Improved postoperative recovery profile in pediatric oral rehabilitation with low-dose dexmedetomidine as an opioid substitute for general anesthesia: a randomized double-blind clinical trial

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Background: Low-dose dexmedetomidine may be a suitable alternative to opioids for pediatric ambulatory procedures under general anesthesia (GA). However, the recovery profile remains unclear. Herein, we aimed to evaluate the effects of low-dose dexmedetomidine on the recovery profile of children.

Methods: Seventy-two children undergoing ambulatory oral rehabilitation under GA were randomly and equally distributed into two groups (D and F). Group D received an infusion of dexmedetomidine 0.25 μg/kg for 4 min for induction, followed by maintenance of 0.4 μg/kg/h. Group F received an infusion of fentanyl 1 μg/kg over 4 min for induction, followed by maintenance at 1 μg/kg/h. The primary outcome was the extubation time. The secondary outcomes were awakening time, end-tidal sevoflurane (ET-Sevo) requirement, change in hemodynamic parameters, Richmond Agitation–Sedation Scale (RASS), Children's Hospital of Eastern Ontario pain scale (CHEOPS) score, length of PACU stay, and incidence of adverse events.

Results: Statistically significant differences were observed in the recovery profile between the groups: the median time for extubation was 3.65 (3.44–6.2) vs. 6.25 (4.21–7) minutes in groups D vs. F (P=0.001), respectively, while the corresponding awakening times were 19 (18.75–21) and 22.5 (22–24) minutes, respectively (P < 0.001). The mean ET-Sevo was low in group D (1.1 vs. 1.2; P < 0.001). The heart rate was significantly low across all time points in group D, without resulting in bradycardia. The median RASS and CHEOPS scores were also significantly lower in group D. No significant differences were observed in the mean arterial pressure, incidence of adverse events, or length of PACU stay.

Conclusion: Low-dose dexmedetomidine was more effective than fentanyl as an opioid substitute at providing a better recovery profile in pediatric ambulatory oral rehabilitation under GA. Dexmedetomidine also significantly reduced sevoflurane consumption without causing adverse events or prolonging hospital stay.

Keywords: Children; Dental Care; Dexmedetomidine; Recovery.

INTRODUCTION

Over the past few decades, several studies have shown a significant increase in early childhood dental caries (ECC) worldwide [1,2], with children under the age of six being especially vulnerable [2]. Recently, health professionals have been challenged by immense demands

and an increase in the number of such patients [1]. The purpose of providing general anesthesia (GA) in uncooperative pediatric patients with ECC is to restore optimum dental health in one visit and prevent apprehension related to multiple dental chair visits, which necessitates substantial dental work [3]. Ensuring a suitable anesthetic approach in this scenario is essential for ensuring risk-free, prompt, effective, and cost-efficient anesthesia.

Opioids have been a central component of routine pediatric anesthesia for decades. However, their side effects include respiratory distress, itching, retention of urine, nausea, vomiting, constipation, mood changes, and unintentional opioid dependence among children [4-7]. Fentanyl can augment hyperalgesia [8]. However, there is inadequate data to establish an outcome [9]. Recently, there has been a trend towards use opioid-free anesthesia in pediatric ambulatory procedures [10-12]. An ideal opioid-free anesthetic agent should be rapid in onset and offset, with smooth emergence, minimal cardiovascular effects, and a predictable response. As a highly selective α-2 adrenergic agonist, dexmedetomidine possesses several of these desirable properties, which are beneficial in the ambulatory setting [13-15]. Dexmedetomidine exhibits anxiolytic, analgesic, sympatholytic, and opioid-sparing effects at low doses (< 0.5 μg/kg) [15-21]. Many pediatric studies have also reported other benefits of low-dose dexmedetomidine [16-21], such as decreased incidence of emergence agitation [19,22,23], emergence delirium [19,24], postoperative pain [23,19], and reduced sevoflurane consumption [19] with a better hemodynamic profile [18-21]. However, evidence related to the recovery characteristics of low-dose dexmedetomidine is scarce. To our knowledge, no study has evaluated the opioid-equivalent efficacy of low-dose dexmedetomidine in pediatric patients for GA, although this has been reported in adults [15,25].

We designed this randomized controlled trial to compare the recovery parameters of low-dose dexmedetomidine and fentanyl in children undergoing ambulatory oral rehabilitation dental procedures under GA. We

speculated that the application of low-dose dexmedetomidine as an opioid substitute would accelerate recovery. We also analyzed the effects of low-dose dexmedetomidine on hemodynamic indices, sevoflurane requirement, length of PACU stay, incidence of adverse events, postoperative sedation, and pain profile.

METHODS

1. Study design

This randomized, controlled, double-blind clinical trial was conducted at the Oral Health Sciences Center of the Post Graduate Institute of Medical Education and Research, Chandigarh, a tertiary care hospital in India. We aimed to compare the recovery characteristics of fentanyl and low-dose dexmedetomidine in pediatric patients undergoing ambulatory oral rehabilitation under GA.

2. Ethics

After obtaining approval from the institutional ethics committee, the trial was registered in the clinical trial registry of India (CTRI/2019/01/017252). Before enrolment and randomization to the study arms, written informed consent was obtained from the parents/legal guardians of the patients.

3. Participants

Children aged 1 to 4 years with American Society of Anesthesiologists (ASA) physical status I and II were included. Children with a history of allergy to any anesthetic agent, renal or liver dysfunction, or those who disallowed premedication were excluded from the trial.

4. Randomization

Pediatric patients were randomly and equally allocated into two groups (D and F) using a computer-based simple randomization method. Group D received a bolus dose of dexmedetomidine 0.25 μg/kg over 4 mins for induction, followed by a maintenance infusion of 0.4 μ

g/kg/h until 10 mins before the end of the procedure. Group F received a bolus dose of fentanyl 1 μg/kg over 4 min for induction, followed by a maintenance infusion of 1 μg/kg/h until 10 min before the end of the procedure. The drugs were prepared by a separate anesthesiologist who was not involved in the study who received information regarding the drugs to use in a sealed envelope. The drugs were diluted in 50 ml of normal saline and administered through a syringe infusion pump by a blinded anesthesiologist. Coded labels (drugs 1 or 2) were affixed over the 50 cc syringe so that the attending anesthesiologist would be unaware of the grouping of the children. Thus, the syringes and volumes of the prepared solutions were the same; only the rate of drug infusion differed according to the weight of each child. The anesthesiologist, pedodontist, and observer were blinded to the study protocol. The master code was in the possession of an individual not involved in the trial.

5. Anesthesia

In the preoperative recovery room, children were premedicated using midazolam syrup 0.5 mg/kg orally, 20 minutes before induction of anesthesia. After shifting inside the procedure room, ASA standard monitors and bispectral index (BIS) electrodes were attached to ensure not to agitate the child. Venous cannulation was secured after inhalation induction using 5–8% sevoflurane with 100% oxygen. Anesthesia induction was initiated with infusion bolus doses of low-dose dexmedetomidine (group D) or fentanyl (group F) at the doses mentioned above in the randomization. After checking for adequate bag and mask ventilation, the muscle relaxant atracurium 0.5 mg/kg was administered intravenously, and anesthesia was maintained with sevoflurane, targeting a BIS of 50. After 4 min, the airway was secured with an endotracheal tube, and mechanical ventilation was initiated with a tidal volume of 6–8 ml/kg to sustain normocapnia (35–45 mmHg), guided by end-tidal CO_2 monitoring. Anesthesia was maintained using a continuous intravenous infusion of low-dose dexmedetomidine or fentanyl, oxygen, and N_2O mixture (50:50), and sevoflurane. The ET-Sevo was

adjusted to attain a BIS of 50 throughout the procedure. As a routine institutional practice, body temperature was monitored throughout the procedure, and forced air-warm blankets and warm intravenous fluids were administered to maintain normothermia. At the end of the procedure, 15 mg/kg of intravenous paracetamol was administered for analgesia. Intravenous infusion of fentanyl or dexmedetomidine was stopped 10 minutes before the end of the procedure. At the end of the procedure, sevoflurane and nitrous oxide were discontinued, and the child was extubated after the return of spontaneous respiration and adequate muscle tone. The children were then moved to the PACU, and a parent was allowed to accompany the child. Until their discharge from the PACU, patients were monitored continuously by a trained nurse or anesthesiologist who was blinded to the study trial.

6. Outcome and measurements

The primary outcome was the time for extubation (time from the end of surgery until removal of the endotracheal tube). The secondary outcomes were awakening time (time from the end of drug infusion to eye opening in response to a voice), ET-Sevo requirement, percentage change in hemodynamic parameters, sedation scoring, pain scoring, length of PACU stay, rescue analgesia requirement, incidence of vomiting, incidence of emergence agitation, and any other adverse events.

Perioperative hemodynamic parameters (heart rate [HR], systolic, diastolic, and mean arterial pressure [MAP]) were obtained at the following time points: at baseline, at the initiation of the loading dose, after the loading dose, post-intubation, every 10 min during the procedure, after extubation, on arrival at the PACU, and every 15 min until discharge from the PACU. The Richmond agitation sedation score (RASS) was used for sedation assessment from the time of arrival at the PACU until discharge, with a score range of − 5 (no response to voice or physical stimulation) to + 4 (overtly combative or violent). Post-procedure pain was evaluated using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS; 4–13 score range). A CHEOPS score of > 6
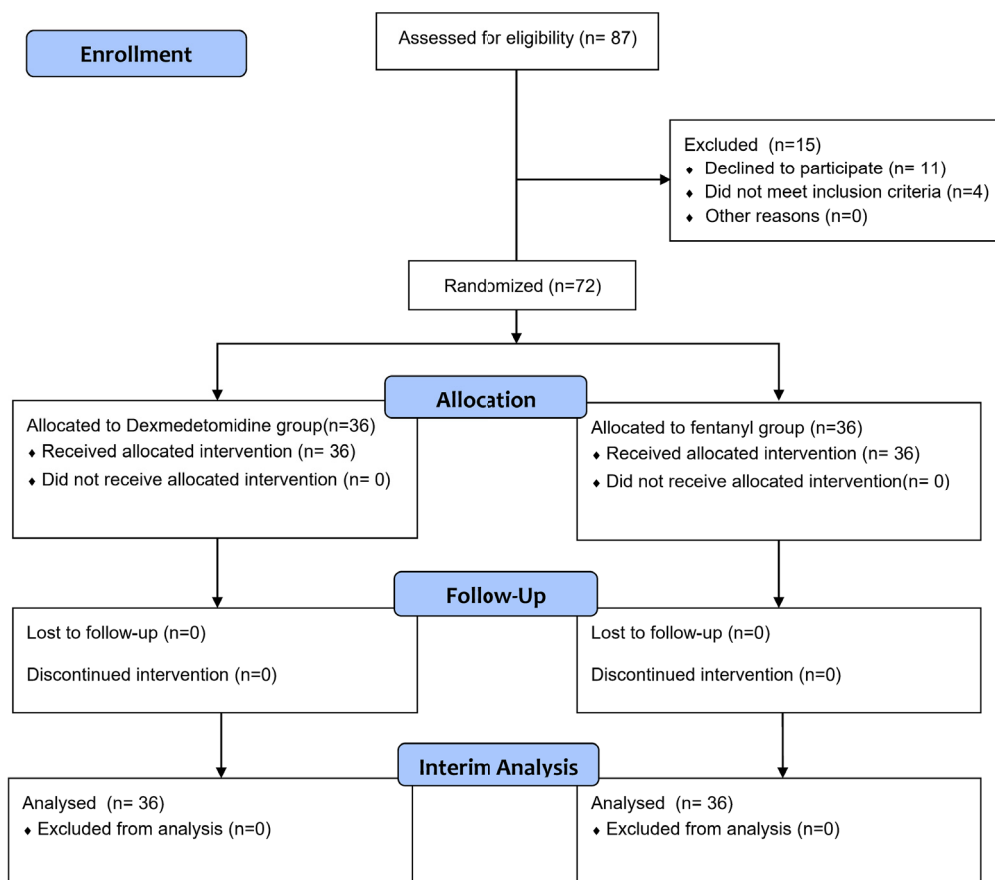
Fig. 1. CONSORT flow diagram. CONSORT, consolidated standards of reporting trials; Group D, dexmedetomidine group; Group F, fentanyl group; n, number.

was regarded as an endpoint for rescue analgesia with intravenous fentanyl 0.5 μg/kg. Children with modified Aldrete scores $\geq$ 9 were deemed fit for discharge from the PACU.

7. Statistics

The calculated sample size was 36 per group, with a 95% confidence interval (two-sided), considering an 80% power of the study and significance level of 5%, and to demonstrate a difference of 2.7 minutes with a pooled SD of 3.8 [16] in the primary objective between groups and considering a dropout rate of 10%. Unpaired t-tests or Mann-Whitney U tests were used to compare continuous data based on the normality of distribution. Repeated measures were analyzed using repeated-measures ANOVA or GEE (Generalized Estimating Equations, with exchangeable correlation matrix and identity link function). Pairwise comparisons were

adjusted using the Bonferroni correction. Categorical data were compared using the chi-squared test. Statistical significance was set at $P < 0.05$. All analyses were performed using the Stata 15 software (StataCorp. 2017. Stata statistical software: Release 15. College Station, TX, StataCorp LLC).

RESULTS

In total, 83 children were initially enrolled in the study (Fig. 1), of whom 72 were subsequently randomized after fulfilment of the eligibility criteria. The baseline demographic parameters were comparable between the two groups (Table 1). There were no significant differences in age, sex, weight, procedure time, baseline heart rate, or mean MAP.

The time to extubation (represented as the median [Q1,

Table 1. Demographic and baseline variables

	Dexmedetomidine (n = 36)	Fentanyl (n = 36)	P-value
Age (years), mean (SD)	2.6 (0.9)	2.5 (0.6)	0.486[a]
Weight (kg), mean (SD)	12.3 (2.2)	12.6 (2.9)	0.525[a]
Gender (male/female), number (%)	25 (69.4) / 11 (30.6)	19 (52.8) / 17 (47.2)	0.147[b]
Duration of surgery (in min), mean (SD)	96.3 (7.9)	93.9 (11.3)	0.294[a]
Mean arterial pressure (mmHg), mean (SD)	63.0 (3.6)	59.6 (2.4)	1.000[a]
Heart rate (bpm), mean (SD)	133.8 (6.2)	131.3 (7.4)	0.133[a]

[a]Unpaired T test, [b]Chi-square test; P < 0.05 has been considered significant. n, number; SD, standard deviation.
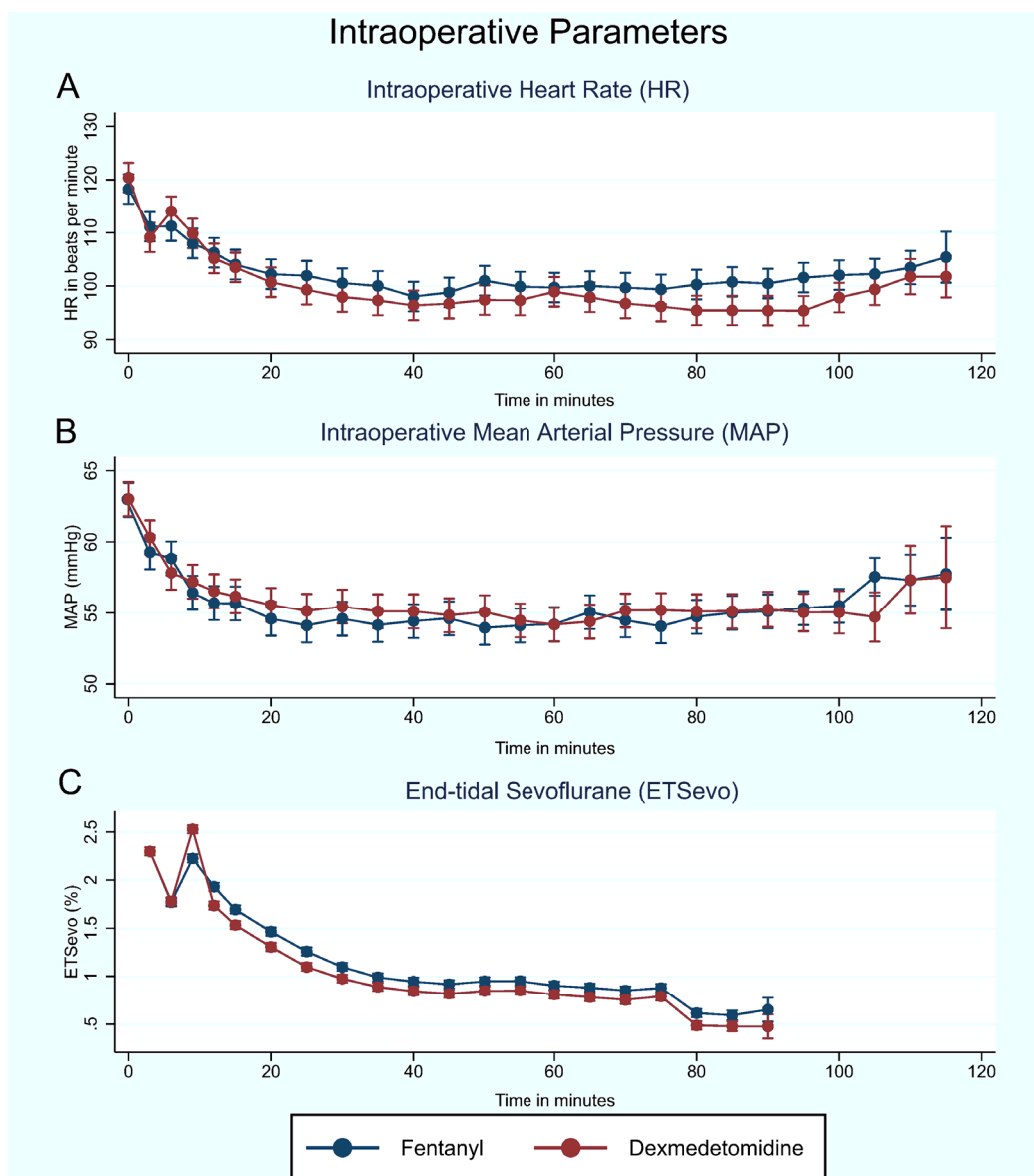

Fig. 2. Intraoperative hemodynamics (mean with 95% confidence intervals). (A) Heart rate, (B) Mean arterial pressure, and (C) End-tidal sevoflurane concentration over time in minutes

Q3]) was significantly shorter in group D (3.65 [3.44–6.2] vs. 6.25 [4.21–7]; P = 0.001) than in group F. Awakening time was also significantly reduced in the dexmedetomidine group (19 [18.75–21] vs. 22.5 [22–24]; P < 0.001).

Table 2. Outcome parameters

	Dexmedetomidine (n = 36)	Fentanyl (n = 36)	P-value
Time to extubate, median [Q1,Q3]	3.65 [3.44–6.2]	6.25 [4.21–7]	0.001[c]
Awakening time(min), median [Q1,Q3]	19.0 [18.75–21]	22.5 [22–24]	< 0.001[c]
Mean end-tidal sevoflurane (%), mean (SD)	1.1 (0.0)	1.2 (0.0)	< 0.001[a]
PACU Stay (min), mean (SD)	53.3 (4.0)	55.8 (8.0)	0.106[a]
Need for rescue analgesia, number (%)	7 (19.4)	10 (27.8)	0.405[b]
CHEOPS immediate post-procedure, median [Q1,Q3]	5.0 [5.0, 5.0]	5.0 [5.0,5.0]	0.392[c]
CHEOPS 10 minutes post-procedure, median [Q1,Q3]	4.5 [4.0, 5.0]	5.0 [4.0,5.0]	0.463[c]
RASS immediate post-procedure, median [Q1,Q3]	0.0 [0.0, 0.0]	1.0 [1.0,1.0]	< 0.001[c]
RASS at 10 minutes post-procedure, median [Q1,Q3]	-1.0 [-1.0, -1.0]	0.0 [0.0,1.0]	< 0.001[c]

[a]Unpaired T test, [b]Chi-square test, [c]Mann-Whitney U test. P < 0.05 has been considered significant. CHEOPS, Children's Hospital of Eastern Ontario pain scale; n, number; PACU, post anesthesia care unit; Q, quartile; RASS, Richmond agitation–sedation scale; SD, standard deviation.
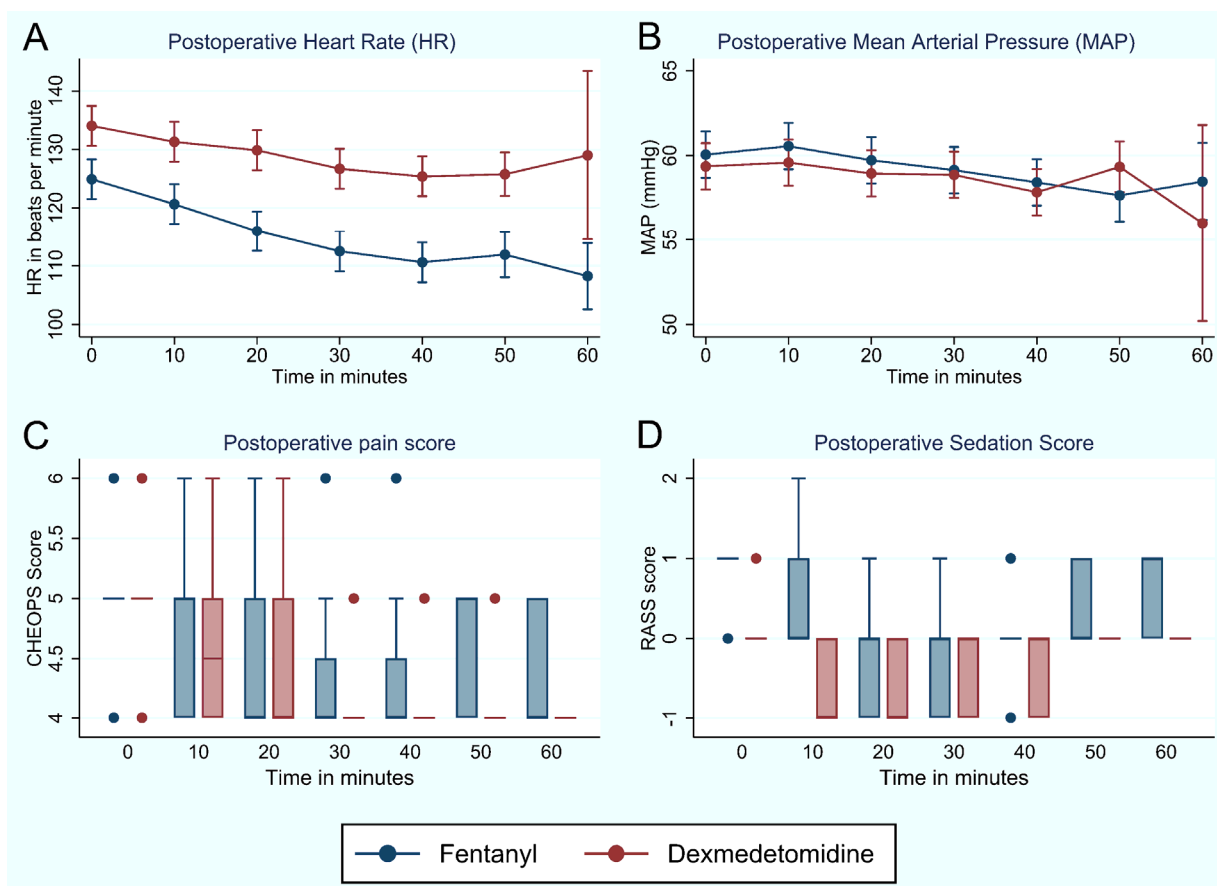
Fig. 3. Post-procedure parameters. (A) Heart rate (mean with 95% confidence intervals), (B) mean arterial pressure (mean with 95% confidence intervals); boxplots (median with Tukey limits) of (C) CHEOPS (Children's Hospital of Eastern Ontario Pain Scale), and (D) Richmond Agitation Sedation Scale (RASS) over time in minutes.

Intraoperatively, the ET-Sevo concentration required to maintain a BIS of 50 was lower at almost all time points in the dexmedetomidine group than in the fentanyl group, as shown in Figure 2C. This difference was statistically significant (1.2% vs. 1.1%; P < 0.001; Table 2).

Intraoperative heart rate was lower in the dexmedetomidine group than in the fentanyl group at most points in time (Fig. 2A and 3A), showing a significant group time interaction both intraoperatively (P < 0.025, Table 3) and postoperatively (P = 0.056).

Table 3. Analysis of repeated measures

Variable	Effect of group (P-value)	Effect of time (P-value)	Effect of group over time (P-value)	Test
Intraoperative Heart rate	0.135	< 0.001	0.023	ANOVA
Intraoperative MAP	0.378	< 0.001	0.107	ANOVA
Intraoperative Sevoflurane	< 0.001	< 0.001	< 0.001	ANOVA
Post-procedure Heart rate	< 0.001	0.017	0.056	ANOVA
Post-procedure MAP	0.682	0.245	0.267	ANOVA
CHEOPS score	0.124	0.038	0.027	GEE
Post-procedure RASS score	0.087	0.470	0.001	GEE

P < 0.05 is considered as statistically significant. ANOVA, analysis of variance; CHEOPS, Children's Hospital of Eastern Ontario pain scale; GEE, generalized estimating equations; MAP, mean arterial pressure; RASS, Richmond agitation sedation score.

However, there were no significant differences in the perioperative MAP among the groups (Table 3; Fig. 2B and 3B). Moreover, none of the patients developed bradycardia (defined as an HR decrease of $\geq$ 30% from the baseline value) or hypotension throughout the study period.

After the dental procedure, the median RASS and CHEOPS scores with quartiles (Q1 and Q3) were analyzed (Fig. 3C and 3D). The RASS was significantly lower in the dexmedetomidine group over time (P = 0.001; Table 2). The CHEOPS score was also lower in the dexmedetomidine group over time (P = 0.027; Fig. 3C). However, this difference was more due to changes in CHEOPS over time (P = 0.038; Table 3) than due to the treatment effect (P = 0.124; Table 3). Rescue analgesia was required in 10 (27.8%) children in the fentanyl group and 7 (19.4%) in the dexmedetomidine group (P = 0.405; Table 2).

The mean (SD) duration of PACU stay was comparable between the fentanyl and dexmedetomidine groups (55.8 [8] and 53.3 [4] min, respectively; P = 0.106). Out of 72 patients, four experienced vomiting episodes in the fentanyl group compared with none in the dexmedetomidine group; however, this difference was not statistically significant.

DISCUSSION

The use of GA for pediatric dental treatment of ECC has shown an increasing trend [25], mainly because of the state of cognitive function in children at that stage and the complexity of oral rehabilitation, especially in those with multiple dental caries [2,26].

Anesthesiologists generally use dexmedetomidine in the pediatric population for premedication and procedural sedation as an opioid-sparing agent [27], and to avert and treat postoperative emergence agitation [14]. Although there is a substantial body of evidence on dexmedetomidine use in pediatric patients, studies on its opioid-equivalent efficacy and recovery characteristics are scarce. Low-dose dexmedetomidine has been studied as an opioid substitute in adults [15,25]; however, to our knowledge, this is the first RCT evaluating the opioid substitution property and recovery characteristics of low-dose dexmedetomidine against fentanyl in a pediatric population.

The recovery characteristics of dexmedetomidine are related to its infusion dose and rate; with increasing dosage, the recovery time is significantly prolonged [17]. Our selection of 0.25 μg/kg loading dose of dexmedetomidine was based on a recent RCT by Sun et al. involving children (1–5 years of age) undergoing laparoscopic hernia repair [19]. They demonstrated a shorter recovery time with smooth emergence at low doses of dexmedetomidine. Conversely, as there is no recommended dose of dexmedetomidine in the 1–5-year-old population, different dosing and rate of infusions were used in every published study [17-20]. In a study by Chen et al. [17], dexmedetomidine at different

doses (0.25, 0.5, 0.75, and 1.0 μg/kg) was administered intraoperatively at a rate of less than 5 s. Conversely, Zhou et al. [18] administered low-dose dexmedetomidine of 0.5 μg/kg within 3 minutes preoperatively, while Xie et al. [20] administered dexmedetomidine at a loading dose of 0.5 μg/kg over 10 mins for anesthesia induction, followed by maintenance of 0.5 μg/kg/h.

Our findings suggest that low-dose dexmedetomidine as an opioid substitute drug provides a good recovery profile with stable hemodynamics and without prolonging hospital stay in children undergoing ambulatory oral rehabilitation procedures under GA. The shorter recovery time associated with low-dose dexmedetomidine in our study was consistent with the findings of a recent meta-analysis [21], which reported a significantly shorter recovery time (5.9 minutes with low-dose dexmedeto-midine). Nevertheless, the definition of recovery time differed in the included RCTs. Certain studies [19,20] defined it as the time to spontaneous eye-opening post-extubation, whereas another RCT [17] defined it as the duration of PACU stay.

Inhalational volatile anesthetics, particularly sevoflurane, have been associated with increased agitation [23] and delirium [24] during emergence from anesthesia in the pediatric population. Dexmedetomidine at low doses decreases both emergence agitation and delirium by reducing the requirement for sevoflurane [19], although evidence to support this in children is scarce [23,24]. In our study, 0.25 μg/kg of dexmedetomidine followed by a maintenance infusion of 0.4 μg/kg decreased sevoflurane requirement by 16.7%. A previous study demonstrated that 0.5 μg/kg of dexmedetomidine decreased sevoflurane requirement by 33% in children undergoing minor surface surgery under GA [28]. However, we believe that their induction doses of dexmedetomidine (1–2 μg/kg) were high under GA. Several studies have reported severe bradycardia [29,30] and cardiac arrest [31,32] with high-bolus dosing regimens of dexmedetomidine in pediatric patients owing to its unpredictable hemodynamic response. Mason et al. reported that the dosing and rate of dexmedetomidine

infusion significantly impacted the hemodynamic profile of patients [29]. Conversely, in a recent meta-analysis, Josephine et al. [21] reported a better hemodynamic profile and shorter recovery time with ≤ 0.5μg/kg of dexmedetomidine than those associated with higher doses (> 0.5 μg/kg).

No cases of hypotension or bradycardia were reported in either study group, since both fentanyl and low-dose dexmedetomidine were infused slowly over 4 minutes, instead of in a quick bolus. The HR was significantly lower at most time points in the dexmedetomidine group. However, MAP was normal in all patients. The maximum decrease in mean HR from baseline in the dexmedetomidine group was 26% and the maximum decrease in MAP was 17%, which was clinically insignificant. Chen et al. [17] reported a similar decrease in HR of less than 30% from the baseline following the administration of dexmedetomidine at doses of 0.25 and 0.5 μg/kg in children. However, this difference was clinically insignificant, and no patient required any additional treatment.

In the dexmedetomidine group, all children were calm post-extubation and had significantly lower RASS and CHEOPS scores with no incidence of emergence agitation. Our findings support the high-quality evidence from a recent meta-analysis by Zhang et al. [33], which demonstrated the benefits of maintenance infusion of dexmedetomidine on emergence agitation in children. Our findings also demonstrate that dexmedetomidine minimizes PONV and the need for rescue analgesia without delaying discharge from the PACU. These findings are consistent with those of earlier meta-analyses [33-35].

Our study had two main limitations. First, we did not include a placebo-controlled group; unfortunately, this was not feasible, as not administering any opioid or non-opioid analgesic can trigger acute emergence delirium, and ambulatory anesthesia may not be possible due to parents' apprehension due to the children's unusual behavior post-procedure. Second, we compared fentanyl and dexmedetomidine based on their optimum and safe

dosing for ambulatory procedures, without considering their equivalent doses. To further elucidate our findings, a future pharmacokinetic/pharmacodynamic clinical dose-response study may be necessary.

In conclusion, fentanyl and low-dose dexmedetomidine were comparable in terms of safety, analgesic requirement, and length of PACU stay. Our findings showed a rapid and smooth recovery with low-dose dexmedetomidine than fentanyl, which implies that dexmedetomidine at a dose < 0.4 μg/kg can be used safely as an opioid substitute. Multi-centric studies incorporating a wide range of cases and procedure settings in the pediatric population are warranted to establish the promising role of low-dose dexmedetomidine as an opioid substitute for GA.

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