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Research Article

Comparative study between novel sedative drug (dexmedetomidine) versus midazolam–propofol for conscious sedation in pediatric patients undergoing oro-dental procedures

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KEYWORDS

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Abstract *Objective:* A comparative study to evaluate the effect of dexmedetomidine as a sedative in pediatric dental patients in comparison to the currently used combination of midazolam and propofol.

Methods: Sixty ASA I children (4–10 years old) referred from the outpatient clinic of the pediatric dentistry department for sedation for dental procedures. They were randomly classified into two groups, group I (dexmedetomidine group) was given as 2 μg/kg loading dose over 5 min followed by 0.4 μg/kg/h continuous infusion. Group II (midazolam–propofol group) midazolam was given as 0.05 mg/kg and propofol was given loading dose as 1 mg/kg over 5 min followed by 5 mg/kg/h continuous infusion. Heart rate, mean arterial blood pressure, oxygen saturation, respiratory rate were recorded every 5 min till discharge. The onset of sedation, procedure time, recovery time, discharge time and the need of analgesia were recorded. The incidence of occurrence of adverse effects was observed.

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Results: In group I, the mean onset of sedation was significantly longer than in group II, but recovery time was significantly shorter in group I than group II, there are significantly hemodynamics effects in the first 15 min and more incidence of occurrence of side effects in group II than group I. There are more analgesic effects of dexmedetomidine in group I than group II postoperatively.
Conclusion: Dexmedetomidine is safe and effective when used for sedation in pediatric patients undergoing dental procedures.

1. Introduction

The field of pediatric dentistry beholds the greatest challenge among the various other branches of dentistry in providing dental care without inflicting any adverse psychological impact upon the child [1]. Uncooperative behavior in the dental setting is most typically attributed to behavioral manifestations of anxiety; such uncooperative behavior has been rated by dentists as being the major problem in the dental chair. Major consequences of such uncooperative behavior may include a delay or termination of treatment before completion, or a decrease in the quality of care provided [2]. Today modern pediatric dentistry describes so many techniques to manage the behavior of the child dental patient. The use of range of drugs as adjuvant to behavioral psychology should enable the dentist to handle most of unmanageable children [3]. Among drugs used in conscious sedation, we can mention midazolam which is a benzodiazepine derivative as well as propofol which is a short acting intravenous sedative agent, but they are potential respiratory depressant [4,5]. Dexmedetomidine is a centrally acting α_2 agonist that has sedative and analgesic effect and shorter half-life of 1.5–3 h after intravenous dosing so make it easier to titrate, quicker to recover [6]. Dexmedetomidine provides sedation and analgesia with no accompanying respiratory depression when administered within clinical dosing guidelines even some consider that dexmedetomidine actually mimics some aspects of natural sleep, however, it produces dose dependant decrease in blood pressure and heart rate as a result of its α_2 agonist effect on the sympathetic ganglia with resulting sympatholylic effects [7].

Propofol when used alone in uncooperative pediatric patients undergoing dental procedures was accompanied by pain on injection and coughing despite rapid onset of action, while midazolam when used showed the longest duration of action but was not very effective in terms of treatment completion due to increased movements and crying [8]. Thus combination of small doses of midazolam with propofol can be considered superior in sedation over single drug used. The aim of the study is to compare the safety and efficacy of midazolam–propofol combinations to dexmedetomidine for conscious sedation in pediatric patients undergoing oro-dental procedures.

2. Methods

Following the approval from ethical committee and obtaining parental written informed consent, 60 ASA I physical status child aged 4–10 years old, were enrolled in the period between December 2007 and December 2008 in general Anesthesia Unit, Department of Pediatric and Preventive Dentistry, Faculty of Oral and Dental Medicine, Cairo University. Patients enrolled have no history of drug allergy scheduled for dental procedure (pulpotomy with amalgam filling, cavity preparation with amalgam filling, teeth extraction) (Table 4), fasting for 8 h with allowing clear fluids up to 2 h; referred for sedation. All children were subjected for complete medical examination, weighted in kg and sedative agent was prepared according to the body weight. All patients had a 22G cannulae inserted as an IV line before start of conscious sedation using EMLA cream, then received 20 mg lidocaine 2% (1 ml) and atropine 0.01 mg/kg as anti sialogouge, and O_2 supplementation via a nasal cannulae at 4 l/min before the injection of the sedative agent. All facilities for securing and maintaining a patent airway, providing O_2, artificial ventilation and cardiopulmonary resuscitation were available. Restraining belt was applied to prevent unwanted movement during the procedure.

Children were then randomized into two equal groups using closed envelope technique into group I (dexmedetomidine group, $n = 30$) where 2 μg/kg dexmedetomidine was administered over 5 min to achieve a Ramsay sedation scale (RSS) of $\geqslant 5$ (Table 1) [9], followed by of 0.4 μg/kg/h dexmedetomidine as continuous infusion using a syringe pump, if at any time unwanted movement or unfavorable sedation level had been achieved, the dentist is asked to stop the procedure momentarily and increments of 0.4 μg/kg dexmedetomidine was administered until the desired RSS $\geqslant 5$ was restored. And group II (propofol–midazolam group, $n = 30$) where 0.05 mg/kg midazolam was administered followed by 1 mg/kg propofol over 5 min to achieve a Ramsay sedation scale (RSS) of $\geqslant 5$ (Table 1) [9] then continuous propofol infusion of 5 mg/kg/h using a syringe pump, if at any time unwanted movement or unfavorable sedation level had been achieved, the dentist is asked to stop the procedure momentarily and increments of 0.5 mg/kg propofol was administered until the desired RSS $\geqslant 5$ was restored. Following randomization drugs were prepared according to body weight and all syringes to be administered including loading, top up doses and maintenance were covered by aluminum foil and code labeled. Syringes were given to anesthetist that is blinded to experimental protocol. Following sedation the dentist used local infiltration anesthesia with lidocaine 2% at a maximum dose of 4 mg/kg.

Table 1 Ramsay sedation scale [9].

Score	Response
1	Anxious or restless or both
2	Cooperative, oriented and tranquil (calm)
3	Responding to command
4	Brisk (quick) response to stimulus
5	Sluggish (slow moving) response to stimulus
6	No response to stimulus

Table 2 Steward Recovery score [10].

Consciousness	
Awake	2
Responding to stimuli	1
Not responding	0
Airway	
Coughing on command or crying	2
Maintaining good airway	1
Airway requires maintenance	0
Movement	
Moving limbs purposefully	2
Non purposeful movements	1
Not moving	0

3. Measurements

A physician that is blinded to experimental protocol was given a spread sheet titled by the label code of syringe and was asked to complete the following data in the spread sheet.

Heart rate, mean arterial blood pressure, respiratory rate and oxygen saturation were recorded prior to sedation and then every 5 min till discharge, patients were discharged when Steward Recovery score of 6 (Table 2) [10]. The following times were also recorded:

- Onset of sedation = is the time from the end of the loading dose to achievement of RSS of 5 or more.
- Procedure time = is the time from achieving the required RSS till the end of the procedure (stoppage of drug infusion).
- Recovery time = is the time from stoppage of drug infusion till reaching the RSS of 2.
- Discharge time = is the time from stoppage of drug infusion till the discharge of the child from density clinic, Steward Recovery score of 6.

Incidence of occurrence of adverse effects, and unwanted movements during the procedure were also recorded. Children were then transferred to the recovery area where another physician blinded to the experimental protocol is responsible for documenting the time at which child achieved Stewart Recovery score of 6 and also he is responsible to observe the needs for analgesia postoperatively according to CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) [11] (Table 3); analgesia will be declofenac 25 mg supp. when CHEOPS > 4.

4. Statistical analysis

Parametric data are presented as mean ± SD. Nominal data and qualitative data are presented as absolute value and % of total. Hemodynamic data (HR, MAP, etc.) were analyzed using repeated measure ANOVA; if statistical significance was reached a Tukey post hoc test was performed to identify level of significance. Age, weight and times recorded were analyzed using independent *t*-test, while gender, type of procedure,

Table 3 The CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) [11].

Item	Behavioral		Definition
Cry	No cry	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalizing silent cry
	Crying	2	Child is crying, but the cry is gentle or whimpering
	Scream	3	Child is in a full-lunged cry; sobbing; may be scored with complaint or without complaint
Facial	Composed	1	Neutral facial expression
	Grimace	2	Score only if definite negative facial expression
	Smiling	0	Score only if definite positive facial expression
Child verbal	None	1	Child not talking
	Other complaints	1	Child complains, but not about pain, e.g., "I want to see mommy" of "I am thirsty"
	Pain complaints	2	Child complains about pain
	Both Complaints	2	Child complains about pain and about other things, e.g., "It hurts; I want my mommy"
	Positive	0	Child makes any positive statement or talks about others things without complaint
Torso	Neutral	1	Body (not limbs) is at rest; torso is inactive
	Shifting	2	Body is in motion in a shifting or serpentine fashion
	Tense	2	Body is arched or rigid
	Shivering	2	Body is shuddering or shaking involuntarily
	Upright	2	Child is in a vertical or upright position
	Restrained	2	Body is restrained
Touch	Not touching	1	Child is not touching or grabbing at wound
	Reach	2	Child is reaching for but not touching wound
	Touch	2	Child is gently touching wound or wound area
	Grab	2	Child is grabbing vigorously at wound
	Restrained	2	Child's arms are restrained
Legs	Neutral	1	Legs may be in any position but are relaxed; includes gentle swimming or separate-like movements
	Squirm/kicking	2	Definitive uneasy or restless movements in the legs and/or striking out with foot or feet
	Drawn up/tensed	2	Legs tensed and/or pulled up tightly to body and kept there
	Standing	2	Standing, crouching or kneeling
	Restrained	2	Child's legs are being held down

incidence of adverse effects and need for analgesia were analyzed using chi-square or Fischer's exact test as appropriate. The software SPSS version 15.0 for windows was used for statistical analysis. A p-value < 0.05 was considered as statistically significant.

5. Results

Sixty ASA physical status I children (4–10 years old) who were referred for conscious sedation because of their anxiety and behavior management problem from outpatient clinic of the pediatric dentistry department, had completed the study protocol and dental procedure. Demographic data were comparable among both groups (Table 4). Heart rate, oxygen saturation and respiratory rates were comparable among both groups and during all recorded times (Figs. 1–3).

Mean arterial blood pressure (MAP) was significantly lower in group II compared to group I at 5, 10 and 15 min ($p < 0.0001$), also MAP in group II was significantly lower during same periods (5, 10 and 15 min) compared to baseline and all other recorded times (Fig. 4).

Onset of sedation to achieve RSS $\geqslant 5$ was extremely significantly longer in group I compared to group II (8.7 ± 1.8 versus 4.4 ± 1.1 min, respectively, $p < 0.0001$). Also recovery time to achieve a RSS of 2 was extremely significantly shorter in group I compared to group II (18.3 ± 5.9 versus 25.2 ± 8.2 min, respectively, $p < 0.0004$). However, the procedure time which ranging from (14.4 ± 5.1) in group I versus (14.2 ± 5.5) in group II and discharge times which ranging from (19.2 ± 4.9) in group I versus (20.1 ± 3.9) in group II were comparable among both groups (Table 5).

None of patients among both groups studied had experienced any form of allergic reaction; none of patients had required mechanical ventilation. In group I 3 (10%) patients had unwanted movements compared to 2 (6.7%) in group II, $p = 1.0$. In group II 2 (6.7%) patients had experienced short periods of apnea (>20 s and responded to bag and mask ventilation) while none (0%) of patients had experienced any period of apnea in group I. Eight (26.7%) patients in group I required supplemental analgesia in the recovery area compared to 20 (66.7%) patients in group II, $p = 0.004$.

Table 4 Demographic data of the groups (mean ± SD).

	Group I (30 children)	Group II (30 children)	p-value
Age (y)	6.7 ± 2.3	7.2 ± 2.2	0.39
Weight (kg)	23.4 ± 3.7	24.6 ± 3.6	0.21
Sex (M/F) (n)	16/14	18/12	0.79
Procedure performed			
Pulpotomy with amalgam filling	8	7	1.0
Cavity preparation with amalgam filling	10	11	1.0
Teeth extraction	12	12	1.0

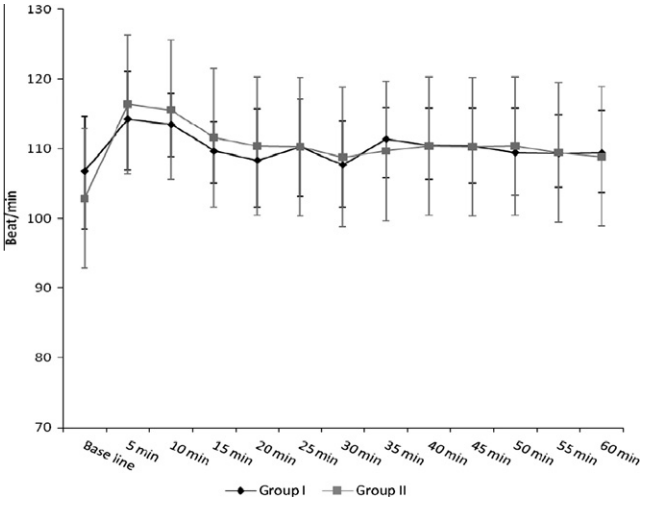

Figure 1 Mean heart rate in both groups. Group I = dexmedetomidine group ($n = 30$) and group II = midazolam–propofol group ($n = 30$).

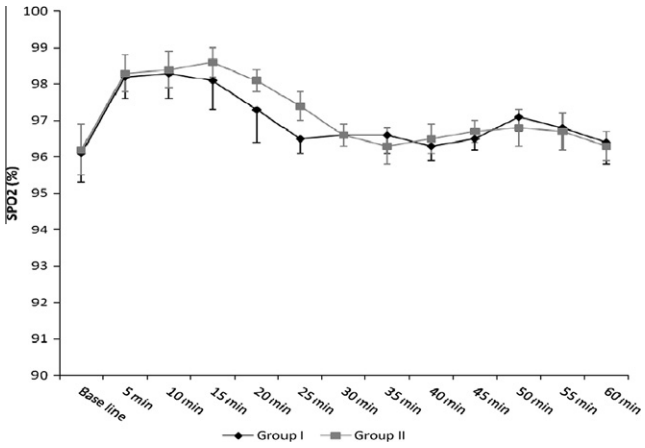

Figure 2 Oxygen saturation (%). Group I = dexmedetomidine group ($n = 30$) and group II = midazolam–propofol group ($n = 30$).

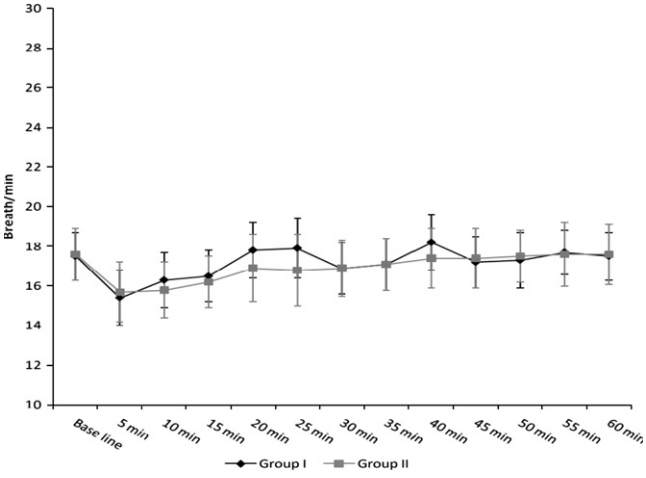

Figure 3 Respiratory rate (breath/min). Group I = dexmedetomidine group ($n = 30$) and group II = midazolam–propofol group ($n = 30$).

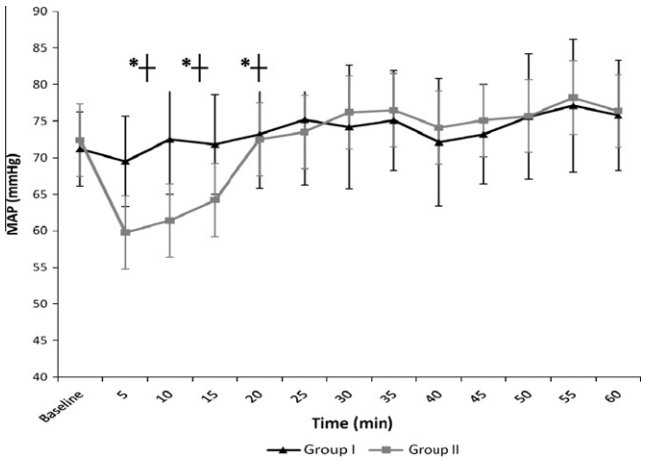

Figure 4 Mean arterial blood pressure (MAP mmHg). Group I = dexmedetomidine group ($n = 30$) and group II = midazolam–propofol group ($n = 30$). * Denotes significantly lower compared to other measurements within the same group ($p < 0.0001$). † Denotes significantly lower compared to group I (dexmedetomidine) ($p < 0.0001$).

Table 5 Onset time of sedation, procedure time, recovery time, and discharge time represented in form of mean ± standard deviation.

Measurement	Group I ($n = 30$)	Group II ($n = 30$)	p-value
Onset time of sedation (min)	8.7 ± 1.8*	4.4 ± 1.1	> 0.0001
Procedure time (min)	14.4 ± 5.1	14.2 ± 5.5	0.88
Recovery time (min)	18.3 ± 5.9*	25.2 ± 8.2	0.0004
Discharge time (min)	19.2 ± 4.9	20.1 ± 3.9	0.43

* Denotes significance.

6. Discussion

The main finding in the current randomized trial involving 60 ASA I physical status children (4–10 years) requiring sedation during dentistry procedure at a dentistry outpatient clinic can be summarized as follows: (A) Both sedative techniques (dexmedetomidine versus propofol–midazolam) can be used safely in outpatient dentistry clinic. (B) Propofol–midazolam combination can achieve rapid induction compared to dexmedetomidine alone, reflected by shorter duration required to achieve RSS $\geqslant 5$. (C) Dexmedetomidine had faster recovery compared to propofol–midazolam combinations reflected by rapid restoration of RSS of 2. (D) Patients receiving dexmedetomidine requires less analgesia supplementation in the early recovery period compared to propofol–midazolam combination.

Adequate anxiety control is a fundamental part of the practice of dentistry, conscious sedation is a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation, it is important that a wide margin of safety for conscious sedation is maintained [12]. Oxygen supplementation is considered to be an important issue in conscious sedation to minimize desaturation even in presence of apnea [12]. In the current study no significant adverse effects had been associated with both sedative techniques, also efficacy of both sedative technique were comparable reflected by comparable number of patients that showed undesired movements during the procedure 3 in group I compared to 2 in group II. The main difference in regard to safety was that patients in group II had demonstrated transient reversible decrease in their mean arterial blood pressure (Fig. 4) and that 2 patients had experienced short period of apnea that responded to bag and mask ventilation in group II while all patients in group I demonstrated intact respiratory drive and comparable hemodynamic parameters throughout the whole procedure. Dexmedetomidine exerts its effects by binding to α_2 receptors presynaptically and postsynaptically in the locus ceruleus and in the spinal cord. It decrease norepinephrine release and inhibits sympathetic activity. The inhibition of sympathetic activity may lower heart rate and blood pressure [13]. In the current trial dexmedetomidine exhibits a very stable hemodynamics and the mainstay is that in both groups atropine sulphate were administered and we believe that such premedication was responsible for abolishing bradycardia associated with dexmedetomidine with subsequent hypotension. Moreover in a comparative study between effects of dexmedetomidine and propofol, in adult population, the dexmedetomidine treated patients showed higher blood pressures compared to propofol group with an average of 11 ± 3 mmHg [14] and that finding is consistent with our finding at times where blood pressure had dropped (5, 10 and 15 min). However, we can tell that in regard to safety and efficacy.

In the current study we demonstrated rapid onset of sedation with midazolam–propofol combinations compared to dexmedetomidine alone (4.4 ± 1.1 min versus 8.7 ± 1.8 min). Arian and Ebert [14] demonstrated rapid onset of targeted sedation level with propofol (10 min) compared to dexmedetomidine (25 min). Although we demonstrated rapid onset of sedation with propofol over dexmedetomidine, however, our onset of targeted sedation in both groups were faster than those reported by Arian. First, in Arian study he used bispectral index (BIS) targeted to 70–80, second he used propofol in doses of 75 μg/kg as loading dose unlike us we used 1 mg/kg as loading dose together with 0.05 mg/kg midazolam, Third, the loading dose for dexmedetomidine in his trial was 1 μg/kg over 10 min while we used 2 μg/kg over 5 min, finally patient population is different in both trials as we were dealing with pediatric population 4–10 years while in his trial average patient population was 62 years.

Reports for recovery times in respect to dexmedetomidine use had been reported with great variability; in the current trial it was significantly shorter in dexmedetomidine group than the combination group. In agreement with our finding Venn and Grounds [15] and Lee et al. [16] had reported faster recovery times when dexmedetomidine was used, however, Koroglu et al. [17] reported that there is no difference regarding the recovery time between the dexmedetomidine and propofol. Moreover Pandharipande et al. [18] demonstrated longer recovery times with dexmedetomidine compared to lorazepam. These conflicting results regarding recovery times can be attributed to one of the most interesting properties of dexmedetomidine, which is the ability to achieve sedation with preserved arousability [6,19], thus rendering judging on recovery time to be more

subjective rather than objective. And in most reports even if recovery time was prolonged such times did not affect discharge criteria [14–18]. In the current trial we experienced better recovery time with dexmedetomidine compared to combination group (18.3 ± 5.9 versus 25.2 ± 8.2 min) while discharge times were comparable among both groups (Table 5). In this respect we can attribute prolonged recovery times in combination group to the use of midazolam with propofol and in this respect we had previous reports regarding that midazolam when used in pediatric dentistry demonstrated longer duration of action compared to propofol and ketamine [8].

Also in the current trial patients receiving dexmedetomidine required less analgesic supplementation compared to the combination group, in fact this finding is consistent with numerous reports due to analgesic effect of the α_2 agonist dexmedetomidine. Arian and Ebert [14] demonstrated that patients who received dexmedetomidine for sedation had reduced pain scores and reduced use of morphine compared to propofol patients, also in a subsequent paper. Arian et al. [20] demonstrated that dexmedetomidine was superior than patients receiving morphine alone for postoperative analgesia. The analgesic effects of dexmedetomidine had also been appreciated in various settings and various patient populations [21–26].

In summary, we can tell that both sedative techniques were safe and effective and can be used to alleviate anxiety, unwanted movements and provide adequate sedation for pediatrics undergoing dental procedures. The fact that dexmedetomidine had possessed relatively more stable hemodynamic and respiratory profiles, together with adequate postoperative analgesia renders such drug to be in a superior position. However, such statement should be thoroughly investigated, since dexmedetomidine was only FDA approved as a sedative for non intubated patients only on late 2008, thus it is difficult to find randomized controlled trials that focuses in such issue.

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