

The Efficacy and Safety of Dexmedetomidine for Procedural Sedation in Patients Receiving Local Anesthesia Outside the Intensive Care Unit: A Prospective, Double-Blind, Randomized Clinical Phase III Trial in Japan

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ABSTRACT

Background Few studies (in other countries than the US) have reported on the efficacy and safety of dexmedetomidine for sedation of patients undergoing surgical or medical procedures under local anesthesia without intubation outside the intensive care unit. We performed a randomized, double-blind study in Japan.

Methods Adult patients were randomly allocated to receive placebo, dexmedetomidine 0.5 µg/kg (DEX 0.5 group), or dexmedetomidine 1.0 µg/kg (DEX 1.0 group) over 10 min. Then, both dexmedetomidine groups received dexmedetomidine 0.2–0.7 µg/kg/h for maintaining an Observer's Assessment of Alertness/Sedation Scale (OAA/S) score of ≤ 4; however, propofol was administered to rescue patients whose score exceeded this value. The primary endpoint was the percentage of patients who did not require rescue propofol to achieve and maintain an OAA/S score of ≤ 4.

Results In total, 162 patients were included in the placebo ($n = 53$), DEX 0.5 ($n = 53$), and DEX 1.0 ($n = 56$) groups. Propofol was not required in significantly more patients in the dexmedetomidine 0.5 and 1.0 µg/kg groups (52.8% and 57.1%, respectively) compared with the placebo group (1.9%) ($P < 0.001$ for both). Common adverse events were protocol-defined hypotension, respiratory depression and bradycardia. The incidence of bradycardia was significantly higher in the DEX 0.5 (26.4%) and DEX 1.0 (30.4%) groups than in the placebo group (9.4%) ($P = 0.041$ and $P = 0.008$, respectively).

Conclusion We concluded that a loading dose of 0.5 or 1.0 µg/kg dexmedetomidine followed by infusion at a rate of 0.2–0.7 µg/kg/h provided effective and well-tolerated sedation in patients undergoing surgical or medical procedures under local anesthesia without intubation.

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Key words anesthesia; dexmedetomidine; local; propofol

Dexmedetomidine, a centrally acting α_2 adrenergic receptor agonist, has properties that make it attractive to use for monitored sedation during a variety of surgical and diagnostic procedures.¹ Chief among these is that dexmedetomidine lacks a significant respiratory depressant effect,² distinguishing it from the other two sedatives commonly used for monitored sedation, midazolam³ and propofol.⁴ In addition, dexmedetomidine can easily be titrated to achieve the desired level of sedation, it has analgesic-sparing effects that reduce intra- and post-operative opioid requirements, it has a sympatholytic effect that attenuates tachycardia and hypertension, patients are easily roused after therapy with it, and patients tend to remain awake and cooperative during dexmedetomidine infusion.^{2, 5–10}

At present, dexmedetomidine is used to sedate patients during artificial respiratory management and after tracheal extubation in the intensive care unit. Its unique properties may also provide the same clinical benefits to patients undergoing surgical or medical procedures under local or regional anesthesia outside the intensive care unit. The efficacy and safety of dexmedetomidine as a sedative for monitored sedation in these settings

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Abbreviations: ASA, American Society of Anesthesiologists; bpm, beats per minute; DBP, diastolic blood pressure; DEX, dexmedetomidine; FAS, full analysis set; NYHA, New York Heart Association; N.A., not applicable; N, number; OAA/S, Observer's Assessment of Alertness/Sedation Scale; SBP, systolic blood pressure; SD, standard deviation; SpO₂, oxygen saturation; TEAE, treatment-emergent adverse event; VAS, visual analogue scale

have previously been demonstrated in the United States.⁹ While its use has become routine in Japan, racial and genetic differences should be clarified.^{11–13} Indeed, it is unknown whether dexmedetomidine has comparable efficacy and safety for monitored sedation in Japanese patients.

We conducted this study to evaluate the efficacy and safety of dexmedetomidine for monitored sedation in Japanese patients undergoing surgical or medical procedures, seeking to expand the availability of dexmedetomidine for clinical applications in Japan.

SUBJECTS AND METHODS

Study design

A prospective, randomized, placebo-controlled, double-blind, parallel-arm study was conducted as a phase 3 clinical study at 18 sites in Japan between June 2011 and February 2012. This study was designed by the representatives of ten participating sites in cooperation with two pharmaceutical companies (Hospira Japan Co., Ltd., Osaka, Japan, currently Pfizer Japan Inc., Tokyo, Japan and Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). The study protocol was approved by the institutional review board at each site, and all patients provided written informed consent.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, and according to the Japanese Pharmaceutical Affairs Law, Japanese Good Clinical Practice and all relevant regulatory standards. The study protocol was registered in the Japan Pharmaceutical Information Center (JapicCTI-No. 111520) on 15 June 2011 and was also registered in ClinicalTrials.gov (NCT01438931).

Patient selection

Patients were included if they required sedation during an elective surgical or medical procedure expected to last ≥ 30 min without needing tracheal intubation. The main inclusion criteria were as follows: (1) age ≥ 20 years; (2) American Society of Anesthesiologists physical status I–III; (3) New York Heart Association classification I–III; and (4) requirement of local or regional anesthesia at the time of pre-operative diagnosis. Regional anesthesia included brachial plexus block, femoral nerve block, ilioinguinal nerve block and obturator nerve block.

The exclusion criteria were as follows: (1) patients who required general, epidural, or spinal anesthesia or an α_2 adrenergic receptor agonist or antagonist within 7 days prior to consent; (2) patients with respiratory failure who required intubation or a laryngeal mask; (3) patients with central nervous system pathology that could

lead to increased intracranial pressure, uncontrolled seizures, or psychiatric disorders that could be confused with the response to sedation; (4) patients who required neurosurgical or cerebrovascular catheter procedures or interventions; (5) contraindications to the drugs used in the study; (6) patients with unstable angina or acute myocardial infarction diagnosed within 6 weeks prior to consent; (7) heart rate < 50 beats per minute (bpm), systolic blood pressure (SBP) < 90 mmHg, or oxygen saturation (SpO₂) $< 92\%$ prior to study drug administration; (8) patients with third-degree atrioventricular block without an implanted pacemaker; (9) patients with increased transaminase enzymes $> 2 \times$ the upper limit of normal within 2 months prior to consent, or a history of liver insufficiency; (10) pregnant or lactating women; and (11) patients who had any symptoms or factors that might increase the risk to the patient if they participated or that might preclude obtaining satisfactory study data.

Treatment

Patients were randomly allocated (1:1:1) using a block design to a placebo group, a dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ group (DEX 0.5 group), and a dexmedetomidine 1.0 $\mu\text{g}/\text{kg}$ group (DEX 1.0 group). The placebo vials contained 2 mL of saline but were marked with an indistinguishable label from that of the dexmedetomidine vials, whereas the dexmedetomidine vial contained 2 mL of dexmedetomidine hydrochloride (100 $\mu\text{g}/\text{mL}$, base) in saline. These vials were prepared by independent pharmacists. For the initial loading infusions, the placebo group received two placebo vials, the DEX 0.5 group received one placebo and one dexmedetomidine vial, and the DEX 1.0 group received two dexmedetomidine vials. For maintenance infusion of the study drug (dexmedetomidine or placebo), each 2 mL (total amount) of study drug was diluted 25-fold in 48 mL of saline. All preparations were used within 24 h and the patients, investigators, and trial sponsors remained blinded throughout the study.

Patients received intravenous administration of the allocated study drug at 0.75 mL/kg/h over 10 min (placebo or dexmedetomidine 3.0 or 6.0 $\mu\text{g}/\text{kg}/\text{h}$). After completing the loading infusion, the maintenance infusion was started at an initial infusion rate of 0.1 mL/kg/h (placebo or dexmedetomidine 0.4 $\mu\text{g}/\text{kg}/\text{h}$) that was then titrated within a range of 0.05–0.175 mL/kg/h (placebo or dexmedetomidine 0.2–0.7 $\mu\text{g}/\text{kg}/\text{h}$) to achieve the target Observer's Assessment of Alertness/Sedation (OAA/S) score¹⁴ of 3–4 during the drug administration. OAA/S scores were assessed just before the loading infusion (baseline), every 5 min during loading and maintenance infusion, and then every 15 min until 1 h

after maintenance infusion or until the Aldrete score reached ≥ 9 .¹⁵ Vital signs and SpO₂ were monitored at the same time as mentioned above, every 5 min for the first 15 min of the drug infusion and then every 15 min until 1 h after the infusion.

Local or regional anesthetic block was performed after initiation of the study drug infusion when the OAA/S score was ≤ 4 . If the score was 5 at any time during the maintenance infusion or surgery, the maintenance infusion rate of the study drug was increased to a maximum rate of 0.175 mL/kg/h (0.7 μ g/kg/h of dexmedetomidine or placebo). If the maintenance infusion was at the maximum rate and the OAA/S score was still 5, a 0.2 mg/kg propofol bolus was administered slowly and repeated at 5 min intervals until the target OAA/S score was achieved. If the OAA/S was < 3 at any time during the infusion, the maintenance infusion rate was decreased to the minimum infusion rate of 0.05 mL/kg/h (0.2 μ g/kg/h of dexmedetomidine or placebo). The study drug infusion was discontinued at the discretion of the investigator after the surgical or medical procedure had been completed.

Supplemental analgesia was administered when a patient verbally complained or had clinical symptoms such as perspiration, tachycardia, or increased SBP. An intravenous bolus of fentanyl 0.5 μ g/kg was administered to treat pain and could be repeated at minimum intervals of 15 min. All patients were observed for 24 h after the drug infusion was stopped and were followed up for 30 days. The development of any adverse events was recorded during the follow-up.

Efficacy and safety evaluation

The primary efficacy endpoint was the percentage of patients who did not require rescue propofol to achieve and maintain an OAA/S score ≤ 4 during study drug administration. Secondary endpoints included the following: (1) the frequency of administration of propofol required to achieve and maintain an OAA/S score ≤ 4 , and the time to the first rescue dose; (2) the percentages of time spent at OAA/S scores of ≤ 4 and 3–4 during infusion of the study drug; (3) the percentage of patients who did not require rescue fentanyl and; (4) the time to achieve an Aldrete score ≥ 9 ¹⁵ following discontinuation of infusion of the study drug.

Within 24 h after discontinuation of infusion of the study drug, the investigator rated the ease of maintaining sedation, hemodynamic stability, respiratory stability, and patient cooperation, using a visual analogue scale (VAS). Patients also rated their satisfaction with sedation during surgery and any anxiety associated with the surgical or anesthetic procedure. Finally, safety

Table 1. Criteria for hemodynamic and respiratory adverse events

Parameter	Measured value	Adverse event name
SBP	< 80 mmHg or $\geq 30\%$ decrease from baseline	Hypotension
	> 180 mmHg or $\geq 30\%$ increase from baseline	Hypertension
DBP	< 50 mmHg	Hypotension
	> 100 mmHg	Hypertension
Heart rate	< 40 bpm or $\geq 30\%$ decrease from baseline	Bradycardia
	> 120 bpm or $\geq 30\%$ increase from baseline	Tachycardia
Respiration rate	< 8 bpm or $> 25\%$ decrease from baseline	Respiratory depression
SpO ₂	$< 90\%$ or $> 10\%$ decrease from baseline	Hypoxia

bpm, beats or breaths per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpO₂, oxygen saturation.

evaluation included collecting data on the incidences of adverse events, such as hypotension, hypertension, bradycardia, tachycardia, respiratory depression and hypoxia (as defined in Table 1), as well as post-surgical nausea and vomiting, and abnormal laboratory values.

Sample size

Assuming an efficacy rate of 40% in the dexmedetomidine groups and 10% in the placebo group, a sample size of 47 patients per group was required to detect inter-group differences at a two-sided significance level of 5% with a power of 90% based on the χ^2 test. Thus, 162 patients (54 patients per group) were required to allow for exclusions and drop-outs.

Statistical analysis

A closed testing procedure was used to control family-wise error rate for multiple comparisons in each efficacy endpoint.¹⁶ The DEX 1.0 group and the placebo group were compared first, and comparison between the DEX 0.5 group and the placebo group was only subsequently performed when a significant difference was observed in the first comparison. Efficacy and safety analyses were conducted on the full analysis set, defined as all patients who received any study drug. In addition, subgroup analyses were performed for the primary efficacy endpoint, the secondary efficacy endpoints and the safety evaluations, stratified by age (< 65 and ≥ 65

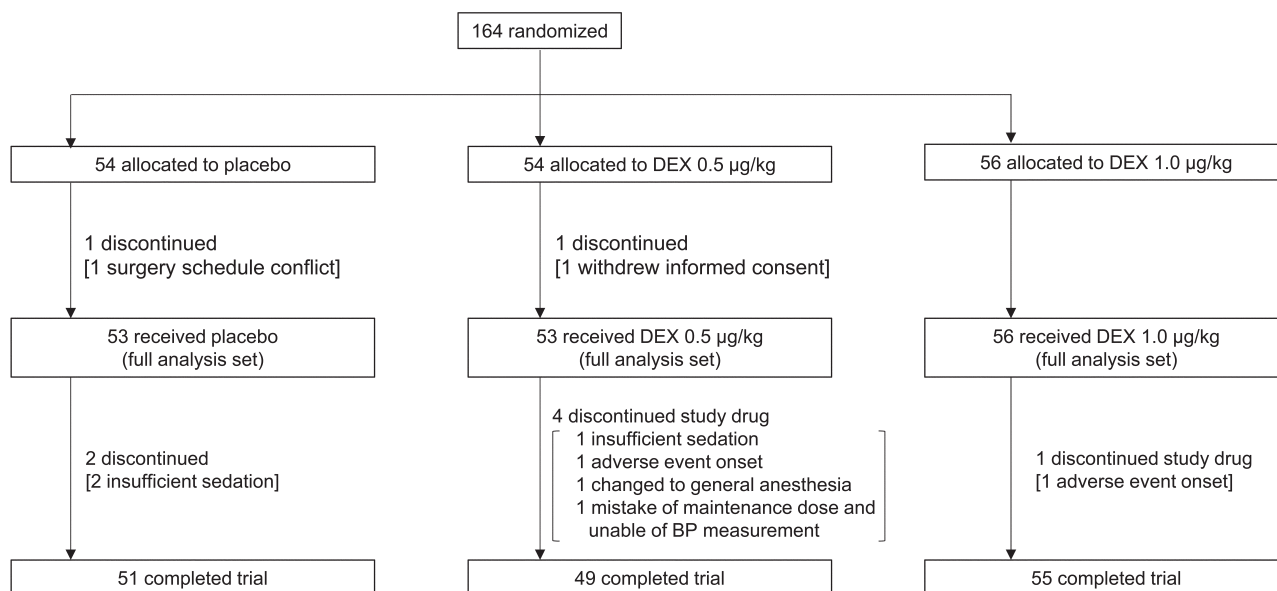


Fig. 1. Study flowchart. The full analysis set was used for efficacy and safety analyses. DEX, dexmedetomidine.

years) and type of surgery or medical procedure. A p -value < 0.05 was considered as statistically significant.

The main comparisons between the dexmedetomidine groups and the placebo groups were adjusted by the type of surgery or medical procedure. Mantel–Haenszel tests were used for primary analysis of the percentage of patients who did not require propofol rescue sedation and for secondary analyses of the percentage of patients who did not require fentanyl analgesia. Cochran–Mantel–Haenszel tests were used for secondary analysis of the propofol and fentanyl frequencies, the percentages of time spent at OAA/S scores ≤ 4 and 3–4 during the infusion, and the patient’s evaluation of satisfaction and anxiety. Stratified log-rank tests were used, and a 95% confidence limit was also calculated for secondary analysis of time to the first rescue with propofol and time to reach an Aldrete score of ≥ 9 . An analysis of covariance was used for the investigator’s VAS scores, and descriptive statistics were presented by group for each score. Finally, the incidences of total and individual adverse events were calculated by group and χ^2 tests were performed to compare the dexmedetomidine and placebo groups. For this calculation, the incidences of individual adverse events were adjusted by type of surgery or medical procedure.

RESULTS

Baseline characteristics

A total of 164 patients were randomized, of whom two did not receive the study drug because their procedures were cancelled. Consequently, 162 patients were

included in the full analysis set [the placebo group ($n = 53$), DEX 0.5 group ($n = 53$), and DEX 1.0 group ($n = 56$)] as shown in Fig. 1. Baseline characteristics were similar in the groups (Table 2 and Supplemental Table S1).

Main efficacy measures

Dexmedetomidine met the primary efficacy endpoint, and the percentage of patients who did not require rescue propofol during infusion was significantly higher in the DEX 0.5 and 1.0 groups than the placebo group ($P < 0.001$ for both, Table 3).

Sedative effect was also assessed as secondary endpoints, including the frequency of propofol administration and the time to the first rescue dose of propofol. The sedative effect was notably superior for all of these endpoints in the dexmedetomidine groups compared with the placebo group ($P < 0.001$, for each comparison, Table 3). The sedative effect of dexmedetomidine was also demonstrated by the percentages of time spent with OAA/S scores ≤ 4 and 3–4, which were both significantly higher in the dexmedetomidine groups compared with placebo ($P < 0.001$ for both, Table 3).

Dexmedetomidine at a higher loading dose led to a more rapid decrease in the OAA/S score. It took 25 min for the DEX 0.5 group and 15 min for the DEX 1.0 group on average to reach ≤ 4 for the mean OAA/S score. Compared to the placebo group, the DEX 0.5 and 1.0 groups showed significant decreases in the mean OAA/S scores during the first 10 min after the start of administration ($P < 0.001$ for both) and maintained

Table 2. Baseline characteristics

Parameter		Placebo	DEX 0.5	DEX 1.0
		<i>n</i> = 53	<i>n</i> = 53	<i>n</i> = 56
Sex [<i>n</i> (%)]	Male	33 (62.3%)	28 (52.8%)	25 (44.6%)
Age	Mean ± SD (years)	57.1 ± 16.5	56.4 ± 16.5	57.8 ± 17.0
	≥ 65 [<i>n</i> (%)]	19 (35.8%)	19 (35.80%)	23 (41.1%)
Surgery/medical procedure type* [<i>n</i> (%)]	Type 1	18 (34.0%)	20 (37.7%)	21 (37.5%)
	Type 2	18 (34.0%)	17 (32.1%)	18 (32.1%)
	Type 3	17 (32.1%)	16 (30.2%)	17 (30.4%)
Anesthesia [<i>n</i> (%)] (multiple responses)	Block anesthesia	10 (18.9%)	11 (20.8%)	12 (21.4%)
	Local infiltration anesthesia	46 (86.8%)	44 (83.0%)	44 (78.6%)
	Others	2 (3.8%)	3 (5.7%)	1 (1.8%)
	Not conducted	0	0	1 (1.8%)
Surgery/medical procedure site [<i>n</i> (%)]	Head	4 (7.5%)	6 (11.3%)	4 (7.1%)
	Oral cavity	5 (9.4%)	6 (11.3%)	6 (10.7%)
	Upper limb	15 (28.3%)	18 (34.0%)	15 (26.8%)
	Chest	5 (9.4%)	3 (5.7%)	7 (12.5%)
	Heart	11 (20.8%)	10 (18.9%)	10 (17.9%)
	Abdomen	1 (1.9%)	2 (3.8%)	0
	Lower limb	9 (17.0%)	7 (13.2%)	10 (17.9%)
	Others	2 (3.8%)	1 (1.9%)	3 (5.4%)
	Discontinued before procedure	1 (1.9%)	0	1 (1.8%)
Duration of Surgery/medical procedure (min)**	Mean ± SD (<i>n</i>)	86.5 ± 57.0 (52)	94.6 ± 74.4 (53)	73.4 ± 47.9 (55)
	Range	10–195	8–330	14–213
ASA physical condition [<i>n</i> (%)]	I	28 (52.8%)	29 (54.7%)	29 (51.8%)
	II	16 (30.2%)	17 (32.1%)	21 (37.5%)
	III	9 (17.0%)	7 (13.2%)	6 (10.7%)
NYHA classification [<i>n</i> (%)]	I	10 (18.9%)	10 (18.9%)	7 (12.5%)
	II	1 (1.9%)	0	3 (5.4%)
	III	0	0	0
	N.A.	42 (79.2%)	43 (81.1%)	46 (82.1%)
Body weight (kg)	Mean ± SD	61.91 ± 10.95	62.48 ± 14.67	57.79 ± 12.10
	Range	41.0–90.7	40.4–98.3	33.8–90.4
Height (cm)	Mean ± SD	163.2 ± 9.0	161.7 ± 9.8	158.8 ± 11.2
	Range	144–180	143–183	134–181

*Type of surgery/medical procedure: Type 1 = orthopedic, otorhinolaryngological and oral surgeries; Type 2 = plastic surgery, excision of lesion, breast biopsy and catheter ablation; Type 3 = arteriovenous fistula, arteriovenous shunt and vascular stent. **Patients who did not undergo a surgery/medical procedure were excluded from the calculation. ASA, American Society of Anesthesiologists; DEX, dexmedetomidine; N.A., not applicable; NYHA, New York Heart Association; SD, standard deviation.

significantly lower OAA/S values until 60 min after study drug administration.

The analgesic efficacy of dexmedetomidine is not clearly demonstrated in Table 3. There was not a significant difference in the number of patients who required

rescue fentanyl during infusion between the placebo and the DEX groups. However, the frequency of rescue fentanyl use was both significantly lower in the DEX 0.5 group ($P = 0.010$) and the DEX 1.0 group ($P = 0.008$) compared with the placebo group.

Table 3. Results for the sedative and analgesic effects of DEX

Endpoint		Parameter	Placebo <i>n</i> = 53	DEX 0.5 <i>n</i> = 53	DEX 1.0 <i>n</i> = 56
Primary endpoint (sedation)	No rescue propofol as an additional sedative ¹⁾	<i>n</i> (%)	1 (1.9%)	28 (52.8%)	32 (57.1%)
		<i>P</i> -value		< 0.001	< 0.001
Sedative effect (rescue propofol)	Frequency of rescue propofol administration ²⁾ (times)	Mean (SD)	11.0 (6.9)	1.5 (2.7)	0.8 (1.3)
		Median	10.0	0.0	0.0
		Range	0–30	0–16	0–6
		<i>P</i> -value		< 0.001	< 0.001
	Time taken between the start of study drug administration and the start of propofol administration ³⁾ (min)	Median	20.0	86.0	125.0
		95% CI	—	37.0—	72.0—
		<i>P</i> -value		< 0.001	< 0.001
Sedative effect (OAA/S score)	Percentage of time maintained at OAA/S score ≤ 4 during the study drug administration ²⁾	Mean (SD)	37.95 (20.00)	71.49 (17.88)	72.59 (16.38)
		Median	32.40	74.00	77.70
		Range	0.0–83.8	26.2–96.0	26.8–94.5
		<i>P</i> -value		< 0.001	< 0.001
	Percentage of time maintained at OAA/S score 3–4 during the study drug administration ²⁾	Mean (SD)	37.49 (20.07)	66.42 (18.21)	63.88 (20.18)
		Median	32.40	67.70	66.85
		Range	0.0–83.8	26.2–96.0	0.0–94.5
		<i>P</i> -value		< 0.001	< 0.001
Analgesic effect	No additional administration of fentanyl ¹⁾	<i>n</i> (%)	30 (56.6)	40 (75.5)	40 (71.4)
		<i>P</i> -value		-	0.107
	Frequency of rescue fentanyl administration ²⁾ (times)	Mean (SD)	1.4 (2.2)	0.4 (0.8)	0.4 (0.7)
		Median	0.0	0.0	0.0
		Range	0–9	0–3	0–4
		<i>P</i> -value		0.010	0.008

¹⁾Mantel–Haenszel test adjusted by type of surgery/medical procedure with a closed testing procedure. ²⁾Cochran–Mantel–Haenszel test adjusted by type of surgery/medical procedure with a closed testing procedure. ³⁾Stratified log-rank test adjusted by type of surgery/medical procedure with a closed testing procedure. '—' = unable to calculate, '-' = undetermined. CI, confidence interval; DEX, dexmedetomidine; SD, standard deviation.

Other efficacy measures

The median recovery time (Aldrete score ≥ 9) following discontinuation of the study drug infusion was 15 min in all treatment groups (Table 4). As more patients required a longer time than 15 min in the DEX 0.5 and DEX 1.0 groups compared to the placebo group, a significantly longer time was needed in both groups (Hazard ratio: 0.685 and 0.651, $P = 0.001$ and $P < 0.001$, respectively).

Patient condition was evaluated by the investigator within 24 h after the drug administration, using a VAS score (Table 4). Ease of maintaining the sedation level was significantly better in the DEX 0.5 and 1.0 groups than in the placebo group ($P < 0.001$ each). There were no significant differences between the placebo and the DEX 1.0 groups in the VAS score for hemodynamic stability ($P = 0.131$), respiratory stability ($P = 0.173$) or

patient cooperation ($P = 0.620$).

Regarding patient's satisfaction and anxiety, the satisfaction score for monitored sedation was significantly better in the DEX 1.0 group than the placebo group ($P = 0.034$) (Table 4). In the other patient-rated items concerning treatment-related pain, satisfaction and anxiety, there were no significant differences between the DEX 1.0 and placebo groups.

Although the small number of patients in each stratum posed limitations on the analysis, we performed subgroup analysis by age and type of surgery or medical procedure. Regardless of age (patients aged < 65 years and ≥ 65 years), the efficacies in the percentage of patients who did not require propofol, the frequency of propofol administration, and the percentage of time with an OAA/S score ≤ 4 were significantly higher in the DEX 0.5 and 1.0 groups than the placebo group (P

Table 4. Results for other efficacy measures

Endpoint		Parameter	Placebo <i>n</i> = 53	DEX 0.5 <i>n</i> = 53	DEX 1.0 <i>n</i> = 56
Evaluation of recovery	Time to attain an Aldrete score ≥ 9 from the end of study drug administration ¹⁾ (min)	Median	15.0	15.0	15.0
		Hazard ratio (95% CI)		0.685 (0.453–1.037)	0.651 (0.427–0.991)
		<i>P</i> -value		0.001	< 0.001
VAS score evaluation by investigator [†]	Ease of maintaining sedation level ²⁾ (cm)	Mean (SD)	7.41 (2.62)	3.27 (3.18)	3.04 (2.46)
		<i>P</i> -value		< 0.001	< 0.001
	Hemodynamic stability ²⁾ (cm)	Mean (SD)	1.89 (2.36)	2.42 (2.47)	2.44 (2.36)
		<i>P</i> -value		-	0.131
	Respiratory stability ²⁾ (cm)	Mean (SD)	1.94 (2.46)	2.32 (2.24)	2.55 (2.50)
		<i>P</i> -value		-	0.173
Subject's cooperativeness ²⁾ (cm)	Mean (SD)	1.66 (2.37)	1.50 (2.03)	1.46 (1.76)	
	<i>P</i> -value		-	0.620	
Subject's satisfaction evaluation score*	A. I was satisfied with the anesthesia care. ²⁾	Mean (SD)	1.9 (1.1)	1.8 (1.0)	1.5 (0.8)
		<i>P</i> -value		0.330	0.034
	B. I felt no pain during the surgery/medical procedure. ²⁾	Mean (SD)	1.9 (1.0)	1.9 (1.0)	1.7 (1.0)
<i>P</i> -value			-	0.103	
C. I would have the same anesthetic again. ²⁾	Mean (SD)	1.8 (1.0)	1.7 (1.0)	1.6 (0.9)	
	<i>P</i> -value		-	0.157	
Subject's anxiety evaluation score**	D. Anxiety assessment before surgery/ medical procedure ²⁾	Mean (SD)	2.8 (1.5)	2.5 (1.5)	2.7 (1.6)
		<i>P</i> -value		-	0.491
	E. Anxiety assessment during surgery/ medical procedure ²⁾	Mean (SD)	2.0 (1.2)	1.6 (1.1)	1.8 (1.2)
<i>P</i> -value			-	0.419	
F. Anxiety assessment after surgery/ medical procedure ²⁾	Mean (SD)	1.4 (0.7)	1.4 (0.8)	1.4 (0.9)	
	<i>P</i> -value		-	0.714	

¹⁾Stratified log-rank test adjusted by type of surgery or medical procedure with a closed testing procedure. ²⁾Cochran–Mantel–Haenszel test adjusted by type of surgery or medical procedure with a closed testing procedure. [†]VAS score ranged from 0 to 10 cm with 0 cm as the most favourable score. *Satisfaction Assessment A, B and C: scores ranged from 1 to 4 with 1 as the most favourable score. **Anxiety Assessment D, E and F: scores ranged from 1 to 5 with 1 as the most favourable score. '—' = unable to calculate, '-' = undetermined. CI, confidence interval; DEX, dexmedetomidine; SD, standard deviation; VAS, visual analogue scale.

< 0.001, for each stratum) (Supplemental Tables S2–S4). In addition, the proportion of patients who did not require propofol was numerically greater and the frequency of propofol administration was numerically lower in patients aged ≥ 65 years compared with those aged < 65 years (Supplemental Tables S5–S6). The surgical or medical procedure did not affect the efficacy of dexmedetomidine (Supplemental Tables S7–S11).

Safety

Most of the patients in this study experienced at least one adverse event, but most events were mild. There were no patients receiving rescue treatments in any study groups. No significant differences were observed in the total incidences of adverse events or the severity

of adverse events between the placebo group and each of the DEX groups. There was one serious adverse event of shunt occlusion (moderate) that occurred 16 minutes after the end of administration in the DEX 0.5 group. This event was judged to be caused by severe stenosis in the intermediate cephalic vein that was presumed to have existed before surgery. Thus, it was considered unrelated to the study drug.

Dexmedetomidine infusion was discontinued in two cases. The first case was a patient in the DEX 0.5 group who developed mild restless legs syndrome. The restless body movements made it impossible to perform the surgical procedure; therefore, administration of the study drug was discontinued 75 min after the onset of restless legs syndrome. The symptom was judged to be

Table 5. Treatment-emergent adverse events that occurred under the study treatment with high frequency (10% or higher in any group)

Severity	Placebo (n = 53)				DEX 0.5 (n = 53)				DEX 1.0 (n = 56)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Number of patients with events (%)	42 (79.2%)	3 (5.7%)	0	45 (84.9%)	43 (81.1%)	5 (9.4%)	0	48 (90.6%)	41 (73.2%)	9 (16.1%)	0	50 (89.3%)
Hypotension	24 (45.3%)	1 (1.9%)	0	25 (47.2%)	34 (64.2%)	1 (1.9%)	0	35 (66.0%)	31 (55.4%)	4 (7.1%)	0	35 (62.5%)
Respiratory depression	28 (52.8%)	0	0	28 (52.8%)	28 (52.8%)	0	0	28 (52.8%)	26 (46.4%)	0	0	26 (46.4%)
Bradycardia	5 (9.4%)	0	0	5 (9.4%)	14 (26.4%)	0	0	14 (26.4%)	16 (28.6%)	1 (1.8%)	0	17 (30.4%)
Hypertension	11 (20.8%)	0	0	11 (20.8%)	10 (18.9%)	0	0	10 (18.9%)	13 (23.2%)	2 (3.6%)	0	15 (26.8%)
Tachycardia	13 (24.5%)	0	0	13 (24.5%)	7 (13.2%)	0	0	7 (13.2%)	7 (12.5%)	1 (1.8%)	0	8 (14.3%)
Hypoxia	6 (11.3%)	2 (3.8%)	0	8 (15.1%)	4 (7.5%)	3 (5.7%)	0	7 (13.2%)	6 (10.7%)	2 (3.6%)	0	8 (14.3%)

DEX, dexmedetomidine.

causally unrelated to dexmedetomidine. The second case presented with moderate unrest that developed in the DEX 1.0 group approximately 30 min after starting the infusion. Since the patient did not cooperate with the surgery, dexmedetomidine was discontinued 10 min after the onset of unrest. This adverse event was judged as probably related to dexmedetomidine.

Table 5 summarizes the treatment-emergent adverse events with an incidence of more than 10%, as evaluated in accordance with the protocol-defined criteria. The most frequent adverse event in the DEX groups was hypotension, followed by respiratory depression, bradycardia, hypertension, tachycardia and hypoxia. Of these, the incidence of bradycardia was significantly higher in the DEX 0.5 group (26.4%) and the DEX 1.0 group (30.4%) compared with the placebo group (9.4%) ($P = 0.041$ and $P = 0.008$, respectively). The incidences of nausea and vomiting were low (1 case of nausea in the placebo group; 2 cases of nausea and 2 cases of vomiting in the DEX 1.0 group; not significant). Subgroup analysis found no major differences in the incidence by age (65 years old) or the type of surgery or medical procedure. However, only eight patients aged > 80 years received dexmedetomidine and all of them developed any of the protocol-defined treatment-emergent adverse events (TEAEs): 6 respiratory depression, 5 hypotension, 4 bradycardia, 2 hypoxia, 2 tachycardia and 1 hypertension.

DISCUSSION

In this study, a significant majority of patients who received dexmedetomidine did not require rescue propofol to achieve and maintain adequate sedation compared with placebo, indicating that the primary endpoint for efficacy was met. The results of all major secondary efficacy endpoints also supported the sedative efficacy of dexmedetomidine. Concerning the change in OAA/S scores, the initial loading dose in the DEX 1.0 group resulted in a more rapid decrease in the OAA/S score compared with the DEX 0.5 group. Therefore, we conclude that dexmedetomidine had an appropriate sedative effect in patients undergoing surgery or medical procedures without intubation under local or regional anesthesia.

Comparable results on the sedative effect of dexmedetomidine have been reported previously.⁹ In the study, the percentage of patients who did not require rescue sedation was 40.3% in the DEX 0.5 group and 54.3% in the DEX 1.0 group; the corresponding percentages in our study were 52.8% and 57.1%, respectively. The previous study was performed in a racially mixed population of approximately 60% Caucasians, 20% African Americans, and 15% Hispanics. These findings indicate that any potential racial differences in the sedative effects of dexmedetomidine are probably negligible.

In the present research, we also showed that dexmedetomidine had an analgesic-sparing effect. Concerning the secondary endpoints, the frequency of fentanyl administration was significantly lower in the

dexmedetomidine groups than the placebo group. This effect may have led to the greater patient satisfaction with the anesthetic care in the DEX 1.0 group. Systemic administration of dexmedetomidine prolongs the duration of both sensory and motor nerve blocks, as shown with ulnar nerve block using ropivacaine,¹⁷ which may account for this finding.

In the safety examination, high incidences of hypotension and bradycardia were observed in both dexmedetomidine groups, and hypertension was observed during initial loading with a high dose of dexmedetomidine. However, none of these adverse events were severe, and when necessary, discontinuation or appropriate intervention led to a satisfactory resolution. These adverse events were also considered attributable to the known pharmacology.¹⁰ Given that treatment has already been established for these eventualities, continuous monitoring of a patient's hemodynamic status will not only help to prevent these adverse events, but also prompt their early treatment. Interestingly, the incidences of bradycardia and hypotension were higher in this study than previously reported⁹; namely 22.2% (36/162 patients) and 58.6% (95/162 patients), respectively, in this study and 2.1% and 8.9%, respectively, in the previous study.⁹ These differences can be considered to result from differences in study protocols and the criteria used to define adverse events. Definitions of bradycardia and hypotension in the previous study meant a change of 30% or more from baseline, respectively.⁹ The definitions in the present study add the criteria of less than 40 bpm to 30% or more change from baseline for bradycardia, and less than 80 mmHg to 30% or more change from baseline for hypotension. Moreover, the initial maintenance dose was started at 0.2 $\mu\text{g}/\text{kg}/\text{h}$ in the previous study,⁹ while it was started at 0.4 $\mu\text{g}/\text{kg}/\text{h}$ in the present study. These differences were likely to cause hypotension and bradycardia more frequently in the present study. There are a couple of reports on racial differences as to the effects of drugs including analgesic and cardiovascular agents.^{18–21} These reports suggest that racial differences on the effects of drugs definitely exists. However, it hasn't been known whether or not Japanese subjects have a similar sedative efficacy and safety with dexmedetomidine for monitored sedation compared to American subjects. Alterations of plasma concentration of dexmedetomidine in the same dosage over time between Japanese and American subjects were similar in the exploratory dose-response studies. (unpublished data from the interview form on dexmedetomidine). Therefore, we may need to consider the possibility that the sympatholytic effect of dexmedetomidine is stronger in Japanese than in Americans.

Given that no patients had to be intubated in this study, it is perhaps not surprising that respiratory depression and hypoxia occurred at fairly high frequencies, and glossoptosis also occurred in some cases. However, there were no differences in the incidences of these events between the placebo and the dexmedetomidine groups, and there were also no severe adverse events. All patients recovered from the respiratory adverse events with or without treatment (e.g. oxygen administration, airway management including jaw lifting, insertion of airway and manual assist ventilation using an anesthetic mask, dose reduction and patient stimulation). Thus, it seemed that respiratory adverse events during dexmedetomidine sedation are manageable with continuous monitoring of the respiratory condition and by giving proactive therapy.

When comparing the two doses of dexmedetomidine, a more potent sedative effect was observed with an initial dose of 1.0 $\mu\text{g}/\text{kg}$ (6 $\mu\text{g}/\text{kg}/\text{h}$ for 10 min), even though the sedative effect was significant at both doses. In the safety evaluation, only hypertension was observed at a slightly higher proportion in the DEX 1.0 group, but this needs to be considered in the context of no significant differences in the incidence of hypertension between the placebo and dexmedetomidine groups. The onset of hypertension during the initial loading dose is also an expected side effect that is manageable with established treatment. Bradycardia and hypotension seldom occur due to greater activation of α_{2B} than α_{2A} during the initial loading dose.¹⁴ However, since the difference in the incidences between the two doses was comparatively small, we considered that the initial loading dose does not affect safety. Based on the results of higher efficacy observed with the higher dose, the optimum initial loading dose for dexmedetomidine is therefore recommended to be 1.0 $\mu\text{g}/\text{kg}$ (6 $\mu\text{g}/\text{kg}/\text{h}$ for 10 min), followed by a maintenance dose of 0.2–0.7 $\mu\text{g}/\text{kg}/\text{h}$, to ensure adequate sedation.

In the subgroup analyses, patients aged ≥ 65 years achieved a sufficient sedating effect at an initial loading dose of 0.5 $\mu\text{g}/\text{kg}$ over 10 min, suggesting higher sensitivity to dexmedetomidine in this population. Moreover, only eight patients aged >80 years received dexmedetomidine and they tended to be over-sedated on these dosing regimens. Thus, more careful monitoring is needed during sedation in patients aged > 80 years. There were no differences in the efficacy of dexmedetomidine by the type of surgery or medical procedure.

In patients requiring monitored sedation for surgical or medical procedures under local or regional anesthesia, dexmedetomidine at initial loading doses of 0.5 or 1.0 $\mu\text{g}/\text{kg}$ over 10 min, followed by a maintenance

infusion of 0.2–0.7 µg/kg/h, provided a marked sedative effect (OAA/S scale ≤ 4). These regimens were also well-tolerated with manageable adverse events regardless of age or a type of surgery or medical procedure. Although the efficacy of dexmedetomidine in Japanese patients was comparable to that reported in other countries, it appears that dexmedetomidine is more likely to induce hypotension and bradycardia in Japanese patients.

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CONFLICTS OF INTEREST

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DATA-SHARING STATEMENT

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the USA and/or EU, or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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APPENDIX

1. Detailed baseline characteristics

Table S1. Baseline characteristics

Parameter		Placebo <i>n</i> = 53	DEX 0.5 <i>n</i> = 53	DEX 1.0 <i>n</i> = 56
Sex [<i>n</i> (%)]	Male	33 (62.3%)	28 (52.8%)	25 (44.6%)
	Female	20 (37.7%)	25 (47.2%)	31 (55.4%)
Age (years) [<i>n</i> (%)]	Mean ± SD	57.1 ± 16.5	56.4 ± 16.5	57.8 ± 17.0
	Range	20–90	25–87	24–87
	20–35	5 (9.4%)	7 (13.2%)	7 (12.5%)
	36–55	22 (41.5%)	19 (35.8%)	15 (26.8%)
	56–65	7 (13.2%)	9 (17.0%)	14 (25.0%)
	≥ 66	19 (35.8%)	18 (34.0%)	20 (35.7%)
Surgery/medical procedure type [<i>n</i> (%)]	Type 1	18 (34.0%)	20 (37.7%)	21 (37.5%)
	Type 2	18 (34.0%)	17 (32.1%)	18 (32.1%)
	Type 3	17 (32.1%)	16 (30.2%)	17 (30.4%)
Anesthesia method [<i>n</i> (%)] (multiple responses)	Block anesthesia	10 (18.9%)	11 (20.8%)	12 (21.4%)
	Local infiltration anesthesia	46 (86.8%)	44 (83.0%)	44 (78.6%)
	Others	2 (3.8%)	3 (5.7%)	1 (1.8%)
	Not conducted	0	0	1 (1.8%)
Surgery/medical procedure site [<i>n</i> (%)]	Head	4 (7.5%)	6 (11.3%)	4 (7.1%)
	Oral cavity	5 (9.4%)	6 (11.3%)	6 (10.7%)
	Upper limb	15 (28.3%)	18 (34.0%)	15 (26.8%)
	Chest	5 (9.4%)	3 (5.7%)	7 (12.5%)
	Heart	11 (20.8%)	10 (18.9%)	10 (17.9%)
	Abdomen	1 (1.9%)	2 (3.8%)	0
	Lower limb	9 (17.0%)	7 (13.2%)	10 (17.9%)
	Others	2 (3.8%)	1 (1.9%)	3 (5.4%)
	Discontinuation before surgery/ medical procedure	1 (1.9%)	0	1 (1.8%)
	Surgery/medical procedure [<i>n</i> (%)]	Invasive osteosynthesis	2 (3.8%)	3 (5.7%)
Pin removal		3 (5.7%)	2 (3.8%)	3 (5.4%)
Arthroplasty		1 (1.9%)	2 (3.8%)	1 (1.8%)
Carpal tunnel release		0	1 (1.9%)	5 (8.9%)
Tumor/mass excision		13 (24.5%)	11 (20.8%)	9 (16.1%)
Surgery of nasal sinuses		2 (3.8%)	2 (3.8%)	2 (3.6%)
Implant surgery		1 (1.9%)	2 (3.8%)	2 (3.6%)
Tooth extraction		1 (1.9%)	1 (1.9%)	2 (3.6%)
Blepharoptosis surgery		0	2 (3.8%)	1 (1.8%)
Manipulative reduction		1 (1.9%)	0	1 (1.8%)
Catheter ablation		8 (15.1%)	7 (13.2%)	7 (12.5%)
Arteriovenous fistula operation		0	2 (3.8%)	0
Shunt surgery		7 (13.2%)	5 (9.4%)	6 (10.7%)
Vascular stent		2 (3.8%)	1 (1.9%)	3 (5.4%)
Percutaneous transluminal coronary angioplasty		0	2 (3.8%)	2 (3.6%)
Percutaneous transluminal angioplasty		4 (7.5%)	5 (9.4%)	4 (7.1%)
Contrast examination		4 (7.5%)	1 (1.9%)	1 (1.8%)
Other orthopedic surgery		2 (3.8%)	2 (3.8%)	2 (3.6%)
Other oral surgery		0	1 (1.9%)	1 (1.8%)
Other plastic surgery		1 (1.9%)	1 (1.9%)	2 (3.6%)
Discontinued before surgery/ medical procedure	1 (1.9%)	0	1 (1.8%)	

Table S1. (Continued)

Parameter		Placebo <i>n</i> = 53	DEX 0.5 <i>n</i> = 53	DEX 1.0 <i>n</i> = 56
Duration of surgery/ medical procedure (min)*	Mean ± SD (<i>n</i>)	86.5 ± 57.0 (52)	94.6 ± 74.4 (53)	73.4 ± 47.9 (55)
	Range	10–195	8–330	14–213
ASA physical condition [<i>n</i> (%)]	I	28 (52.8%)	29 (54.7%)	29 (51.8%)
	II	16 (30.2%)	17 (32.1%)	21 (37.5%)
	III	9 (17.0%)	7 (13.2%)	6 (10.7%)
NYHA classification [<i>n</i> (%)]	I	10 (18.9%)	10 (18.9%)	7 (12.5%)
	II	1 (1.9%)	0	3 (5.4%)
	III	0	0	0
	N.A.	42 (79.2%)	43 (81.1%)	46 (82.1%)
Smoking habit [<i>n</i> (%)]	No	25 (47.2%)	24 (45.3%)	28 (50.0%)
	Yes	14 (26.4%)	16 (30.2%)	13 (23.2%)
	Ex-smoker	14 (26.4%)	13 (24.5%)	15 (26.8%)
Alcohol habit [<i>n</i> (%)]	No	24 (45.3%)	20 (37.7%)	19 (33.9%)
	Yes	24 (45.3%)	27 (50.9%)	30 (53.6%)
	Ex-drinker	5 (9.4%)	6 (11.3%)	7 (12.5%)
Body weight (kg)	Mean ± SD	61.91 ± 10.95	62.48 ± 14.67	57.79 ± 12.10
	Range	41.0–90.7	40.4–98.3	33.8–90.4
Height (cm)	Mean ± SD	163.2 ± 9.0	161.7 ± 9.8	158.8 ± 11.2
	Range	144–180	143–183	134–181

*The patients not receiving surgery/medical procedure were excluded from the calculation. Surgery/medical procedure type: Type 1 = orthopedic, otorhinolaryngologic and oral surgeries; Type 2 = Plastic surgery, excision of lesion, breast biopsy and catheter ablation; Type 3 = Arteriovenous fistula, arteriovenous shunt and vascular stent. ASA, American Society of Anesthesiologists; DEX, dexmedetomidine; Ex-drinker, excessive drinker; Ex-smoker, excessive smoker; N.A., not applicable; NYHA, New York Heart Association; SD, standard deviation.

2. Examination of Subgroups

The below stratified analysis in FAS was conducted regarding primary endpoint, secondary endpoints.

1) Age: < 65, ≥ 65

2) Surgery and medical procedure types

Type 1: Orthopedic, otorhinolaryngology and oral surgeries

Type 2: Plastic surgery, excision of lesion, breast biopsy and catheter ablation

Type 3: Arteriovenous fistula, arteriovenous and vascular stent

(1) Analysis by age

The proportion of the patients not requiring administration of rescue propofol during administration of the study drug, the frequency propofol during administration of the study drug, and the percentage of time maintained at OAA/S score ≤ 4 during administration of the study drug by age in FAS are shown in Tables S2, S3, and S4, respectively.

For these endpoints, the efficacy was significantly higher in the 0.5 µg/kg and 1.0 µg/kg groups compared to the placebo group for both < 65 years and ≥ 65 years.

In addition, there was a tendency that the proportion of the patients not requiring rescue administration

of propofol during administration of the study drug was significantly higher both in the 0.5 µg/kg and 1.0 µg/kg groups for the stratum of ≥ 65 years than for the stratum of < 65 years, which showed higher efficacy. For the frequency of rescue propofol during administration of the study drug (bolus administration of 0.2 mg/kg per dose) (mean ± SD), it was lower in the 1.0 µg/kg group (0.9 ± 1.2 times) than in the 0.5 µg/kg group (2.0 ± 3.2 times) for the stratum of < 65 years, while it was comparable between the 0.5 µg/kg group (0.7 ± 1.0 times) and the 1.0 µg/kg group (0.8 ± 1.4 times) for the stratum of > 65 years. While additional administration of propofol was fewer for the stratum of > 65 years than that for the stratum of < 65 years, the percentage of time periods maintained at OAA/S score ≤ 4 was comparable between the 0.5 µg/kg and 1.0 µg/kg group, showing that the efficacy for the strata of < 65 years and ≥ 65 years was similar.

The proportion of the patients not requiring rescue administration of fentanyl during administration of the study drug and the frequency of rescue fentanyl according to age during administration of the study drug in FAS are shown in Tables S5 and S6, respectively.

There was no difference in the efficacy in these endpoints for the strata of < 65 years and ≥ 65 years.

Table S2. Proportion of patients who did not require rescue propofol according to age during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Age < 65	<i>n</i> = 34	<i>n</i> = 34	<i>n</i> = 33
Did Not Require Rescue Propofol	1 (2.9)	16 (47.1)	17 (51.5)
Required Rescue Propofol	33 (97.1)	18 (52.9)	16 (48.5)
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Age ≥ 65	<i>n</i> = 19	<i>n</i> = 19	<i>n</i> = 23
Did Not Require Rescue Propofol	0	12 (63.2)	15 (65.2)
Required Rescue Propofol	19 (100.0)	7 (36.8)	8 (34.8)
<i>P</i> -value ¹⁾		< 0.001	< 0.001

n (%). ¹⁾ χ^2 test (Comparisons between the placebo group and each dexmedetomidine group).

Table S3. Administration frequency of rescue propofol (times) according to age during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Age < 65	<i>n</i> = 34	<i>n</i> = 34	<i>n</i> = 33
Mean ± SD	12.1 ± 7.8	2.0 ± 3.2	0.9 ± 1.2
Median	10.5	1.0	0.0
Q1–Q3	6.0–14.0	0.0–3.0	0.0–1.0
Min–Max	0–30	0–16	0–4
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Age ≥ 65	<i>n</i> = 19	<i>n</i> = 16	<i>n</i> = 23
Mean ± SD	9.2 ± 4.7	0.7 ± 1.0	0.8 ± 1.4
Median	8.0	0.0	0.0
Q1–Q3	6.0–11.0	0.0–2.0	0.0–1.0
Min–Max	2–18	0–3	0–6
<i>P</i> -value ¹⁾		< 0.001	< 0.001

¹⁾Wilcoxon 2-sample test (Comparisons between the placebo group and each dexmedetomidine group).

Table S4. Percentage of time maintained at OAA/S score ≤ 4 according to age during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Age < 65	<i>n</i> = 34	<i>n</i> = 34	<i>n</i> = 33
Mean ± SD	33.99 ± 20.96	69.76 ± 19.48	71.61 ± 16.31
Median	27.40	73.80	76.90
Q1–Q3	20.80–46.30	59.70–84.50	63.00–84.00
Min–Max	0.0–83.8	26.2–96.0	26.8–94.5
<i>p</i> -value ¹⁾		< 0.001	< 0.001
Age ≥ 65	<i>n</i> = 19	<i>n</i> = 19	<i>n</i> = 23
Mean ± SD	45.04 ± 16.36	74.59 ± 14.57	74.00 ± 16.74
Median	48.30	78.10	78.90
Q1–Q3	32.40–59.70	64.30–90.90	64.90–86.70
Min–Max	8.8–66.7	45.5–93.2	31.3–94.1
<i>P</i> -value ¹⁾		< 0.001	< 0.001

¹⁾Wilcoxon 2-sample test (Comparisons between the placebo group and each dexmedetomidine group).

Table S5. Percentage of patients who did not require rescue fentanyl according to age during the study drug administration (FAS)

	Placebo	DEX 0.5	DEX 1.0
Age < 65	<i>n</i> = 34	<i>n</i> = 34	<i>n</i> = 33
No rescue fentanyl	21 (61.8)	26 (76.5)	24 (72.7)
With rescue fentanyl	13 (38.2)	8 (23.5)	9 (27.3)
<i>P</i> -value ¹⁾		0.294	0.437
Age ≥ 65	<i>n</i> = 19	<i>n</i> = 19	<i>n</i> = 23
No rescue fentanyl	9 (47.4)	14 (73.7)	16 (69.6)
With rescue fentanyl	10 (52.6)	5 (26.3)	7 (30.4)
<i>P</i> -value ¹⁾		0.184	0.209

n (%). ¹⁾ χ^2 test (Comparisons between the placebo group and each dexmedetomidine group).

Table S6. Administration frequency of rescue fentanyl (times) according to age during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Age < 65	<i>n</i> = 34	<i>n</i> = 34	<i>n</i> = 33
Mean ± SD	1.0 ± 1.6	0.3 ± 0.7	0.4 ± 0.8
Median	0.0	0.0	0.0
Q1–Q3	0.0–2.0	0.0–0.0	0.0–1.0
Min–Max	0–6	0–3	0–4
<i>P</i> -value ¹⁾		0.097	0.161
Age ≥ 65	<i>n</i> = 19	<i>n</i> = 16	<i>n</i> = 23
Mean ± SD	2.2 ± 2.8	0.5 ± 1.0	0.4 ± 0.7
Median	1.0	0.0	0.0
Q1–Q3	0.0–4.0	0.0–1.0	0.0–1.0
Min–Max	0–9	0–3	0–2
<i>P</i> -value ¹⁾		0.049	0.031

¹⁾Wilcoxon 2-sample test (Comparisons between the placebo group and each dexmedetomidine group).

(2) Analysis by surgery/medical procedure type

The proportion of the patients not requiring rescue administration of propofol during administration of the study drug, the frequency of rescue propofol during administration of the study drug, and the percentage of time spent in OAA/S score ≤ 4 during administration of the study drug by type of surgery/procedure in FAS are shown in Tables S7, S8, and S9, respectively.

For these endpoints, the efficacy was significantly higher in the 0.5 µg/kg and 1.0 µg/kg groups for any type of the operations/procedures compared to the placebo group.

The proportion of the patients not requiring rescue fentanyl administration during administration of the study drug and the frequency of rescue fentanyl during

administration of the study drug according to type of surgery/procedure in FAS are shown in Tables S10 and S11, respectively.

For these endpoints, the efficacy in Type 2 was lower than that in other types. In the patients undergoing catheter ablation, it was a must to administer fentanyl within 15 minutes before electrical cardioversion or ablation. It was considered that additional administration of fentanyl was more frequently performed for Type 2 including such patients compared to the other types.

Table S7. Proportion of patients who did not require rescue propofol according to surgery/procedure types during the study drug administration (FAS)

	Placebo	DEX 0.5	DEX 1.0
Type 1	<i>n</i> = 18	<i>n</i> = 20	<i>n</i> = 21
No rescue propofol	0	9 (45.0)	10 (47.6)
With rescue propofol	18 (100.0)	11 (55.0)	11 (52.4)
<i>P</i> -value ¹⁾		0.001	< 0.001
Type 2	<i>n</i> = 18	<i>n</i> = 17	<i>n</i> = 18
No rescue propofol	0	10 (58.8)	11 (61.1)
With rescue propofol	18 (100.0)	7 (41.2)	7 (38.9)
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Type 3	<i>n</i> = 17	<i>n</i> = 16	<i>n</i> = 17
No rescue propofol	1 (5.9)	9 (56.3)	11 (64.7)
With rescue propofol	16 (94.1)	7 (43.8)	6 (35.3)
<i>P</i> -value ¹⁾		0.002	< 0.001

n (%). Type 1: Orthopedic, otorhinolaryngologic and oral surgeries. Type 2: Plastic surgery, excision of lesion, breast biopsy and catheter ablation. Type 3: Arteriovenous fistula, arteriovenous shunt and vascular stent. ¹⁾ χ^2 test (comparisons between the placebo group and each dexmedetomidine group).

Table S8. Administration frequency of rescue propofol (mg/kg) according to surgery/procedure types during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Type 1	<i>n</i> = 18	<i>n</i> = 20	<i>n</i> = 21
Mean \pm SD	10.7 \pm 7.0	2.1 \pm 2.4	1.1 \pm 1.3
Median	9.5	1.0	1.0
Q1–Q3	5.0–14.0	0.0–4.0	0.0–2.0
Min–Max	2–25	0–7	0–4
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Type 2	<i>n</i> = 18	<i>n</i> = 17	<i>n</i> = 18
Mean \pm SD	12.9 \pm 8.1	1.6 \pm 3.9	0.7 \pm 1.4
Median	11.0	0.0	0.0
Q1–Q3	6.0–17.0	0.0–2.0	0.0–1.0
Min–Max	3–30	0–16	0–6
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Type 3	<i>n</i> = 17	<i>n</i> = 16	<i>n</i> = 17
Mean \pm SD	9.5 \pm 5.2	0.8 \pm 1.2	0.6 \pm 1.0
Median	9.0	0.0	0.0
Q1–Q3	6.0–13.0	0.0–1.5	0.0–1.0
Min–Max	0–18	0–4	0–3
<i>P</i> -value ¹⁾		< 0.001	< 0.001

Type 1: Orthopedic, otorhinolaryngologic and oral surgeries. Type 2: Plastic surgery, excision of lesion, breast biopsy and catheter ablation. Type 3: Arteriovenous fistula, arteriovenous shunt and vascular stent. ¹⁾Wilcoxon 2-sample test (comparisons between the placebo group and each dexmedetomidine group).

Table S9. Percentage of time spent in OAA/S score ≤ 4 according to surgery/procedure types during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Type 1	<i>n</i> = 18	<i>n</i> = 20	<i>n</i> = 21
Mean \pm SD	31.96 \pm 19.58	66.56 \pm 21.45	70.18 \pm 16.21
Median	27.95	71.90	76.90
Q1–Q3	24.10–37.50	52.85–80.00	63.00–82.40
Min–Max	0.0–83.8	26.2–95.1	26.8–88.9
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Type 2	<i>n</i> = 18	<i>n</i> = 17	<i>n</i> = 18
Mean \pm SD	30.35 \pm 16.08	71.83 \pm 14.54	69.60 \pm 17.36
Median	27.05	70.90	68.05
Q1–Q3	20.60–46.30	59.20–84.00	55.20–85.20
Min–Max	5.6–62.8	49.0–92.2	31.3–92.0
<i>P</i> -value ¹⁾		< 0.001	< 0.001
Type 3	<i>n</i> = 17	<i>n</i> = 16	<i>n</i> = 17
Mean \pm SD	52.35 \pm 17.10	77.30 \pm 15.22	78.74 \pm 14.68
Median	59.50	80.45	82.5
Q1–Q3	39.70–61.90	66.35–89.15	78.30–87.70
Min–Max	20.8–83.4	45.5–96.0	50.0–94.5
<i>P</i> -value ¹⁾		< 0.001	< 0.001

Type 1: Orthopedic, otorhinolaryngologic and oral surgeries. Type 2: Plastic surgery, excision of lesion, breast biopsy and catheter ablation. Type 3: Arteriovenous fistula, arteriovenous shunt and vascular stent. ¹⁾Wilcoxon 2-sample test (comparisons between the placebo group and each dexmedetomidine group).

Table S10. Percentage of patients who did not require rescue fentanyl according to surgery/procedure types during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Type 1	<i>n</i> = 18	<i>n</i> = 20	<i>n</i> = 21
No rescue fentanyl	13 (72.2)	18 (90.0)	19 (90.5)
With rescue fentanyl	5 (27.8)	2 (10.0)	2 (9.5)
<i>P</i> -value ¹⁾		0.222	0.215
Type 2	<i>n</i> = 18	<i>n</i> = 17	<i>n</i> = 18
No rescue fentanyl	7 (38.9)	9 (52.9)	7 (38.9)
With rescue fentanyl	11 (61.1)	8 (47.1)	11 (61.1)
<i>P</i> -value ¹⁾		0.505	> 0.999
Type 3	<i>n</i> = 17	<i>n</i> = 16	<i>n</i> = 17
No rescue fentanyl	10 (58.8)	13 (81.3)	14 (82.4)
With rescue fentanyl	7 (41.2)	3 (18.8)	3 (17.6)
<i>P</i> -value ¹⁾		0.259	0.259

n (%). Type 1: Orthopedic, otorhinolaryngologic and oral surgeries. Type 2: Plastic surgery, excision of lesion, breast biopsy and catheter ablation. Type 3: Arteriovenous fistula, arteriovenous shunt and vascular stent. ¹⁾ χ^2 test (comparisons between the placebo group and each dexmedetomidine group).

Table S11. Frequency of rescue fentanyl according to surgery/procedure types during infusion of the study drug (FAS)

	Placebo	DEX 0.5	DEX 1.0
Type 1	<i>n</i> = 18	<i>n</i> = 20	<i>n</i> = 21
Mean ± SD	0.9 ± 1.8	0.1 ± 0.3	0.1 ± 0.3
Median	0.0	0.0	0.0
Q1–Q3	0.0–1.0	0.0–0.0	0.0–0.0
Min–Max	0–6	0–1	0–1
<i>P</i> -value ¹⁾		0.135	0.119
Type 2	<i>n</i> = 18	<i>n</i> = 17	<i>n</i> = 18
Mean ± SD	2.0 ± 2.4	0.8 ± 1.1	0.8 ± 1.0
Median	1.5	0.0	1.0
Q1–Q3	0.0–3.0	0.0–1.0	0.0–1.0
Min–Max	0–9	0–3	0–4
<i>P</i> -value ¹⁾		0.163	0.190
Type 3	<i>n</i> = 17	<i>n</i> = 16	<i>n</i> = 17
Mean ± SD	1.4 ± 2.2	0.3 ± 0.8	0.2 ± 0.6
Median	0.0	0.0	0.0
Q1–Q3	0.0–2.0	0.0–0.0	0.0–0.0
Min–Max	0–8	0–3	0–2
<i>P</i> -value ¹⁾		0.116	0.079

Type 1: Orthopedic, otorhinolaryngologic and oral surgeries. Type 2: Plastic surgery, excision of lesion, breast biopsy and catheter ablation. Type 3: Arteriovenous fistula, arteriovenous shunt and vascular stent. ¹⁾Wilcoxon 2-sample test (comparisons between the placebo group and each dexmedetomidine group).