ORIGINAL CLINICAL RESEARCH REPORT

Pharmacokinetics and Pharmacodynamics of 3 Doses of Oral-Mucosal Dexmedetomidine Gel for Sedative Premedication in Women Undergoing Modified Radical Mastectomy for Breast Cancer

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BACKGROUND: Buccal dexmedetomidine (DEX) produces adequate preoperative sedation and anxiolysis when used as a premedication. Formulating the drug as a gel decreases oral losses and improves the absorption of buccal DEX. We compared pharmacokinetic and pharmacodynamic properties of 3 doses of buccal DEX gel formulated in our pharmaceutical laboratory for sedative premedication in women undergoing modified radical mastectomy for breast cancer.

METHODS: Thirty-six patients enrolled in 3 groups (n = 12) to receive buccal DEX gel 30 minutes before surgery at 0.5 μg/kg (DEX 0.5 group), 0.75 μg/kg (DEX 0.75 group), or 1 μg/kg (DEX 1 group). Assessments included plasma concentrations of DEX, and pharmacokinetic variables calculated with noncompartmental methods, sedative, hemodynamic and analgesic effects, and adverse effects.

RESULTS: The median time to reach peak serum concentration of DEX (T_{max}) was significantly shorter in patients who received 1 μg/kg (60 minutes) compared with those who received 0.5 μg/kg (120 minutes; P = .003) and 0.75 μg/kg (120 minutes; P = .004). The median (first quartile–third quartile) peak concentration of DEX (maximum plasma concentration [C_{max}]) in plasma was 0.35 ng/mL (0.31–0.49), 0.37 ng/mL (0.34–0.40), and 0.54 ng/mL (0.45–0.61) in DEX 0.5, DEX 0.75, and DEX 1 groups (P = .082). The 3 doses did not produce preoperative sedation. The 1 μg/kg buccal DEX gel produced early postoperative sedation and lower intraoperative and postoperative heart rate values. Postoperative analgesia was evident in the 3 doses in a dose-dependent manner with no adverse effects.

CONCLUSIONS: Provided that it is administered 60–120 minutes before surgery, sublingual administration of DEX formulated as an oral-mucosal gel may provide a safe and practical means of sedative premedication in adults. (Anesth Analg 2021;132:456–64)

KEY POINTS

- **Question:** Does formulating the drug as a gel decreases oral losses and improves the absorption of buccal dexmedetomidine applied for sedative premedication in 3 dose cohorts (0.5, 0.75, and 1 μg/kg) in women undergoing modified radical mastectomy?
- **Findings:** The median time to reach peak serum concentration of dexmedetomidine (T_{max}) was significantly shorter in patients who received 1 μg/kg (60 minutes) compared with those who received 0.5 μg/kg (120 minutes; P = .003) and 0.75 μg/kg (120 minutes; P = .004).
- **Meaning:** Provided that it is administered 60–120 minutes before surgery, sublingual administration of dexmedetomidine formulated as an oral-mucosal gel may provide a safe and practical means of sedative premedication in adults.

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GLOSSARY

ASA = American Society of Anesthesiologists; **AUCall** = area under the concentration–time curve from time 0 to the last measurable sampling time point; **AUCinf** = area under dexmedetomidine plasma concentration–time curve extrapolated to infinity; **AUCINF (observed)/D** = dose normalized AUCINF (observed); **BMI** = body mass index; **CL/F** = apparent clearance; C_{max} = maximum plasma concentration; **DEX** = dexmedetomidine; **ESI** = electrospray ionization; **HR** = heart rate; **IQR** = interquartile range; **IV-PCA** = intravenous patient-controlled analgesia; **m/z** = mass-to-charge ratio; **MRM** = multiple reactions monitoring; **SICU** = surgical intensive care units; **SPSS** = Statistical Package for the Social Sciences; **t1/2** = elimination half-life; T_{max} = time to peak plasma concentration; **V/F** = apparent volume of distribution; **VAS** = visual analog scale; **w/v** = weight/volume

Dexmedetomidine (DEX) is a highly selective α-2 adrenergic agonist with potent anxiolytic, sedative, and analgesic actions that are devoid of respiratory depression even at higher doses.[1] DEX use as a sedative premedicant before general anesthesia has been shown to relieve preoperative anxiety, reduce intraoperative anesthetic and analgesic requirements, and augment postoperative analgesia.[2–4] Such benefits would be desirable for some selected surgical patients such as women with breast cancer undergoing modified radical mastectomy.[5] In those patients, high levels of preoperative anxiety negatively impact postoperative recovery and tumor recurrence as well.[6]

Rapid intravenous administration of DEX has been associated with hemodynamic derangement including bradycardia and hypotension.[7] Alternative routes of administration with slower absorption of DEX seem to have the advantage of fewer and less pronounced adverse effects. Sublingual or buccal administration for sedative premedication is a route that is not widely utilized especially in adults.[8] It is an easy, safe, and simple technique for drug administration with direct systemic drug absorption bypassing the hepatic first-pass metabolism.[8–10]

Pharmacokinetic studies on healthy adults showed that DEX is well absorbed systemically through oral mucosa with buccal bioavailability as high as 82%.[11] However, patients received 2 μg/kg buccal DEX had actual buccal doses from 0.49 to 1.75 μg/kg due to oral losses.[11] Formulating the drug as a gel decreases the oral loss and improves the absorption of buccal DEX so that lower dose ranges can be used. A commercially available oral-mucosal formulation of detomidine hydrochloride gel that is Food and Drug Administration approved has been used in animal settings.[12,13] Pharmacokinetic-pharmacodynamic studies demonstrated its safety and efficacy for sedation in animals during routine procedures.[14,15]

To minimize adverse effects and instruct clinical dosing, it is imperative to gather pharmacokinetic information on oral-mucosal DEX gel for sedative premedication in adults. We hypothesized that oral-mucosal DEX gel would be well tolerated by our patients and can provide adequate preoperative anxiolysis at doses lower than those used for the plain drug. We compared the pharmacokinetic and pharmacodynamic properties of 3 doses of buccal DEX gel formulated in our pharmaceutical laboratory (0.5, 0.75, and 1 μg/kg) for sedative premedication in women undergoing modified radical mastectomy for breast cancer. The primary outcome parameter was the plasma concentrations of DEX and its calculated pharmacokinetic variables. Secondary outcomes were pharmacodynamic assessments that included perioperative hemodynamics, DEX's sedative and analgesic effects, and perioperative adverse effects.

METHODS

Patients and Ethical Considerations

This study protocol was approved by the Research Ethics Committee, South Egypt Cancer Institute, Assiut University, Egypt (ID: IORG0006563/no. 377, February 25, 2017, Head of the Committee: Professor Ashraf Zydan). Written informed consent was obtained from all study participants. The trial was registered before patient enrollment at Clinical Trial. gov. (Identifier: NCT03120247, principal investigator: Professor Hala Saad Abdel-Ghaffar, date of registration: April 5, 2017). The study adheres to the declarations of Helsinki. Enrolled to this prospective randomized double-blind comparative study, women aged 30–60 years, American Society of Anesthesiologists (ASA) physical status I–II, scheduled for unilateral modified radical mastectomy with axillary dissection for breast cancer. Exclusion criteria included significant cardiac, respiratory, renal, central nervous system or hepatic disease; pregnancy; body mass index (BMI) ≥30 kg/m^2; allergy to study drugs; and history of drug addiction.

Randomization and Blindness

Randomization was done using a computer-generated randomization table, with group allocation concealed in closed opaque covers. Thirty-six patients were enrolled in 3 groups of 12 patients' each to receive preoperative sedative premedication with buccal transmucosal DEX gel preparation containing 0.5 μg/kg (DEX 0.5 group), 0.75 μg/kg (DEX 0.75 group), or 1 μg/kg (DEX 1 group). Furtherly, 8 patients were

randomly selected inside each group for pharmacokinetic sampling. The study drug concentrations were administered as oral-mucosal gel administered under the tongue. Study medications were prepared in a 1.5 mL volume in sterilized prefilled syringes and coded by a blinded pharmacist. The attending surgeons, anesthesiologists, data collecting researchers, and the patient were blinded to the group assignment.

Study Protocol

Thirty minutes before anesthesia induction, the fasted unpremedicated patients received the prepared DEX formula according to group assignment. The gel formulation was installed buccally to patients in the sitting position and they were instructed not to swallow for 5 minutes. Monitoring included electrocardiogram, noninvasive arterial blood pressure, pulse oximetry, and end-tidal carbon dioxide capnography. Anesthesia was induced with fentanyl 1 µg/kg, propofol 2–3 mg/kg, and lidocaine 1.5 mg/kg. Cisatracurium 0.15 mg/kg was administered to facilitate endotracheal intubation. Isoflurane in a 50% oxygen/air mixture was used for maintenance of anesthesia and the concentration delivered was carefully titrated in anticipation of the adjuvant effects of the administered DEX. Cisatracurium 0.03 mg/kg was used for maintenance of muscle relaxation. Patients were mechanically ventilated in volume cycled mode with ventilation parameters that achieved normocapnia. At the end of surgery, muscle paralysis was reversed with standard doses of intravenous neostigmine and atropine. Patients were extubated awake and transferred to the surgical intensive care unit (SICU). Postoperatively, all patients received intravenous patient-controlled morphine analgesia (B. Braun Melsungen, Melsungen, Germany). The intravenous patient-controlled analgesia (IV-PCA) solution contained 100-mg morphine in 100 mL 0.9% normal saline (1 mg/mL) and the pump was programmed to provide a 1-mg bolus with a 5-minute lockout time and without continuous background infusion.

Preparation of In Situ Gelling Systems

The pH-triggered in situ gel-forming system of DEX was prepared using Carbopol 934P (bioadhesive polymer, 0.3% weight/volume [w/v]), hydroxyl ethyl cellulose (viscosity-enhancing polymer, 0.2% w/v), boric acid (isotonic modifier, 0.5 w% w/v), and benzalkonium chloride (preservative, 0.01% w/v).[16] The formulations, in their final pack, were subjected to terminal sterilization by autoclaving at 121°C and 15 psi for 20 minutes. This formulation was found to have free-flowing properties at nonphysiological condition that will allow easy instillation sublingually as a liquid (drops) which would undergo a rapid sol-to-gel transition at physiological condition.[17]

Blood Sampling

Seven whole venous blood samples (3 mL for each) were collected into EDTA tubes. Samples were obtained from patients at 15, 30, 45 minutes and 1, 2, 4, and 6 hours after drug administration. The plasma was separated by centrifugation at 2500×*g* for 10 minutes within 2 hours after collection. Resultant plasma was stored at −80°C until assayed.

Sample Extraction and Preparation for Liquid Chromatography-Tandem Mass Spectrometry

Five hundred microliters of plasma were mixed thoroughly with 1 mL of mixture of methanol and acetonitrile (1:1, volume/volume; Sigma-Aldrich, Steinheim, Germany), vortexes 60 seconds and centrifuged at 10,000×*g* for 15 minutes at 4°C. Ten microliters of the resultant clear supernatant was then injected into AB SCIEX LC/MS/MS system (AB SCIEX 3200 Q TRAP, Steinheim, Germany) equipped with electrospray ionization (ESI) source and an Agilent 1260 affinity HPLC system, consisting of a vacuum degasser, a binary pump, and an autosampler. Analyst 1.6 software (AB SCIEX) was used for data acquisition and processing. The analytical column used was XBridge-C18 (150 mm × 2.1 mm × 5 µm, Waters, Ireland) at 25°C. The mobile phase consisting of 2 parts of 0.1% formic acid in water (solvent A) and 1 part of mixture of methanol and acetonitrile (1:1, volume/volume) (solvent B) was delivered at a flow rate of 0.3 mL/min. The mass spectrometer was operated in the positive ESI mode with the spray voltage set at 4.5 kV, at a temperature of 350°C, and a curtain gas flow of 22 L/h. Calculation was done by Multiquant software program (AB SCIEX). Serial dilutions of standards were prepared at concentrations that ranged from 0.05 to 12.5 ng/mL for DEX in drug-free plasma and extracted as mentioned in sample preparation to make calibration curve. The calibration curve showed a linear relationship ($r^2 \geq 0.99$; Supplemental Digital Content, Figure 1, http://links.lww.com/AA/D165).

Typical chromatograms for detection of DEX are displayed in Supplemental Digital Content, Figure 2, http://links.lww.com/AA/D165. They were detected at retention time 4.4 minutes. Quantification was performed with multiple reactions monitoring (MRM) by using curtain gas collision–induced dissociation and the following ion transitions: mass-to-charge ratio (m/z) 201.2:95.1, for DEX, with the declustering potential set at 46 V and the collision energy at 25 eV.

Pharmacokinetic Analysis

Pharmacokinetic parameters were determined using noncompartmental method with WinNonlin professional Version 2.1 software (Pharsight Corporation, Mountain View, CA). The following parameters were determined for plasma concentrations of DEX; area

under the concentration–time curve from time 0 to the last measurable sampling time point (AUCall), area under dexmedetomidine plasma concentration–time curve extrapolated to infinity (AUCinf), maximum plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), apparent volume of distribution (V/F), apparent clearance (CL/F), and elimination half-life ($t1/2$). Pharmacokinetic parameters were obtained for each of the 3 patients' groups.

Pharmacodynamic Assessments

Pharmacodynamic variables were assessed at 3 time-stations (before, during, and after surgery). Preoperatively, the heart rate, noninvasive blood pressure, and the sedation score were recorded baseline and at 5, 10, 20, and 30 minutes after DEX administration. The sedation score was interpreted as 0 = awake, 1 = easily aroused, 2 = awakens after verbal stimulation, 3 = awakens after tactile stimulation, and 4 = not arousable. Intraoperatively, the heart rate and noninvasive blood pressure were recorded at 0, 5, 10, 30, 60, 90, and 120 minutes after intubation. Postoperatively, the heart rate, noninvasive blood pressure, sedation score, and the visual analog pain score were recorded at the admission to the SICU (baseline) and 2, 4, 6, 8, 12, and 24 hours afterward. Any adverse events in the perioperative period were treated and recorded, such as hypertension, hypotension, tachycardia, bradycardia, respiratory depression, shivering, nausea, or vomiting.

Statistics

Power of the Study. The primary outcome parameter was the plasma concentrations of DEX in plasma and its calculated pharmacokinetic variables. Secondary outcomes were pharmacodynamic assessments that included perioperative hemodynamics, DEX's sedative and analgesic effects, and perioperative adverse effects. The sample size selected was in convenience with a previous study that investigated the pharmacokinetics of extravascular DEX using noncompartmental model.[18] Using the G-Power calculator 3.1.9.7 for sample size determination, a total sample size of 21 patients for this study would be sufficient for statistical testing based on a priori analysis with F tests—ANOVA: repeated measures, between factors at a 2-tailed type I error of 0.05, a power of 0.8, effect size of 0.6, and correlation among repeated measures of 0.6. Twenty-four patients were enrolled for pharmacokinetic study (8 patients in each group) that was increased to 12 patients in each group to furtherly investigate the pharmacodynamic effects of the gel formulation and to overcome for the patient dropout.

Statistical Tests. Data were checked for normality by visual inspection of histograms and by the Shapiro–Wilk test. In this study, continuous data were not normally distributed and were presented as median (first quartile–third quartile), interquartile range, and range. We compared the 3 DEX exposure groups on pharmacodynamic and pharmacokinetic parameters overall with the nonparametric Kruskal-Wallis test, between each pair of DEX groups with the Mann-Whitney U test and between each paired comparison inside the same group by Wilcoxon signed-rank test. Categorical data were expressed as number and analyzed with χ^2 test. A P value of <.05 was the cutoff value for statistical significance. Bonferroni correction method was used to control the type I error

Table 1. Personal and Clinical Data

	DEX 0.5 (n = 12)	DEX 0.75 (n = 12)	DEX 1 (n = 12)
Age (y)			
Median (range)	44 (30–60)	43.5 (33–60)	44.5 (33–60)
ASA physical status			
I/II	10/2	9/3	10/2
Weight (kg)			
Median (range)	72.5 (60–85)	73 (60–83)	73 (60–85)
Height (cm)			
Median (range)	160 (155–172)	160 (150–177)	162 (153–170)
BMI (kg/m^2)	27.2	26.4	28.0
Median (range)	(22.6–34.9)	(22.9–36.9)	(21.8–36.3)
Serum albumin (g/L)			
Median (range)	42 (35–47)	42 (35–46)	43 (35–46)
Site: right/left	7/5	6/6	5/7
Extubation time (min)	4.5 (3–5)	5 (3–7)	5 (3–8)
Recovery time (min)	4.5 (3–7)	5 (2–7)	4.5 (3–8)
Adverse effects			
Hypotension (intraoperative)	1	2	4
Need for ephedrine (intraoperative)	1	2	4
Nausea (postoperative)	1	0	0
Vomiting (postoperative)	0	0	1

Data are presented as median (range) and number. No significant differences were recorded between groups.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DEX, dexmedetomidine.

at 5% within each hypothesis. The overall significance level of 0.05 was divided by the number of pairwise comparisons that were performed (3) to obtain the significance criterion of 0.05/3 = 0.0167 for each test within an outcome variable.

Statistical analysis was conducted by the Statistical Package for the Social Sciences (SPSS) software version 19 for Microsoft Windows for the pharmacodynamic and baseline data (SPSS Inc, Chicago, IL) and by Stata version 11.0 for pharmacokinetic data (Stata Corp LP, College Station, TX).

RESULTS

Thirty-six female patients were recruited in this study (12 patients in each group) of whom 24 patients completed the blood sampling and pharmacokinetic analysis (8 patients in each group). Descriptive analysis and pharmacodynamic statistical testing were done for 12 patients in each group, then pharmacokinetic analysis and calculations were done for 8 patients in each group. The baseline and clinical characteristics of the patients were matched in the 3 studied groups (Table 1).

Pharmacokinetic Results

The plasma concentrations of DEX in the 3 studied groups are shown on a logarithmic scale versus time (minutes) in the Figure. The median (Q1–Q3) peak concentration of DEX (C_{max}) in plasma was 0.35 ng/mL (0.31–0.49), 0.37 ng/mL (0.34–0.40), and 0.54 ng/mL (0.45–0.61) in DEX 0.5, DEX 0.75, and DEX 1 groups (P = .082). The median time to reach peak serum concentration of DEX (T_{max}) was significantly shorter in patients who received 1 µg/kg (60 minutes) compared with those who received 0.5 µg/kg (120 minute; P = .003) and 0.75 µg/kg (120 minutes; P = .004). No significant differences between groups were recorded in other pharmacokinetic parameters (Table 2).

Pharmacodynamic Results

Compared to baseline values in each group, the noninvasive systolic and diastolic blood pressure significantly decreased at 20 and 30 minutes after the administration of the DEX gel and at 5 minutes after induction of anesthesia in the 3 studied groups with no significant differences in other studied timepoints. Intergroup comparisons showed no significant differences in the blood pressure at any studied timepoint (data not represented). Intragroup and intergroup comparisons revealed significant decreases in the median heart rate preoperatively at 20 and 30 minutes after administration of the DEX gel (data not represented) and throughout the intraoperative and postoperative periods, with the lowest values recorded in DEX 1 group (Tables 3–4).

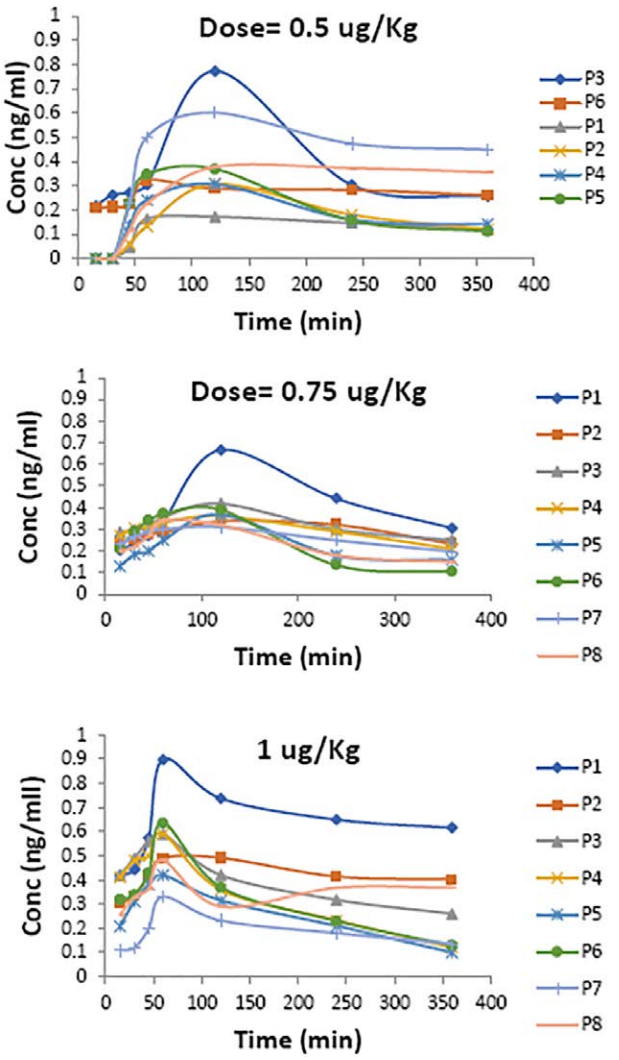

Figure. Dexmedetomidine concentration versus time following the administration of buccal dexmedetomidine gel at 0.5 µg/kg (A), 0.75 µg/kg (B), and 1 µg/kg (C). P indicates patient number.

On admission to the SICU, patients in DEX 1 group showed higher sedation score compared with DEX 0.5 (P = .022) and DEX 0.75 (P = .032) groups (Table 4). Otherwise, the sedation score was 0 (fully conscious) in all patients in this study at all recorded preoperative and postoperative timepoints. Visual analog scale (VAS) pain scores were lower in DEX 1 group compared with DEX 0.5 and DEX 0.75 groups that reached statistical significance at admission to the SICU (Table 4). No patient in DEX 1 group requested for IV morphine-PCA during the study period versus 2 patients in DEX 0.5 and 2 patients in DEX 0.75 groups, respectively.

No significant differences were recorded between groups in the perioperative adverse effects (Table 1). No local irritation adverse events were seen with the oral-mucosal gel preparation and it was well tolerated in all patients in this study.

Table 2. Calculated Pharmacokinetic Parameters for the 3 Studied Concentrations of Dexmedetomidine

	DEX 0.5 (n = 8)		DEX 0.75 (n = 8)		DEX 1 (n = 8)					
	Median (First Quartile–Third Quartile)	IQR	Median (First Quartile–Third Quartile)	IQR	Median (First Quartile–Third Quartile)	IQR	P^a	$P^{b,c}$	$P^{b,d}$	$P^{b,e}$
T_{max} (min)	120 (120–120)	0	120 (120–120)	0	60 (60–60)	0	.013[a]	1.00	.003[a]	.004[a]
C_{max} (ng/mL)	0.35 (0.31–0.49)	0.183	0.37 (0.34–0.40)	0.065	0.54 (0.45–0.61)	0.163	.082	.528	.074	.045
*t*1/2	308.65 (163.27–516.15)	352.9	269.44 (206.04–344.59)	138.55	329.34 (154.19–624.51)	470.32	.854	.674	.833	.590
AUCall	86.13 (64.25–127.12)	62.86	98.92315 (83.23–110.50)	27.26	117.567 (98.86–144.09)	45.23	.269	.462	.172	.207
AUCINF (observed)	163.1 (103.22–523.87)	420.65	197.79 (129.69–240.17)	110.47	202.73 (132.38–497.43)	365.05	.617	1.00	.462	.344
AUCINF (observed)/D	0.33 (0.21–1.05)	0.841	0.264 (0.173–0.320)	0.147	0.203 (0.132–0.497)	0.365	.336	.207	.208	.833
V/F	1340.12 (901.25–1481.73)	580.84	1685.08 (1418.27–1891.54)	473.27	1893.32 (1566.26–1944.83)	378.57	.072	.115	.035	.344
CL/F	3.22 (0.95–4.86)	3.91	3.79 (3.13–5.79)	2.65	6.29 (2.67–7.56)	4.88	.187	.208	.092	.462

Data are presented as median (first quartile–third quartile) and IQR. Significant difference after Bonferroni correction for multiple comparisons. *P* value: overall test between the 3 studied groups.

Abbreviations: AUCall, area under the concentration–time curve from time 0 to the last measurable sampling time point; AUCINF (observed), AUC from time 0 to time infinity; AUCINF (observed)/D, dose normalized AUCINF (observed); C_{max}, maximum plasma concentration; CL/F, apparent clearance; DEX, dexmedetomidine; IQR, interquartile range; *t*1/2, elimination half-life; T_{max}, time to peak plasma concentration; V/F, apparent volume of distribution.

[a]Kruskal-Wallis test.

[b]Mann-Whitney *U* test.

[c]*P* value comparing DEX 0.5 and DEX 0.75.

[d]*P* value comparing DEX 0.5 and DEX 1.

[e]*P* value comparing DEX 0.75 and DEX 1. The significance criterion for pairwise tests is $P < .0167$ after Bonferroni correction.

Table 3. Intraoperative HR

	DEX 0.5 (n = 12)		DEX 0.75 (n = 12)		DEX 1 (n = 12)					
	Median (First Quartile–Third Quartile)	IQR	Median (First Quartile–Third Quartile)	IQR	Median (First Quartile–Third Quartile)	IQR	P^a	$P^{b,c}$	$P^{b,d}$	$P^{b,e}$
At intubation	94.5 (82.0–99.5)	17.5	90.5 (82.5–95.0)	12.5	72.5 (66.0–81.0)	15.0	.009	.469	.008	.012
HR 5 min	79.5 (73.5–87.5) $P^f = .002$	14.0	84.0 (74.0–88.0) $P^f = .003$	14.0	69.5 (61.5–72.0) $P^f = .016$	10.5	.002	.583	.004	.003
HR 10 min	83.5 (76.0–97.5) $P^f = .075$	21.5	79.5 (74.5–85.5) $P^f = .003$	11.0	63.0 (55.0–69.5) $P^f = .003$	14.5	.000	.285	.001	.000
HR 30 min	89.5 (85.0–100.0) $P^f = .754$	15.0	80.5 (73.5–90.0) $P^f = .061$	16.5	66.0 (61.0–76.5) $P^f = .126$	15.5	.002	.093	.002	.008
HR 60 min	93.0 (75.5–100.0) $P^f = .504$	24.5	74.0 (66.5–87.5) $P^f = .010$	21.0	65.0 (56.0–70.0) $P^f = .012$	14.0	.001	.043	.002	.046
HR 90 min	88.0 (79.0–100.0) $P^f = .665$	21.0	77.5 (65.0–88.5) $P^f = .011$	23.5	63.5 (56.5–70.0) $P^f = .006$	13.5	.002	.056	.000	.046
HR 120 min	86.5 (79.5–100.0) $P^f = .239$	20.5	81.5 (75.5–88.5) $P^f = .050$	13.0	65.0 (58.5–71.0) $P^f = .012$	12.5	.003	.236	.002	.010

Data are presented as median (first quartile–third quartile) and IQR. Significant difference after Bonferroni correction for multiple comparisons.

Abbreviations: DEX, dexmedetomidine; HR, heart rate; IQR, interquartile range.

[a]Kruskal-Wallis test. Overall test between the 3 studied groups.

[b]Mann-Whitney *U* test.

[c]*P* value comparing DEX 0.5 and DEX 0.75.

[d]*P* value comparing DEX 0.5 and DEX 1.

[e]*P* value comparing DEX 0.75 and DEX 1.

[f]Wilcoxon signed-rank test. Within-group *P* value compared with the baseline. The significance criterion for pairwise tests is $P < .0167$ after Bonferroni correction.

DISCUSSION

In this pharmacokinetic-pharmacodynamic dose-finding study, we administered DEX sublingually as an oral-mucosal gel at doses of 0.5, 0.75, and 1 µg/kg, 30 minutes before surgery. The median time to reach maximal concentration was significantly shorter in the 1 µg/kg group with no significant differences between groups in other pharmacokinetic parameters. The 3 doses investigated did not produce preoperative sedation. The onset of sedation and maximum sedation

Table 4. Postoperative Sedation Score, HR, and VAS

	DEX 0.5 (n = 12)		DEX 0.75 (n = 12)		DEX 1 (n = 12)					
	Median (First Quartile–Third Quartile)	IQR	Median (First Quartile–Third Quartile)	IQR	Median (First Quartile–Third Quartile)	IQR	P^a	$P^{b,c}$	$P^{b,d}$	$P^{b,e}$
Sedation score on admission to SICU										
Sedation 0	1.0 (1.0–1.0)	0.0	1.0 (1.0–1.0)	0.0	1.0 (1.0–2.0)	1.0	.013[a]	.317	.022	.032
Postoperative HR										
Baseline	84.0 (76.5–91.5)	15.0	80.0 (75.0–86.5)	11.5	71.5 (69.5–80.5)	11.0	.017	.325	.009	.037
2 h	84.0 (77.5–92.5) P^f = .937	15.0	84.0 (80.5–88.5) P^f = .028	8.0	75.0 (71.0–79.5) P^f = .474	8.5	.011	.954	.037	.002
4 h	84.0 (82.5–89.5) P^f = .533	7.0	85.0 (81.0–87.0) P^f = .154	6.0	78.5 (74.0–81.5) P^f = .181	7.5	.072	.954	.034	.068
6 h	85.0 (82.5–94.5) P^f = .207	12.0	88.5 (82.5–91.0) P^f = .005	8.5	80.0 (74.5–84.0) P^f = .091	9.5	.034	.908	.030	.022
8 h	88.5 (83.0–94.0) P^f = .059	11.0	88.5 (82.0–92.0) P^f = .005	10.0	84.5 (76.5–86.0) P^f = .033	9.5	.105	.884	.068	.068
12 h	85.5 (83.5–91.0) P^f = .288	7.5	92.5 (84.5–99.5) P^f = .006	15.0	82.0 (78.5–87.0) P^f = .041	8.5	.019	.111	.093	.011
24 h	86.5 (81.5–90.0) P^f = .624	8.5	86.0 (80.0–96.0) P^f = .004	16.0	80.5 (75.0–88.0) P^f = .012	13.0	.291	.748	.244	.137
VAS										
Baseline	2.0 (2.0–2.0)	0.0	2.0 (1.5–2.0)	0.5	1.0 (1.0–2.0)	1.0	.001[a]	.028	.001[a]	.045
2 h	2.0 (1.5–2.0) P^f= .059	0.5	2.0 (1.5–2.0) P^f = .059	0.5	1.0 (1.0–2.0) P^f = .480	1.0	.106	.814	.081	.062
4 h	2.0 (1.0–2.0) P^f = .014	1.0	2.0 (1.5–2.0) P^f = .014	0.5	1.0 (1.0–2.0) P^f = 1.00	1.0	.221	.916	.180	.105
6 h	2.0 (1.5–2.0) P^f = .063	0.5	2.0 (1.0–2.0) P^f = .063	1.0	1.0 (1.0–2.0) P^f = .655	1.0	.182	.484	.081	.229
8 h	2.0 (1.0–2.0) P^f = .034	1.0	2.0 (1.0–2.0) P^f = .034	1.0	1.0 (1.0–1.5) P^f = .655	0.5	.062	.785	.038	.045
12 h	2.0 (1.5–2.0) P^f = .059	0.5	2.0 (1.0–2.0) P^f = .059	1.0	1.0 (1.0–2.0) P^f = .414	1.0	.072	.210	.029	.229
24 h	2.0 (1.5–2.0) P^f = .034	0.5	1.0 (1.0–2.0) P^f = .034	1.0	1.0 (1.0–2.0) P^f = .102	1.0	.049	.081	.036	.680

Data are presented as median (first quartile–third quartile) and IQR. Significant difference after Bonferroni correction for multiple comparisons.
Abbreviations: DEX, dexmedetomidine; HR, heart rate; IQR, interquartile range; SICU, surgical intensive care units; VAS, visual analog scale.
[a]Kruskal-Wallis test. Overall test between the 3 studied groups.
[b]Mann-Whitney *U* test.
[c]*P* value comparing DEX 0.5 and DEX 0.75.
[d]*P* value comparing DEX 0.5 and DEX 1.
[e]*P* value comparing DEX 0.75 and DEX 1.
[f]Wilcoxon signed-rank test. Within-group *P* value compared with the baseline. The significance criterion for pairwise tests is $P < .0167$ after Bonferroni correction.

level attained were obscured by the operative procedure. The 1 µg/kg oral-mucosal DEX gel produced early postoperative sedation and lower intraoperative and postoperative median heart rate values. The analgesic effect was evident in the 3 doses with the lowest pain scores achieved with the 1 µg/kg.

In this study, the median time to reach peak serum concentration of oral-mucosal DEX gel (T_{max}) was significantly shorter in patients who received 1 µg/kg (60 minutes) compared with those who received 0.5 µg/kg (120 minutes; $P = .003$) and 0.75 µg/kg (120 minutes; $P = .004$). Anttila et al[11] recorded that for 2 µg/kg buccal DEX premedication in healthy volunteers, the mean peak concentration (0.29 ± 0.09 µg/kg) was attained at 1.5 ± 0.2 hours after a short lag-time of 0.13 ± 0.04 hours. Kaukinen et al[14] reported a T_{max} of 110 minutes after buccal detomidine gel preparation of 40 µg/kg in horses, and Messenger et al[15] reported T_{max} for the gel formulation after 1 hour in dogs. However, these studies investigated doses different from the doses we investigated.

The onset time of sedation after buccal DEX is not yet established. Hence, studies differed in the timing of its administration for premedication. Karaaslan et al[19] in their study administered 2.5 µg/kg buccal DEX as a sedative premedication 45 minutes before arthroscopic knee surgery under spinal anesthesia. They reported that the maximum degree of sedation was attained just before spinal block. For the gel formulation, animal studies showed that the time to the onset of sedation was 30 (29–58) minutes in horses[14] and 44 minutes in rabbits,[13] while maximum sedation was detected at 75 minutes in dogs.[12] In this study, we administered DEX oral-mucosal gel 30 minutes before operation. No significant sedation was recorded preoperatively. Patients received 1 µg/kg showed higher early postoperative sedation score compared with those who received 0.5 µg/kg ($P = .022$) and 0.75 µg/kg

($P = .032$), with no significant sedation recorded in any patient afterward. In this study, we could not record the onset of sedation and maximum sedation level attained. We think that both variables were obscured by the operative interference. So, we recommend a longer time interval for oral-mucosal DEX gel administration before surgery to reach its maximum sedative and anxiolytic effects, preoperatively.

Studies reported that bradycardia, hypotension, and significant hemodynamic derangement have been associated with DEX premedication[7,20,21] and that the hypotensive effect of DEX persists in the postoperative period.[19] In accordance, in this study, we recorded a dose-dependent decrease in the intraoperative and postoperative median heart rate values compared to their respective baseline values. This also supports our conclusion that the maximum effect of buccal DEX gel occurred intraoperatively. In agreement with previous studies, these hemodynamic derangements were not clinically significant and the number of patients who required intervention was small and did not differ between groups. However, we recommend careful titration of anesthetic drugs in case of DEX sedative premedication.

Karaaslan et al[19] reported that 2.5 µg/kg buccal DEX premedication offered analgesia until 8 hours after arthroscopic knee surgery. In this study, patients who received 1 µg/kg buccal DEX in the gel formulation did not request for PCA-morphine during the first 24 hours postoperatively. This long-lasting analgesic effect we recorded may be attributed to the slow absorption and reduced oral losses of the gel formulation we used. Further studies of larger sample size are needed.

This study has some limitations. First, we did not include a group of intravenous DEX to calculate the bioavailability of the 3 selected doses of oral-mucosal DEX gel formulation. Second, anesthesia was commenced 30 minutes after DEX administration; therefore, it was difficult to exclude the effect of anesthetic interactions when investigating the sedation depth, hemodynamic and analgesic effects of the 3 doses investigated. Third, although the data for 12 patients were collected, only 8 were included in the analysis for the primary outcome in each group. Indeed, all the 12 enrolled patients should have undergone complete collection and analysis.

In conclusion, as the maximum serum levels of buccal DEX gel were obtained at 60–120 minutes, it is advisable to administer the gel 60–120 minutes, preoperatively to obtain evident preoperative sedation and anxiolysis. The slower absorption of DEX following sublingual administration of the oral-mucosal gel seems to have the advantage of less pronounced adverse effects with an extended postoperative analgesic effect. Thus, sublingual administration of DEX formulated as an oral-mucosal gel may provide a safe and practical means of sedative premedication in adults. Further studies of larger sample size are needed to prove these results.

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DISCLOSURES

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