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Evaluation of the Hypnotic and Hemodynamic Effects of Dexmedetomidine on Propofol-Sedated Swine

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Abstract: This study examined the sedative effect of, and hemodynamic response to dexmedetomidine administration in propofol-sedated swine. Sixteen swine were subjects. After anesthetic induction and preparation, the propofol infusion rate was adjusted to maintain a bispectral index (BIS) value between 55 and 65 (i.e., baseline). With the propofol infusion rate fixed at the baseline rate, dexmedetomidine was infused continuously at a rate of 0.2, 0.4, and 0.7 μg·kg^{-1}·h^{-1} for one hour at each rate. The BIS value and hemodynamic parameters were recorded at each step. Dexmedetomidine decreased the BIS value, mean arterial blood pressure, heart rate, cardiac output, and mixed venous oxygen saturation in a dose-dependent manner. The systemic vascular resistance (SVR) did not change, but the pulmonary vascular resistance (PVR) increased. Oxygen delivery ($\dot{D}O_2$) and oxygen consumption ($\dot{V}O_2$) decreased. A small dose of dexmedetomidine (0.2 μg·kg^{-1}·h^{-1}) greatly enhanced the sedative effects of propofol with only small changes in hemodynamics and systemic oxygen balance, suggesting it may be useful in reducing the propofol dose requirement. However, dexmedetomidine 0.4 μg·kg^{-1}·h^{-1} suppressed cardiac contractility, and 0.7 μg·kg^{-1}·h^{-1} induced hemodynamic instability and further systemic oxygen imbalance while the additional sedative effect was limited. A lower dose of dexmedetomidine may be recommended when using it in combination with propofol.

Key words: dexmedetomidine, propofol, swine

Introduction

Propofol is an intravenous anesthetic agent that provides good control of anesthetic depth. It also has the advantages of rapid onset and recovery [35]. However, it cannot be used alone for anesthesia because it lacks analgesic potency. Previous studies have reported the usefulness of combining it with other sedative or analgesic drugs [15, 31, 33].

α-Agonist drugs have been investigated as sedative agents or as an anesthetic adjuvant [6, 11, 17, 26, 30, 38, 40]. Dexmedetomidine is a hypnotic drug with a high selectivity for the α$_2$-adrenergic receptor, and is commonly used in intensive care. Its advantages are little respiratory suppression, quality of sedation, anti-delirium, anti-agitation, and anesthetic and analgesic-sparing effects [16, 29, 34]. It has also been reported that dexmedetomidine provides protection for organs such as the

brain, heart, and kidney [4, 21, 24, 27]. However, dexmedetomidine can have a contrasting impact on hemodynamics since it non-selectively stimulates the α_{2A}- and α_{2B}-adrenoceptors [5, 8]. Low doses of dexmedetomidine produce hypotension due to α_{2A}-adrenoceptor stimulation in the autonomic nervous system [22, 23]. High doses of dexmedetomidine produce hypertension due to vasoconstriction resulting from stimulation of the α_{2B}-adrenoceptors located on smooth muscle cells in the blood vessels [22]. In most previous studies evaluating the usefulness of dexmedetomidine for anesthesia, dexmedetomidine was administered in a bolus as an anesthetic adjuvant. The effects of continuously-infused dexmedetomidine with other drugs remain unknown.

The present study examined the sedative effect, hemodynamic changes, and cardiovascular responses resulting from dexmedetomidine administration during propofol sedation in swine.

Materials and Methods

Animal preparation

The Institutional Ethics Committee (Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan) approved this study. Sixteen male domesticated swine were subjects. They were aged 3 to 4 months and weighed 36.4 ± 1.4 kg (the mean weight ± the standard deviation [SD]). Pre-anesthetic medications were not administered. Anesthesia was induced by 5% isoflurane inhaled in oxygen at 6 l·min^{-1} with a standard animal mask. After anesthetic induction, the swine were placed in a supine position. Mechanical ventilation was initiated following a tracheostomy. The ventilator was adjusted to maintain an end-tidal CO_2 level between 35 and 45 mm Hg. Maintenance anesthesia was performed by isoflurane inhalation (2.5–3.0%) with a mixture of oxygen and air (oxygen, 3 l·min^{-1}; air, 3 l·min^{-1}). A quad lumen central venous catheter (8.5 Fr., 20 cm, Arrow Japan, Tokyo, Japan) and a pulmonary artery catheter (Opti Q® 8 Fr., Abbott Japan, Tokyo, Japan) were inserted into the right external jugular vein with an open technic for fluid maintenance and drug administration, and for measuring central venous pressure (CVP), mean pulmonary artery pressure (mPAP), pulmonary arterial wedge pressure (PAWP), cardiac

output (CO) and mixed venous oxygen saturation ($S\bar{v}O_2$). A 20-gauge arterial catheter was inserted into the left femoral artery for monitoring the mean arterial blood pressure (mABP) and collecting blood samples. The bispectral index (BIS) was used to evaluate the sedative depth. Electroencephalographic (EEG) monitoring was accomplished by preparing the skin over the frontoccipital regions bilaterally and positioning four cutaneous electrodes (Zipprep, Aspect Medical Systems, Inc., Newton, MA, USA) [14, 20]. Four channels of the EEG were amplified and digitally recorded using the Aspect A-1000® electroencephalographic monitor (algorithm rev. 3.22 software, two-channel referential lead; Aspect Medical Systems, Inc., Newton, MA, USA). Vecuronium bromide at a rate of 5–10 mg·kg^{-1}·h^{-1} was infused continuously during the study to eliminate the influence of any electromyographic activity on BIS monitoring.

Experimental protocol

After the animal was prepared, Ringer's lactate solution was administered at a rate of 100 ml·h^{-1} during the experiment. Propofol (2% propofol Maruishi®, Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) was administered in a 2 mg·kg^{-1} bolus, followed by a continuous infusion of 20 mg·kg^{-1}·h^{-1}. Data obtained from a previous study was used to determine the infusion rate [20]. The administration of inhaled isoflurane was discontinued with the initiation of propofol. An end-expiratory concentration of isoflurane of less than 0.2% confirmed the clearance of isoflurane. When necessary, the propofol infusion rate was adjusted by 0.5 mg·kg^{-1}·h^{-1} every 15 min to maintain the BIS value between 55 and 65. When the BIS value remained steady, the infusion rate of propofol was fixed. After 30 min, we recorded the BIS value, mABP, CVP, mPAP, PAWP, heart rate (HR), CO, and $S\bar{v}O_2$ and collected a blood sample. This established the baseline values of these factors. To measure the CO, we injected the swine with 5 ml frozen glucose liquid three times, and then recorded the mean value.

The experimental protocol is shown in Fig. 1. After the baseline measurement, we initiated dexmedetomidine infusion while maintaining propofol at its baseline infusion rate. After administering 1 μg·kg^{-1} of dexmedetomidine (Precedex®, Maruishi Pharmaceutical Co., Ltd.)
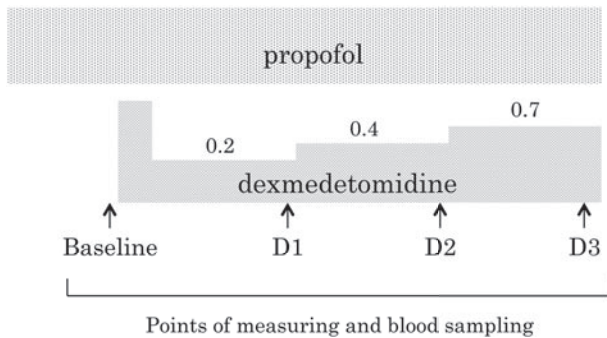
Fig. 1. Outline of the study design. Propofol infusion rate was adjusted aiming at a BIS value of 55–56 at baseline. After loading, constant infusion of dexmedetomidine was started at 0.2 μg·kg^{-1}·h^{-1} and stepped up to 0.4 and 0.7 μg·kg^{-1}·h^{-1} at one-hour intervals.

for ten minutes (i.e., a dose of 6 μg·kg^{-1}· h^{-1}), we initiated a continuous infusion of dexmedetomidine at 0.2 μg·kg^{-1}·h^{-1} while maintaining propofol at its baseline infusion rate. One hour after infusing dexmedetomidine at 0.2 μg·kg^{-1}·h^{-1}, we recorded the BIS value, mABP, CVP, mPAP, PAWP, HR, CO, and S$\bar{\text{v}}$O$_2$ and collected a blood sample (D1). The infusion rate of dexmedetomidine was then increased to 0.4 μg·kg^{-1}·h^{-1} (D2). One hour later, it was increased to 0.7 μg·kg^{-1}·h^{-1} (D3). At D2 and D3, we recorded the BIS value and hemodynamic parameters and collected a blood sample.

Stroke volume (SV), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated from hemodynamic parameters. Systemic oxygen delivery ($\dot{\text{D}}$O$_2$) and oxygen consumption ($\dot{\text{V}}$O$_2$) were calculated using the following formulas:

$\dot{\text{D}}$O$_2$ = CaO$_2$·CO·BW^{-1}·10 (ml·min^{-1}·kg^{-1})

$\dot{\text{V}}$O$_2$ = (CaO$_2$ – C$\bar{\text{v}}$O$_2$)·CO·BW^{-1}·10 (ml·min^{-1}·kg^{-1})

(CaO$_2$: arterial oxygen content, C$\bar{\text{v}}$O$_2$: mixed venous oxygen content).

Blood samples were centrifuged at 5,000 rpm for 15 min immediately after collection. The plasma was cryopreserved at –80°C and used later for measuring the concentrations of propofol and dexmedetomidine. High-performance liquid chromatography (TQC Quantum Ultra®, Thermo Fisher Scientific K.K., Yokohama, Japan) was used to measure the plasma concentrations of dexmedetomidine and propofol.

Statistical analysis

Based on a pilot study, a sample size of 16 is expected to have 80% power in detecting a 10 mmHg difference in mABP at a significance level of 5%. A one-way analysis of variance of repeated measures compared the sedative, hemodynamic, cardiovascular parameters, and calculated variables. The Fisher's protected-least-significant-difference test was used as a post hoc multiple comparison procedure when significance was found. The results are expressed as the mean ± SD. A *P* value of less than 0.05 was considered significant.

Results

The constant infusion rate of propofol at baseline was 18.5 ± 2.1 mg·kg^{-1}·h^{-1}. It took 148 ± 25 min to start the baseline measurement after initiating propofol. The BIS value at baseline was 57 ± 2. The depth of sedation and the hemodynamic variables are shown in Table 1.

The BIS value decreased with dexmedetomidine infusion in a dose-dependent manner. The mABP and HR decreased significantly with dexmedetomidine administration. CVP increased significantly at D3. mPAP decreased at D1. In comparison with its baseline value, PAWP increased significantly at D1, D2, and D3. Dexmedetomidine infusion decreased CO and S$\bar{\text{v}}$O$_2$ in a dose-dependent manner. Stroke volume (SV) decreased significantly at D2 and D3, compared with its baseline value. Dexmedetomidine infusion did not change the SVR. However, the PVR increased significantly at D2 and D3, compared with its baseline level. $\dot{\text{D}}$O$_2$ and $\dot{\text{V}}$O$_2$ decreased but the O$_2$ extraction ratio increased with dexmedetomidine administration in a dose-dependent manner (Table 2). The plasma concentrations of propofol and dexmedetomidine are shown in Table 3.

Discussion

In the present study, a small dose of dexmedetomidine (0.2 μg·kg^{-1}·h^{-1}) decreased the BIS value greatly from 57 ± 3 to 18 ± 8. This suggests that a small dose of dexmedetomidine sufficiently enhances the sedative effect of propofol. However, the decrease in the BIS value was not as large when dexmedetomidine was infused at 0.4 or 0.7 μg·kg^{-1}·h^{-1}. Previous studies have

Table 1. Hypnotic, hemodynamic, and cardiovascular variables

	Baseline	D1	D2	D3
BIS value	57 ± 3	18 ± 8*	14 ± 3*†	11 ± 7*†
mABP (mmHg)	92 ± 8	70 ± 12*	66 ± 12*	61 ± 12*†
CVP (mmHg)	5 ± 1	5 ± 1	6 ± 2	6 ± 1*
mPAP (mmHg)	18 ± 2	17 ± 2*	17 ± 2	18 ± 2
PAWP (mmHg)	7 ± 1	8 ± 2*	8 ± 2*	8 ± 2*
HR (bpm)	131 ± 18	93 ± 9*	90 ± 9*	85 ± 8*†
CO ($l \cdot min^{-1}$)	6.4 ± 0.9	4.6 ± 0.9*	4.1 ± 0.9*†	3.9 ± 0.8*†
S$\bar{v}$O$_2$ (%)	73 ± 9	63 ± 10*	62 ± 10*	58 ± 10*†‡
SV (ml)	50 ± 11	49 ± 12	46 ± 13*†	46 ± 12*
SVR (dynes·s·cm^{-5})	$1,111 \pm 212$	$1,165 \pm 287$	$1,220 \pm 294$	$1,160 \pm 265$
PVR (dynes·s·cm^{-5})	139 ± 37	155 ± 53	211 ± 130*†	225 ± 123*†

Values are expressed as the mean ± SD. *: $P<0.05$, vs. baseline; †: $P<0.05$, vs. D1; ‡: $P<0.05$, vs. D2. BIS: bispectral index; mABP: mean arterial blood pressure; CVP: central venous pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; HR: heart rate; CO: cardiac output; S$\bar{v}$O$_2$: venous oxygen saturation; SV: stroke volume; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance.

Table 2. Systemic oxygen delivery and consumption

	Baseline	D1	D2	D3
$\dot{D}O_2$ (ml·min^{-1}·kg^{-1})	24.4 ± 4.2	17.3 ± 3.7*	15.5 ± 3.9*	14.8 ± 3.6*†
$\dot{V}O_2$ (ml·min^{-1}·kg^{-1})	7.2 ± 2.4	6.6 ± 1.3	6.1 ± 1.2*	6.2 ± 1.2*
O$_2$ extraction ratio (%)	29.4 ± 8.5	39.3 ± 9.0*	40.6 ± 9.4*	43.6 ± 9.4*†‡
C(a-$\bar{v}$)O$_2$ (ml·dl^{-1})	4.1 ± 1.2	5.4 ± 1.4*	5.6 ± 1.4*	6.0 ± 1.6*†‡

Values are expressed as the mean ± SD. *: $P<0.05$, vs. baseline; †: $P<0.05$, vs. D1; ‡: $P<0.05$, vs. D2. $\dot{D}O_2$: oxygen delivery; $\dot{V}O_2$: oxygen consumption; C(a-$\bar{v}$)O$_2$: arteriovenous oxygen content difference. $\dot{D}O_2 = CaO_2 \cdot CO \cdot BW^{-1} \cdot 10$ (ml·min^{-1}·kg^{-1}); $\dot{V}O_2 = (CaO_2 - C\bar{v}O_2) \cdot CO \cdot BW^{-1} \cdot 10$ (ml·min^{-1}·kg^{-1}). CaO$_2$: arterial oxygen content; CaO$_2$ = SaO$_2$·Hb·1.34 + PaO$_2$·0.0031 (ml·dl^{-1}). C$\bar{v}$O$_2$: mixed venous oxygen content; C$\bar{v}$O$_2$ = S$\bar{v}$O$_2$·Hb·1.34 + P$\bar{v}$O$_2$·0.0031 (ml·dl^{-1}). O$_2$ extraction ratio = $\dot{V}O_2 \cdot \dot{D}O_2^{-1}$ (%); C(a-$\bar{v}$)O$_2$ = CaO$_2$ − C$\bar{v}$O$_2$ (ml·dl^{-1}).

Table 3. Plasma concentrations of propofol and dexmedetomidine

	Baseline	D1	D2	D3
Propofol (μg·ml^{-1})	7.06 ± 0.94	7.87 ± 1.22*	8.12 ± 1.21*	8.37 ± 1.39*
Dexmedetomidine (ng·ml^{-1})	0	0.13 ± 0.04*	0.19 ± 0.05*†‡	0.34 ± 0.09*†‡

Values are expressed as the mean ± SD. *: $P<0.05$, vs. baseline; †: $P<0.05$, vs. D1; ‡: $P<0.05$, vs. D2.

shown that the sedative effect of dexmedetomidine declines, even if its infusion dose is increased [12, 42]. Hall *et al*. reported that a decrease of the BIS value with dexmedetomidine infusion at a dose of either 0.2 or 0.6 μg·kg^{-1}·h^{-1} was similar in a human study [12]. From the results of Hall's study and our study, we surmise that a ceiling effect may show in dexmedetomidine sedation.

In the present study, the PVR increased with dexmedetomidine administration, whereas SVR did not change significantly. Talke *et al*. [37] reported that dexmedetomidine infusion resulted in constriction of the peripheral blood vessels and an increase in arterial blood pressure in human subjects anesthetized with propofol, alfentanil, and nitrous oxide. In our study, we observed the same response in the pulmonary blood vessels at D2 and D3. It may be that, after anesthesia has decreased

sympathetic nervous system activity, dexmedetomidine-induced vasoconstriction via the α_{2B}-adrenoceptors can predominate without sympatholytic interference from the α_{2A}-adrenoceptors. Our subjects' systemic vascular response differs from that of Talke's findings. We speculate that the difference in sympathetic nervous system activity and systemic vascular tone was already present before dexmedetomidine infusion and may have influenced our results to some extent.

In our study, systemic and pulmonary blood vessel responses differed. The mechanism for this is not clear. At D2 and D3, the plasma concentrations of propofol were slightly higher than that of baseline. Previous studies reported that propofol induced pulmonary vasoconstriction when vasomotor tone was increased with phenylephrine [9, 18, 25]. The authors of those reports concluded that phenylephrine produced prostacyclin and propofol suppressed this prostacyclin production. It was also reported that prostacyclin production was induced via α_1-adrenoceptor activation [43]. Therefore, we speculate that dexmedetomidine might also suppress prostacyclin production, because dexmedetomidine decreases plasma norepinephrine concentration [5, 8]. However, α_1 agonist-induced prostacyclin production was also observed in systemic arteries [28, 36]. It is uncertain whether suppression of prostacyclin production selectively occurred in pulmonary blood vessels in our study. However, from our results, the combined administration of propofol and dexmedetomidine may specifically stimulate pulmonary vasoconstriction.

The decrease in CO mainly resulted from a decrease in HR. SV decreased with dexmedetomidine at an infusion rate of $0.4~\mu g \cdot kg^{-1} \cdot h^{-1}$ or more. In a previous study using the isolated ventricular myocardium of ferrets, dexmedetomidine did not have any direct effects on cardiac contractility [13]. In another study, a decrease in SV was observed only at high plasma concentrations in human volunteers infused with dexmedetomidine [8]. Our results indicate that even moderate doses of dexmedetomidine in combination with propofol can decrease cardiac contractility.

Dexmedetomidine decreased the $S\bar{v}O_2$ and impaired systemic oxygen supply/demand balance in a dose-dependent manner. In a normal organ, a decrease in oxygen delivery does not lower oxygen consumption because O_2 extraction increases proportionately. When delivery falls below a critical threshold, consumption falls since O_2 extraction exceeds a critical threshold and cannot compensate for the reduction in delivery [32]. Impaired oxygen balance may induce adverse effects such as impairment in organ function.

Our study had some limitations. First, the plasma concentration of propofol increased from 7.06 ± 0.94 $\mu g \cdot ml^{-1}$ at baseline to $8.37 \pm 1.39~\mu g \cdot ml^{-1}$ at D3, although the constant infusion rate of propofol had been determined after the baseline measurement. A previous study reported that such small differences in plasma concentrations of propofol did not affect hemodynamics and cardiac function [7]. To our knowledge, there is no evidence that dexmedetomidine directly affects propofol plasma concentration, but there is a possibility that a decrease in CO delays the elimination of propofol [19].

Secondly, we used BIS monitoring to evaluate the depth of sedation. A linear correlation of BIS with propofol effect-site concentration was confirmed in a previous swine study [20]. However, there is no report of the usefulness of BIS monitoring in a dexmedetomidine-infused animal model. In human clinical studies, BIS monitoring is used to evaluate the sedation level in patients administered dexmedetomidine [1–3, 10, 39, 41]. Therefore, we infer that BIS monitoring is reliable in evaluating the sedative effect of dexmedetomidine.

In conclusion, a small dose of dexmedetomidine (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) greatly enhanced the sedative effects of propofol with only small changes in hemodynamics and systemic oxygen balance and may be useful in reducing propofol dose requirements. However, dexmedetomidine $0.4~\mu g \cdot kg^{-1} \cdot h^{-1}$ suppressed cardiac contractility, and $0.7~\mu g \cdot kg^{-1} \cdot h^{-1}$ induced hemodynamic instability and further systemic oxygen imbalance while the additional sedative effect was limited. When dexmedetomidine is used in combination with propofol, a lower dose of dexmedetomidine may be recommended.

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