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[Original Article]

**THE EFFECT OF OBESITY ON DOSE OF DEXMEDETOMIDINE
WHEN ADMINISTERED WITH FENTANYL DURING POSTOPERATIVE
MECHANICAL VENTILATION - RETROSPECTIVE**

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Abstract : We carried out a retrospective investigation on the effect of obesity on dexmedetomidine (DEX) requirements when administered with fentanyl (FEN) during mechanical ventilation after major surgeries. After Institutional Review Board approval, 14 obese patients with a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ and the same number of non-obese patients with similar backgrounds to the obese patients were selected from medical records. Doses of DEX in the first 48 h or until the end of sedation or extubation were calculated for comparison. In addition to comparison of dosing between the groups, associations between total body weight (TBW), BMI, and lean body mass (LBM) values and doses of DEX (mcg/h), between BMI and various indices (i.e., amount per TBW per hour and amount per LBM per hour) of DEX doses, and between above indices of DEX and FEN doses were also examined. There were no significant differences in DEX dose indices between the groups. However, DEX requirements (mcg/h) were significantly increased with TBW (kg) ($r = 0.51, P = 0.003$), BMI ($r = 0.49, P = 0.006$) and LBM (kg) ($r = 0.42, P = 0.02$), which might have enhanced the DEX metabolism with physiological changes with obesity. These findings will be beneficial for future clinical pharmacological analysis of DEX.

Key words : dexmedetomidine, pharmacokinetics, postoperative, mechanical ventilation, obesity

INTRODUCTION

Dexmedetomidine (DEX) is a highly selective Alpha 2-adrenoceptor agonist with sedative and analgesic effects, which is administered intravenously in the perioperative period. It is recommended that DEX is initiated with a loading dose of 6 mcg/kg/h over 10 to 15 minutes and titrated over a dose range of 0.2 to 0.7 mcg/kg/h based on the total body weight (TBW) of patients. However, in many anes-

thetic agents, obese patients do not require as large a dose as that calculated by TBW¹⁻³⁾ and some types of body weight indices such as lean body mass (LBM) are often used as dosing scalars to calculate administration doses for such patients⁴⁾. Until now, sophisticated pharmacokinetic analysis of DEX and its necessary amount in obese patients when administered with fentanyl (FEN) during postoperative mechanical ventilation have not been well investigated.

In this study, as a preliminary investigation for future pharmacokinetic analyses of DEX, the effect of obesity on DEX requirements when administered with FEN was studied retrospectively.

MATERIALS AND METHODS

The study obtained hospital Institutional Review Board approval and was registered as a UMIN-CTR clinical trial (UMIN000012466). Patients with American Society of Anesthesiologists (ASA) physical status 1 to 3, aged 18–80 years old, had a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ and received DEX and FEN during mechanical ventilation after elective major surgeries between January 2011 and July 2013, were selected as an obese group. The same number of patients, whose background including age-group and sex were matched to those in the obese group and whose BMI was $< 30 \text{ kg/m}^2$, were randomly selected as a non-obese group. The exclusion criteria included patients with history of neuropsychiatric disorder, brain surgery, psychotropic drug usage, preoperative disturbance of consciousness, or hepatectomy, patients with brain injuries that were later identified, and patients with prolonged intra- or postoperative shock and did not respond to treatment.

Total doses of DEX and FEN between the initiation and the time point when sedation was terminated or the patient's trachea was extubated within 48 h, or during the first 48 h when sedation was pro-

longed further, were extracted from medical records. DEX and FEN were titrated according to protocols mainly by nursing staff as below :

Protocol : The initial and maximum doses of DEX were decided by attending anesthesiologists or intensivists. Nursing staff then titrated DEX dose to maintain patients in the target sedation range ; Richmond Agitation and Sedation Scale⁵⁾ 0 to -1 (i.e., alert and calm to drowsy) and -2 to -3 (i.e., light to moderate sedation) during daytime and nighttime, respectively. FEN was also titrated to the Numeric Rating Scale for pain less than or equal to 3 (0 as no pain and 10 as most severe pain).

Indices of DEX and FEN doses, including ; 1) amount per hour (mcg/h), 2) amount per TBW per hour (mcg/kg/h), and 3) amount per LBM⁶⁾ per hour (mcg/LBM/h) were analyzed.

Janmahasatian's equation for LBM⁶⁾

Male :

$$(9.27 \times 10^3 \times \text{TBW}) / (6.68 \times 10^3 + 216 \times \text{BMI})$$

Female :

$$(9.27 \times 10^3 \times \text{TBW}) / (8.78 \times 10^3 + 244 \times \text{BMI})$$

To investigate the confounding effects, the relationships between age, infusion duration and doses of DEX and FEN were also evaluated.

Statistical Analysis

Student *t* tests, Welch *t* tests, or Fisher's exact tests were used to compare the data between the groups. Based on the data from the two groups, correlation analysis was used to examine associa-

Table 1

| | Non-obese | Obese | P values |
|---|-------------|--------------|----------|
| Age (yr) | 55.5 (9.5) | 55.6 (11.7) | 0.972 |
| Male / Female (<i>n</i>) | 10 / 4 | 10 / 4 | 1.000 |
| ASA I / II / III (<i>n</i>) | 1 / 2 / 11 | 0 / 4 / 9 | 0.510 |
| Height (cm) | 164.4 (9.1) | 165.4 (10.5) | 0.799 |
| Body weight (kg) | 62.3 (11.8) | 96.0 (24.2) | < 0.001* |
| BMI (kg/m^2) | 22.9 (3.4) | 34.8 (5.8) | < 0.001* |
| Procedures Cardiovascular / Others (<i>n</i>) | 10 / 4 | 9 / 5 | 1.000 |
| DEX infusion duration (h) | 20.7 (13.0) | 27.0 (16.8) | 0.274 |
| FEN infusion duration (h) | 20.8 (12.3) | 27.3 (16.7) | 0.249 |
| DEX dose (mcg/h) | 27.8 (8.4) | 34.3 (17.3) | 0.227 |
| FEN dose (mcg/h) | 44.8 (8.9) | 60.4 (20.9) | 0.020* |
| DEX dose (mcg/kg/h) | 0.46 (0.14) | 0.36 (0.15) | 0.077 |
| FEN dose (mcg/kg/h) | 0.74 (0.22) | 0.65 (0.24) | 0.336 |
| DEX dose (mcg/LBM/h) | 0.57 (0.17) | 0.55 (0.23) | 0.760 |
| FEN dose (mcg/LBM/h) | 0.93 (0.24) | 0.99 (0.35) | 0.575 |

Data were presented as mean (standard deviation). *, $P < 0.05$. ASA : American Society of Anesthesiologists physical status. DEX : dexmedetomidine, FEN : fentanyl, LBM : Janmahasatian's equation for Lean Body Mass

tions between values of TBW and doses of DEX and FEN, between BMI and doses of DEX and FEN, between values of LBM and doses of DEX and FEN, between BMI and the two indices (2 and 3) of DEX and FEN doses, and between the three indices of DEX and FEN doses. Pearson's correlation coefficients were calculated. $P < 0.05$ was considered statistically significant. R (version 2.13.0, the R foundation for Statistical Computing) was used for statistical analysis.

RESULTS

The demographic data, indices of DEX and FEN doses in obese and non-obese groups are shown in Table 1. Both groups comprised of 14 patients. There were significant differences in TBW and BMI between the groups. There was no difference in infusion durations of DEX and FEN between the groups. There were no significant differences in all

DEX dose indices between the groups. The FEN dose (mcg/h) was significantly larger in the obese group than in the non-obese group despite there being no differences in the other two dose indices of FEN.

Fig. 1 shows the correlation diagram between TBW and DEX amount per hour (A) and between TBW and FEN amount per hour (B). There was a significant correlation between TBW and DEX amount per hour ($r = 0.51, P = 0.003$). Fig. 2(A) and (B) show significant correlations between BMI and DEX and FEN amounts per hour ($r = 0.49, P = 0.006$ and $r = 0.434, P = 0.021$, respectively). Fig. 3(A) and (B) show significant correlations between LBM and DEX amounts per hour ($r = 0.42, P = 0.02$). However, there were no significant correlations between BMI and DEX and FEN amounts per TBW per hour (Fig. 4A and B), and between BMI and DEX and FEN amounts per LBM per hour (Fig. 4C and D). As mentioned in the methods section,

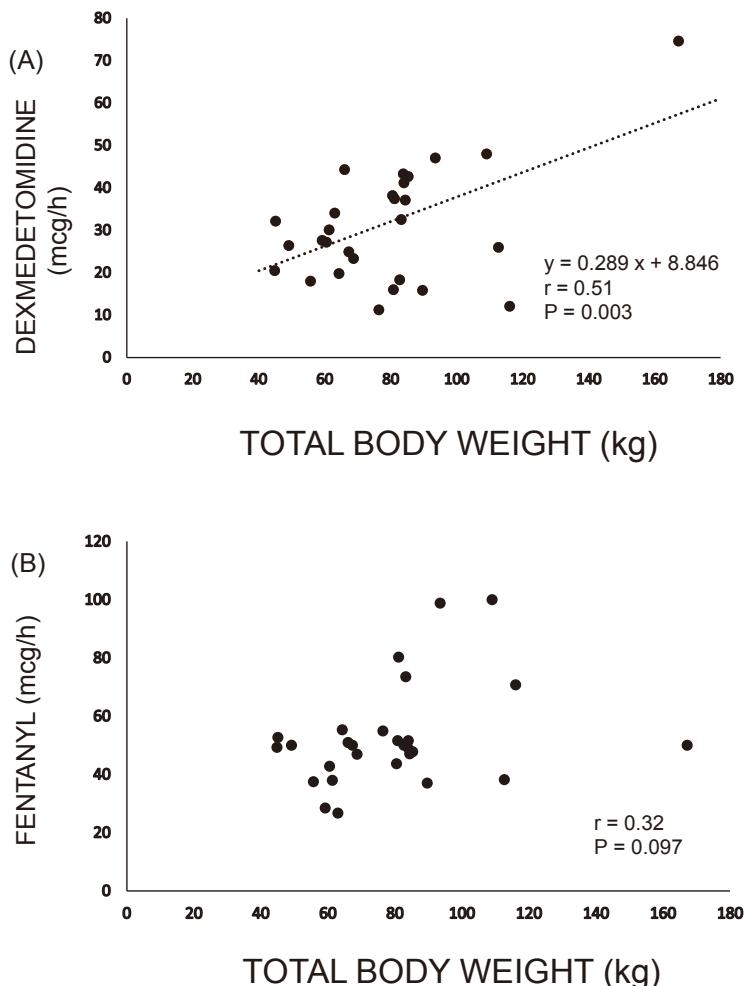


Fig. 1. Correlation diagram between TBW and DEX amount per hour (A) and between TBW and FEN amount per hour (B). All patients were analyzed together. TBW, total body weight (kg).

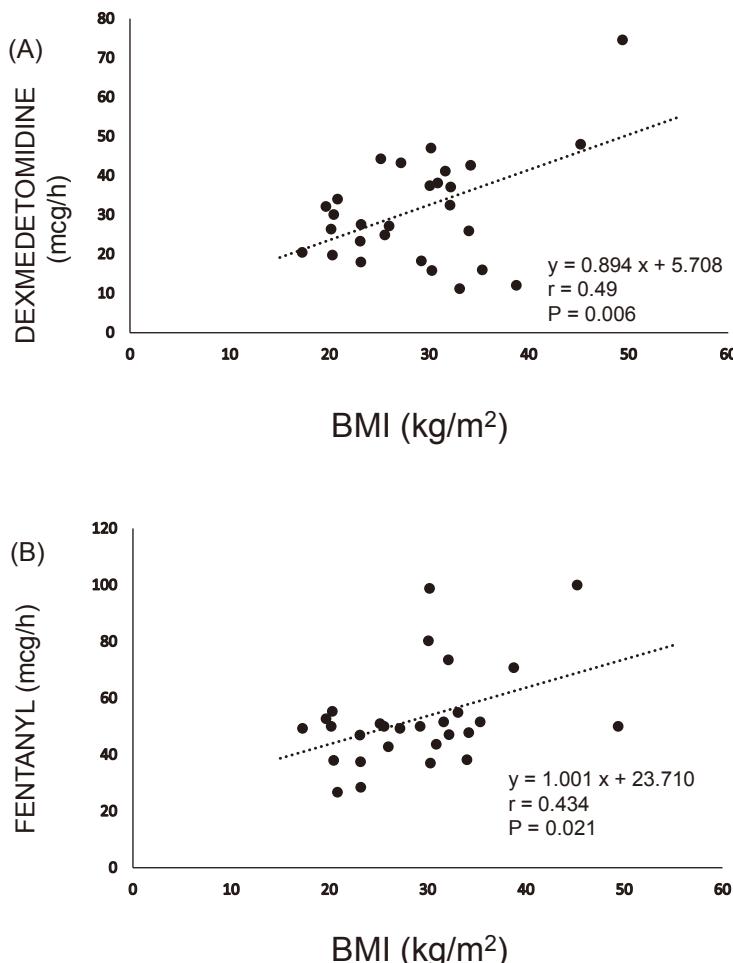


Fig. 2. Correlation diagram between BMI and DEX amount per hour (A) and between BMI and FEN amount per hour (B). All patients were analyzed together. BMI, body mass index (kg/m²).

Fig. 1 to 4 are based on the data from the two groups. Fig. 5(A), (B) and (C) show the correlation between each of the three dose indices of DEX and that of FEN. No significant correlations were observed in the control group, obese group and the combined data from the two groups.

In terms of investigation of potential confounding factors, there were no significant correlations between age, infusion duration, and indices of DEX and FEN amount (data not shown).

DISCUSSION

From the clinical viewpoint, whether the drug doses for obese patients can be calculated simply on per kg basis (i.e., double dose for double body weight) is of paramount importance. With several intravenous anesthetic drugs, such dosing regimen can cause overdose in obese patients. For example, propofol dose calculated not with TBW but with LBM is enough for anesthetic induction in high BMI

patients². FEN dose can also be reduced compared to that calculated with TBW.³ Because DEX overdosing could cause side effects including hypotension, bradycardia, or prolonged sedation due to drug accumulation, discovering an appropriate dose, schedule for administration, and dosing scalar are essential through investigating pharmacokinetics and pharmacodynamics of DEX in obese patients. As a preliminary analysis for a sophisticated pharmacological analysis, we performed a retrospective descriptive study.

The metabolism of DEX is dependent upon hepatic blood perfusion because of the high hepatic extraction ratio⁷ as with propofol. Enlarged liver mass caused by obesity⁸ results in increased hepatic blood flow and more hepatic extraction⁹, which might enhance the increased administered DEX dose associated with the increase of BMI (and its constitute TBW) in this study. Peeters et al reported that hepatic blood flow was a more predictive indicator than cardiac output for propofol clearance,

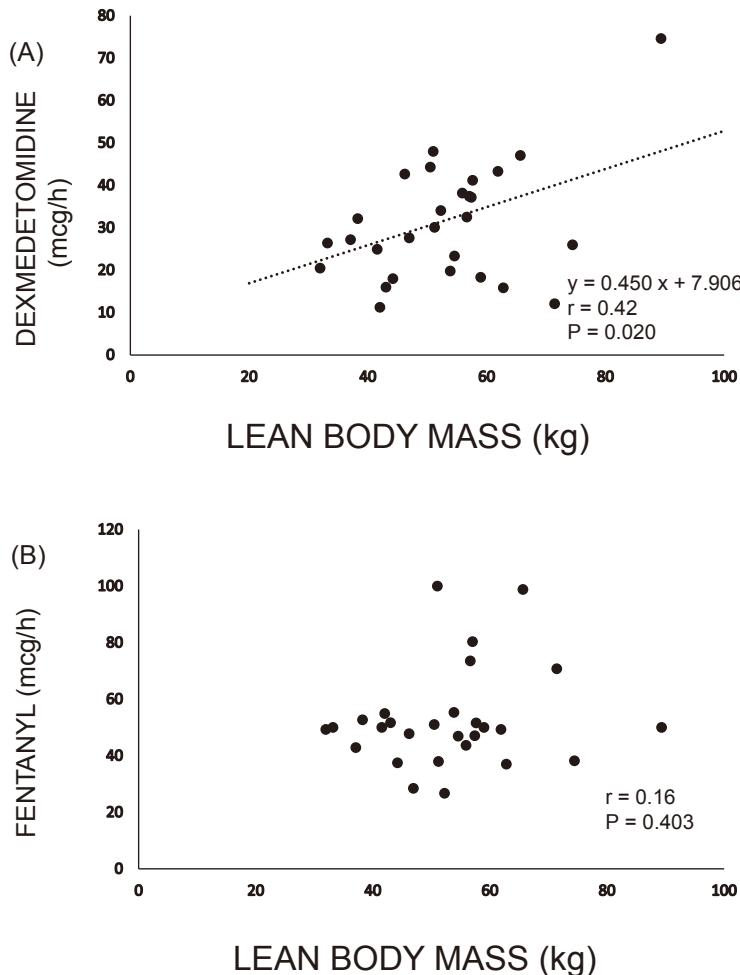


Fig. 3. Correlation diagram between LBM and DEX amount per hour (A) and between LBM and FEN amount per hour (B). All patients were analyzed together. LBM, Janmahasatian's equation for Lean Body Mass (kg).

suggesting that the results can most likely be extrapolated to other highly extracted drugs⁹⁾ like DEX, which support our prediction. Meanwhile, it is estimated that the necessary dose of drugs with high extraction ratio does not increase linearly with body weight as observed in many pharmacokinetic studies of propofol⁴⁾ and FEN³⁾ where drug clearances do not increase in direct proportion to weight. Also in our study, when administered with FEN, a non-linear requirement (i.e., double body weight does not need double dose) of DEX with regards to TBW and LBM was observed. Meanwhile, the increase in DEX amount per hour with BMI is considered to be a 'spurious correlation' because simply TBW and LBM increased with obesity (data not shown). In addition, in the BMI range in our study, the necessary dose of DEX per TBW tended to decrease with BMI increase although it was not statistically significant and the necessary dose of DEX per LBM did not change with BMI, which suggests that LBM can be one of the better options as a dosing

scalar for 'per kg' calculations of DEX than TBW.

There have been some published reports on pharmacokinetics of DEX in which body size covariates were searched. Dyck *et al* built a pharmacokinetic model of DEX which included height as a covariate for central clearance in non-obese (mean body weight of 82 kg) adult volunteers¹⁰⁾. Valitalo *et al.*¹¹⁾ performed a population pharmacokinetic analysis of DEX in critically ill patients in the intensive care unit (ICU) and found that TBW strongly correlates to clearance, and their final model included a TBW covariate on clearance. Because the formula structure that they used was based on the allometric scaling technique which is frequently used for pharmacokinetic analysis of anesthetics in obese patients¹²⁾, the increase in clearance with body weight was at an exponential rate. However, the number of obese patients included in the study was not specified in the literature. Talke *et al.*¹³⁾ also built a pharmacokinetic model of DEX in young and non-obese patients who underwent hypophysectomy

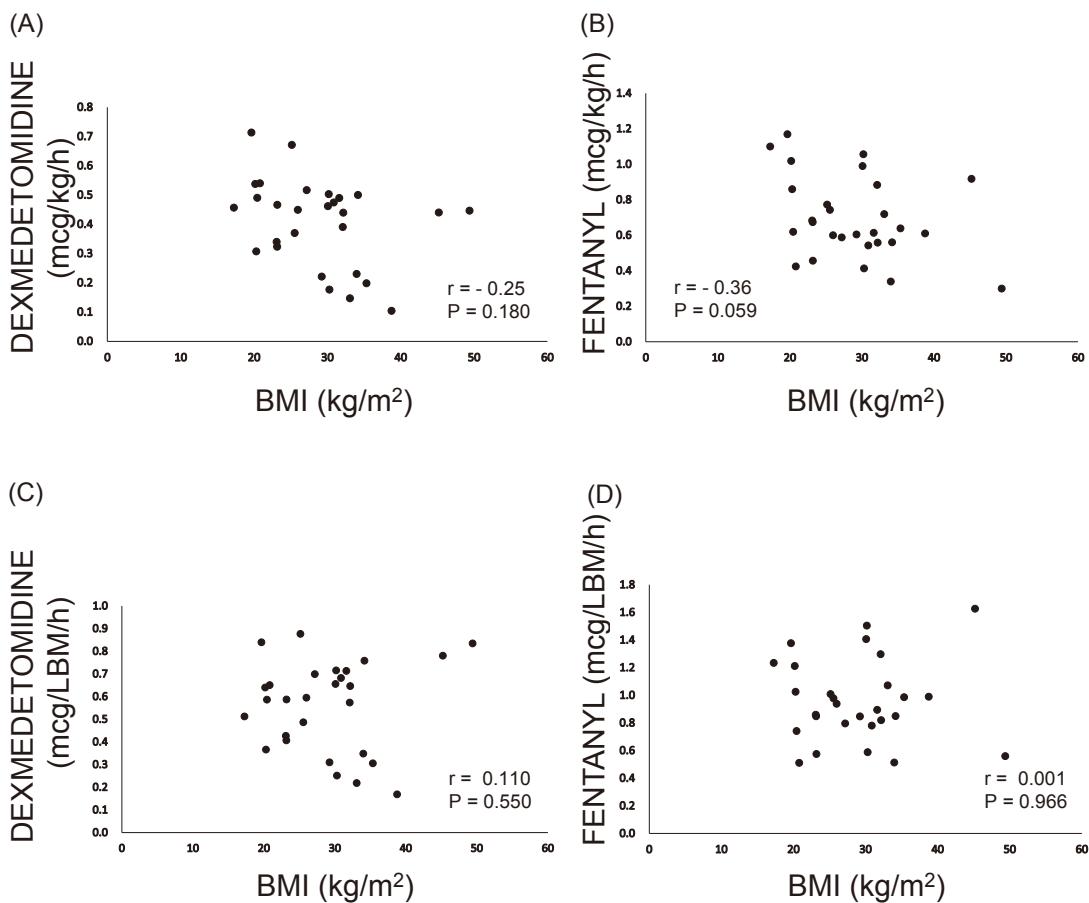


Fig. 4. No significant correlations between BMI and DEX and FEN amounts per TBW per hour (A and B, respectively), and between BMI and DEX and FEN amounts per LBM per hour (C and D, respectively). All patients were analyzed together. BMI, body mass index (kg/m^2) ; LBM, Janmahasatian's equation for Lean Body Mass (kg).

my and found body weight or height not to be a covariate for clearances or distribution volumes. In a pharmacokinetic model of DEX reported by Lin *et al.*¹⁴⁾, height was included as a covariate in central clearance but the study population did not cover obese patients. Another pharmacokinetic model built by Iirola *et al.*¹⁵⁾ showed that DEX systemic clearance significantly decreased with decrease in normalized cardiac output (cardiac output / cadiac output at baseline) which potentially enhances the relationship between body weight and clearance. Lee *et al.*¹⁶⁾ investigated DEX pharmacokinetics in young, healthy, non-obese adult volunteers and found that body weight or height were not covariates for clearances or distribution volumes.

In general, pharmacokinetic simulations can be performed to predict plasma DEX concentrations using drug administration data and pharmacokinetic model parameters indicated in literatures as in those previously mentioned. However, it is strictly incorrect to extrapolate those results into an obese popu-

lation because commonly the results from pharmacokinetic simulations for patients from special populations using pharmacokinetic models which are not built using data from such populations can be inaccurate. Therefore, pharmacokinetic analysis is required in obese population. Our real clinical data might support such study.

Besides the sedative effect, DEX activates Alpha-2 adrenergic receptors in the spinal cord and inhibits pain transmission, which causes an analgesic effect. According to the predicted plasma DEX concentration resulting from the usual clinical dose, the strong analgesic effect by a single agent cannot be proposed¹⁷⁾. However, a synergic effect of DEX with opioids is promising¹⁸⁾ and clinically the consumption of opioids is reported to be reduced when administered together with DEX^{19,20)}. Our study design is not enough to discuss the synergic effect of the two drugs because there was no group to which a single agent or a fixed dose was administered.

In order to examine if the ratio of the doses of

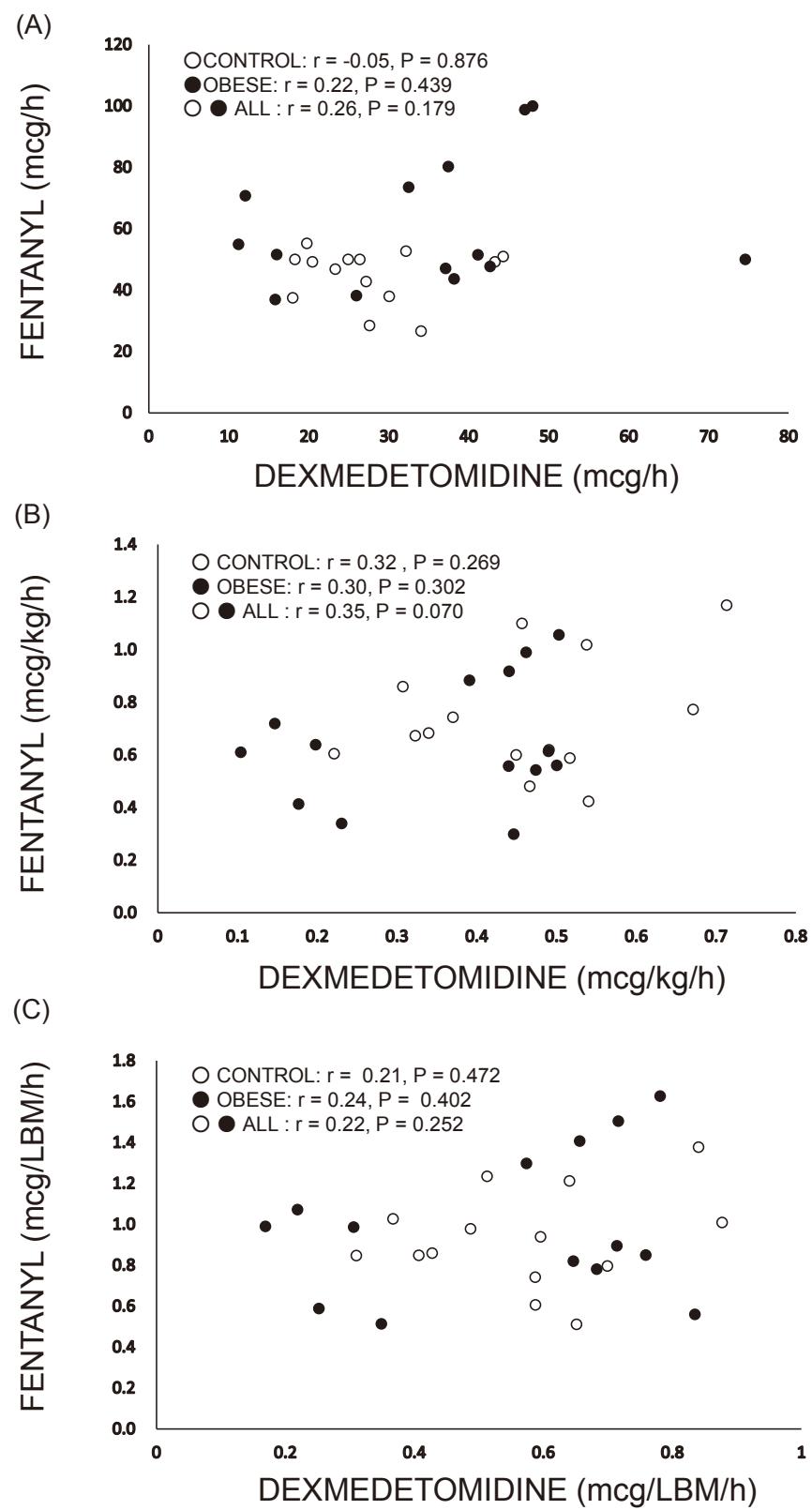


Fig. 5. Plots of the three indices of DEX and FEN doses in terms of the control group (open circle), obese group (closed circle), and combined.

DEX and FEN changes with obesity, we performed the exploratory analysis as illustrated in Figure 5 although no significant correlations between DEX and FEN consumption were observed in the control, obese and combined groups. However, these results may be interpreted as that the real time drug titration by nursing staff were modestly well performed in which sedation and analgesia were assessed independently. Strong significant correlations between two drug dose indices would rather imply the monotonic increase in two drug doses even though clinically there should be various requirements of the ratio of the doses of DEX and FEN. At least, during the observation periods after the initial recovery of consciousness, no patients had RASS score of 5 (i.e., Unarousable) for two consecutive observation points, which represents that the oversedation was potentially avoided in all patients (data not shown).

There are several limitations in this study. First, we had small number of patients because it has not been long since DEX infusion lasting more than 24 h after surgery in the ICU was approved (2010) and we have relatively few obese patients in Japan. Second, patients' conditions were various and co-administered catecholamine dose differed. Cardiac output affects the metabolism of DEX as mentioned earlier but it was not investigated. Third, the inclusion/exclusion criteria did not include administration of lidocaine^{21,22}, which is considered to have a potential analgesic effect. Fourth, the initial and maximum doses of DEX were decided at the discretion of attending anesthesiologists or intensivists who were not blinded to weight of patients, which might have reflected to drug dose. These limitations should be considered when interpreting the results.

In conclusion, DEX requirements were increased with obesity when administered with FEN during mechanical ventilation after surgeries but not as much as those calculated by per kg basis. These findings will be beneficial for future clinical pharmacological analysis of DEX.

DISCLOSURES

Shinju Obara and Masahiro Murakawa received a speaker's honorarium from Maruishi Pharmaceutical CO., Ltd. (Osaka, Japan) which sells dexmedetomidine in Japan for delivering a lecture and for presiding at a meeting, respectively; the contents of the present study were not included in the lecture. All other authors have no Conflict of Interest to de-

clare.

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