperative) (n = 32) n (%)	2 (Anxious but Reassurable) (n = 32) n (%)	3 (Anxious and Not Reassurable) (n = 32) n (%)	4 (Crying or Resisting) (n = 32) n (%)	χ^2 value	P value
Baseline	MK	0 (0.0)	19 (59.4)	13 (40.4)	0 (0.0)		
	DK	0 (0.0)	18 (56.3)	14 (43.8)	0 (0.0)	0.36	0.949
	MF	0 (0.0)	20 (62.5)	12 (37.5)	0 (0.0)		
	DF	0 (0.0)	20 (62.5)	12 (37.5)	0 (0.0)		
Start of Treatment	MK	24 (75.0)	6 (18.8)	2 (6.3)	0 (0.0)		
	DK	30 (93.8)	2 (6.3)	0 (0.0)	0 (0.0)	9.17	0.164
	MF	23 (71.9)	7 (21.9)	2 (6.3)	0 (0.0)		
	DF	29 (90.6)	3 (9.4)	0 (0.0)	0 (0.0)		
During Treatment	MK	21 (65.6)	5 (15.6)	5 (15.6)	1 (3.1)		
	DK	28 (87.5)	2 (6.3)	2 (6.3)	0 (0.0)	8.78	0.457
	MF	20 (62.5)	5 (15.6)	6 (18.8)	1 (3.1)		
	DF	26 (81.3)	4 (12.5)	2 (6.3)	0 (0.0)		
End of Treatment	MK	19 (59.4)	4 (12.5)	7 (21.9)	2 (6.3)		
	DK	31 (96.9)	1 (3.1)	0 (0.0)	0 (0.0)	26.32	0.002**
	MF	18 (56.3)	4 (12.5)	7 (21.9)	3 (9.4)		
	DF	30 (93.8)	1 (3.1)	1 (3.1)	0 (0.0)		

*statistically significant at P value < 0.05. χ^2 value, Chi square test; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; MOAA/S, Modified Observer Assessment and Alertness/Sedation Scale; n, number.

Table 4. Analgesic effect according to FLACC score

FLACC score	MK (n = 32) n (%)	DK (n = 32) n (%)	MF (n = 32) n (%)	DF (n = 32) n (%)	χ^2 value	P value
Relaxed & comfortable	5 (15.6)	14 (43.8)	2 (6.3)	12 (37.5)		
Mild discomfort	8 (25.0)	12 (37.5)	8 (25.0)	10 (31.3)	25.96	0.002**
Moderate pain	13 (40.6)	4 (12.5)	12 (37.5)	6 (18.8)		
Severe discomfort/pain	6 (18.8)	2 (6.3)	10 (31.3)	4 (12.5)		

*statistically significant at P value < 0.05. χ^2 value, Chi square test; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; FLACC, Face, Legs, Activity, Cry and Consolability; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number.

Table 5. Ease of treatment completion according to Houpt score

Ease of treatment completion	MK (n = 32) (%)	DK (n = 32) (%)	MF (n = 32) (%)	DF (n = 32) (%)	χ^2 value	P value
Satisfactory Session	25 (78.1)	30 (93.8)	19 (59.4)	27 (84.4)	12.16	0.007**

*statistically significant at P value < 0.05. χ^2 value, Chi square test; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number.

groups (χ^2 = 26.32, P = 0.002). The calm and cooperative frequencies were significantly higher in the DK and DF groups (χ^2 = 25.25, P < 0.001). In contrast, the frequencies of anxiety and non-reassurability were significantly higher in the MK and MF groups (χ^2 = 12.91, P = 0.005) (Table 3).

3. Analgesic effect - Face, Legs, Activity, Crying, and Consolability Scale (FLACC)

A significant difference was noted in the frequency (%) of the FLACC scores among the four groups (χ^2 = 25.96, P = 0.002), and the "relaxed and comfortable" frequency was significantly higher in the DK and DF groups (Table 4).

Table 6. Parent satisfaction score after 24 hours post sedation sessions

Parent satisfaction score	MK (n = 32) (%)	DK (n = 32) (%)	MF (n = 32) (%)	DF (n = 32) (%)	χ^2 value	P value
1 (Very Disatisfied)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.00	1.000
2 (Disatisfied)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.00	1.000
3 (Neither Satisfied/Nor Disatisfied)	7 (21.9)	1 (3.1)	10 (31.3)	2 (6.3)	12.80	0.005**
4 (Satisfied)	14 (43.8)	11 (34.4)	12 (37.5)	15 (46.9)	1.30	0.730
5 (Very Satisfied)	11 (34.4)	20 (62.5)	10 (31.3)	15 (46.9)	7.87	0.049*

*statistically significant at P value < 0.05. χ^2 value, Chi square test; DF, dexmedetomidine-fentanyl; DK, dexmedetomidine-ketamine; MF, midazolam-fentanyl; MK, midazolam-ketamine; n, number.

4. Ease of treatment completion - Houpt Scale

The treatment session was considered satisfactory, when a rating of either '5' or '6' was obtained on Houpt score throughout the session. The frequency of ease of treatment completion (i.e., satisfactory sessions) was significantly higher in the DK and DF groups, followed by the MK and MF groups (χ^2 = 12.16, P = 0.007) (Table 5).

5. Parent satisfaction

The parent satisfaction score of 5 (i.e., very satisfied) was significantly more frequent in the DK group (χ^2 = 7.87, P = 0.049). Conversely, the parent satisfaction score of 3 (i.e., neither satisfied/nor dissatisfied) was significantly more frequent in the MF group and significantly less frequent in the DK and DF groups (χ^2 = 12.80, P = 0.005). In contrast, the frequency of parent satisfaction scores 1 (i.e., very dissatisfied), 2 (i.e., dissatisfied), and 4 (i.e., satisfied) did not differ among the groups (Table 6).

6. Recovery time

Children in the DK and DF groups exhibited longer time to discharge than those in the other groups. The mean recovery time of the DK group was the highest, followed by that of the DF, MK, and MF groups. Comparing the mean recovery times of the four groups, ANOVA showed a significant difference in recovery time among the groups (F = 378.60, P < 0.001) (Table 1).

7. Adverse events (AEs)

Among the 128 children sedated, a total of four participants (3.125%) had minor AE, and only emesis (vomiting) was registered in patients. In the MK group, emesis was present in two (6.3%) patients; in the DK group, it was present in one (3.1%) patient; in MF group, it was present in one (3.1%) patient, and there was no significant difference among the four groups (χ^2 = 2.07, P = 0.559) (Table 1).

DISCUSSION

This study compared and evaluated the efficacy of four analgesio-sedative combinations administered intranasally to children undergoing dental pulp therapy procedures. From the results of this comprehensive analysis, successful anxiolysis (calm and cooperative) was achieved during dental treatment in children sedated in all four groups. However, at the end of the treatment, the frequency of calm and cooperative behavior was the highest in the DK group, followed by DF, MK, and MF. The results of this study showed no negative postoperative effects of midazolam and dexmedetomidine on the behavioral responses of children. This could be associated with their ability to reduce pain and anxiety during the perioperative phase, which may have an impact on minimizing behavioral changes post-operatively [28].

As stated in various previous studies [16,29], the onset of sedation was significantly delayed in both the DK and DF groups compared to that in the MK and MF groups.

However, the difference was not significant when the MK and, MF as well as, DK and DF groups were compared. This is a very significant clinical finding because it shows that M, K, and F are rapidly absorbed through the IN route as compared to D administered by the same route, as stated in a previous study by Surendar et al. (2014) [30]. The FLACC scale, an observer-rated pain scale, was chosen to evaluate intra- and post-operative analgesic effects because of the inability of children to communicate properly during sedation. Various authors have confirmed that IN ketamine and fentanyl produce significant analgesia, with ketamine having improved analgesic effect compared to fentanyl [31]. This is confirmed by the results of this study, as the DK group produced a more effective analgesic result than the DF group intra- and post-operatively, followed by that of the MK and MF groups. This finding is evident because midazolam does not have an analgesic effect. In this study, the DK and DF groups exhibited additional analgesic benefits provided by dexmedetomidine. A previous study by Yoshitomi et al. confirmed that dexmedetomidine augments the effect of lignocaine by amplifying central neural blockades [32]. Therefore, for dental procedures, dexmedetomidine has an analgesic-sparing effect and is in synergy with both ketamine and fentanyl, thus significantly reducing the required dose of these drugs.

The recovery was fastest in the MF and MK groups in the intergroup comparison [33]. This difference among groups will have a significant influence on dental practice, particularly in an office-based setting, with regard to scheduling, efficiency, and finances [34]. The only adverse effect observed in this study was vomiting in the MK, DK, and MF groups. Importantly, vomiting did not occur during the treatment session, but during the post-anesthetic recovery (RPA) and late post-operative period in all cases. Moreover, when a detailed inquiry was made, it was disclosed that the child who suffered emesis had consumed a meal before the sedation session.

This study had few limitations. A combination of drugs was used; therefore, this study may not be adequately competent to detect and differentiate among the effects/outcomes produced by individual drugs in the groups. The study may not be as proficient in showing differences in parental satisfaction as it would in a crossover study. Within the limitations of this study, the hypothesis regarding no difference among the four combinations with respect to efficacy, safety, time taken to reach an adequate level of sedation, anxiety level, analgesic effects, postoperative sedation effects, and recovery time was partially rejected.

Further studies can be performed with newer sedatives and alternative routes with future exploration and increased usage of mucosal atomization devices in pediatric settings. Future trials can be performed with the incorporation of physiological monitors that use novel technologies as an objective means of determining whether a particular technique can impact risk identification or reduction. Further extensive multicenter trials with larger sample sizes over a broader range of patient age groups are warranted to evaluate the optimal approach and clinical benefits of these regimens.

The intranasal route is an effective and safe method of drug administration for moderate sedation. In conclusion, DK and DF are promising analgesio-sedative combinations considering their successful anxiolytic and analgesic effects in comparison to the traditional MK and MF combinations for pediatric patients during invasive dental procedures in-office; however, the DK and DF combinations prolong the post-anesthetic recovery.

AUTHOR ORCIDs

Abhilasha Agarwal: https://orcid.org/0000-0002-3841-0676
Afroz Alam Ansari: https://orcid.org/0000-0002-7916-4758
Rajendra Nath: https://orcid.org/0000-0002-2373-693X
Rakesh Kumar Chak: https://orcid.org/0000-0002-4652-6791
Rajeev Kumar Singh: https://orcid.org/0000-0002-1348-1750
Richa Khanna: https://orcid.org/0000-0001-6830-8042
Prem Raj Singh: https://orcid.org/0000-0002-5346-6619

AUTHOR CONTRIBUTIONS

Abhilasha Agarwal: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft

Afroz Alam Ansari: Formal analysis, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing

Rajendra Nath: Methodology, Project administration, Supervision, Writing - review & editing

Rakesh Kumar Chak: Validation, Visualization, Writing - review & editing

Rajeev Kumar Singh: Resources, Software, Supervision, Writing - review & editing

Richa Khanna: Data curation, Formal analysis, Supervision, Writing - review & editing

Prem Raj Singh: Formal analysis, Project administration, Supervision, Writing - review & editing

ACKNOWLEDGMENTS: The authors are grateful to the staff members of the department where the study was conducted. We acknowledge the assistance and contribution of this project.

FUNDING: The Institutional Research Cell, King George Medical University, U.P., Lucknow, India, provided financial support of this research.

DECLARATION OF INTERESTS: The authors have no conflicts of interest to declare.

REFERENCES

1. Hosey MT. Anxious children: coping in dental practice. Dent Update 1995; 22: 210-5.
2. Milgrom P, Fiset L, Melnick S, Weinstein P. The prevalence and practice management consequences of dental fear in a major US city. J Am Dent Assoc 1988; 116: 641-7.
3. De Jongh A, Adair P, Meijerink-Anderson M. Clinical management of dental anxiety: what works for whom? Int Dent J 2005; 55: 73-80.
4. Folayan MO, Faponle A, Lamikanra A. Seminars on controversial issues. A review of the pharmacological approach to the management of dental anxiety in children. Int J Paediatr Dent 2002; 12: 347-54.
5. Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet 2006; 367: 766-80.
6. Kain ZN, Hofstadter MB, Mayes LC, Krivutza DM, Alexander G, Wang SM, et al. Midazolam: effects on amnesia and anxiety in children. Anesthesiology 2000; 93: 676-84.
7. Mace SE, Barata IA, Cravero JP, Dalsey WC, Godwin SA, Kennedy RM, et al. Clinical policy: evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department. Ann Emerg Med 2004; 44: 342-77.
8. McMorrow SP, Abramo TJ. Dexmedetomidine sedation: uses in pediatric procedural sedation outside the operating room. Pediatr Emerg Care 2012; 28: 292-6.
9. Nooh N, Sheta SA, Abdullah WA, Abdelhalim AA. Intranasal atomized dexmedetomidine for sedation during third molar extraction. Int J Oral Maxillofac Surg 2013; 42: 857-62.
10. Funk W, Jakob W, Riedl T, Taeger K. Oral preanesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. Br J Anaesth 2000; 84: 335-40.
11. Acworth JP, Purdie D, Clark RC. Intravenous ketamine plus midazolam is superior to intranasal midazolam for emergency pediatric procedural sedation. Emerg Med J 2001; 18: 39-45.
12. Gharde P, Chauhan S, Kiran U. Evaluation of Efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. Ann Card Anaesth 2006; 9: 25-30.
13. Singh C, Pandey RK, Saksena AK, Chandra G. A comparative evaluation of analgo-sedative effects of oral dexmedetomidine and ketamine: a triple-blind, randomized study. Paediatr Anaesth 2014; 24: 1252-9.
14. Roelofse JA, Shipton EA, de la Harpe CJ, Blignaut RJ. Intranasal sufentanil/midazolam versus ketamine/midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: a prospective, double-blind, randomized comparison. Anesth Prog 2004; 51: 114-21.

15. Bennett JA. The consolidated standards of reporting trials (CONSORT): guidelines for reporting randomized trials. Nurs Res 2005; 54: 128-32.
16. Jaikaria A, Thakur S, Singhal P, Chauhan D, Jayam C, Syal K. A comparison of oral midazolam-ketamine, dexmedetomidine-fentanyl, and dexmedetomidine-ketamine combinations as sedative agents in pediatric dentistry: a triple-blinded randomized controlled trial. Contemp Clin Dent 2018; 9(2 Suppl): 197S-203S.
17. Riba HK, Al-Zahrani S, Al-Buqmi N, Al-Jundi A. A review of behavior evaluation scales in pediatric dentistry and suggested modification to the Frankl scale. EC Dental Science 2017; 16: 269-75.
18. Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. Pediatr Dent 2019; 41: E26-52.
19. Sado-Filho J, Viana KA, Corrêa-Faria P, Costa LR, Costa PS. Randomized clinical trial on the efficacy of intranasal or oral ketamine-midazolam combinations compared to oral midazolam for outpatient pediatric sedation. PLoS One 2019; 14: e0213074.
20. Yang F, Liu Y, Yu Q, Li S, Zhang J, Sun M, et al. Analysis of 17 948 pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine. Paediatr Anaesth 2019; 29: 85-91.
21. Ryan PM, Kienstra AJ, Cosgrove P, Vezzetti R, Wilkinson M. Safety and effectiveness of intranasal midazolam and fentanyl used in combination in the pediatric emergency department. Am J Emerg Med 2019; 37: 237-40.
22. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth 2002; 88: 241-5.
23. Jones JE, Dean JA. Local anesthesia and pain control for the child and adolescent. In: McDonald and Avery's dentistry for the child and adolescent. 10th ed. Edited by Dean JA. St. Louis, Elsevier Inc. 2016, pp 274-85.
24. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990; 10: 244-51.
25. Houpt MI, Weiss NJ, Koenigsberg SR, Desjardins PJ. Comparison of chloral hydrate with and without promethazine in the sedation of young children. Pediatr Dent 1985; 7: 41-6.
26. Merkel S, Voepel-Lewis T, Malviya S. Pain assessment in infants and young children: the FLACC scale. Am J Nurs 2002; 102: 55-8.
27. Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics 2003; 112: 116-23.
28. Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth 2011; 107: 430-7.
29. Yu C, Li S, Deng F, Yao Y, Qian L. Comparison of dexmedetomidine/fentanyl with midazolam/fentanyl combination for sedation and analgesia during tooth extraction. Int J Oral Maxillofac Surg 2014; 43: 1148-53.
30. Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. A comparative evaluation of intranasal dexmedetomidine, midazolam and ketamine for their sedative and analgesic properties: a triple blind randomized study. J Clin Pediatr Dent 2014; 38: 255-61.
31. Reynolds SL, Bryant KK, Studnek JR, Hogg M, Dunn C, Templin MA, et al. Randomized controlled feasibility trial of intranasal ketamine compared to intranasal fentanyl for analgesia in children with suspected extremity fractures. Acad Emerg Med 2017; 24: 1430-40.
32. Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. Dexmedetomidine enhances the local anesthetic action of lidocaine via an alpha-2A adrenoceptor. Anesth Analg 2008; 107: 96-101.
33. Roelofse JA, Shipton EA, de la Harpe CJ, Blignaut RJ Intranasal sufentanil/midazolam versus ketamine/midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: a prospective, double-blind,

randomized comparison. Anesth Prog 2004; 51: 114-21.
34. Homer T, Maguire A, Douglas GVA, Innes NP, Clarkson JE, Wilson N, et al. Cost-effectiveness of child caries management: a randomised controlled trial (FiCTION trial). BMC Oral Health 2020; 20: 45.