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ORIGINAL ARTICLE

Effect of remifentanil on three effect-site concentrations of propofol and their relationship during electroencephalography at loss of response, at maximum alpha power, and at onset of burst suppression: a prospective randomized trial

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Abstract

Purpose The effect-site concentration (Ce) at loss of response (Ce-LOR) to propofol closely correlates both with Ce as electroencephalographic alpha power becomes highest (Ce-alpha) and with Ce at onset of burst suppression (BS) (Ce-OBS), when no opioids are administered. Co-administration of opioids dose-dependently decreases Ce-LOR. We investigated the influence of remifentanil on the relationship between these three Ces.

Methods After receiving approval from our local ethical committee, with written informed consent, we enrolled 90 participants (ASA-PS I or II) who were scheduled for elective surgery. Participants were randomly assigned to three groups: constant remifentanil Ce 0 ng/ml (Remi_0); 1 ng/mL (Remi_1); and 2 ng/mL (Remi_2). We recorded both raw EEG and EEG-derived parameters on a computer. After reaching remifentanil equilibrium, we administered propofol using a target-controlled infusion pump such that propofol Ce increased to about 0.3 μg/mL/min. After determining Ce-LOR, we administered 0.6 mg/kg of rocuronium and started mask ventilation. The study protocol ended after observation of BS.

Results Three participants were excluded. Ce-LOR in each group (Remi_0, Remi_1, Remi_2) was 2.00 ± 0.58 μg/mL, 1.43 ± 0.49 μg/mL, and 1.37 ± 0.42 μg/mL. Ce-alpha was 2.91 ± 0.63 μg/mL, 2.30 ± 0.41 μg/mL, and 2.12 ± 0.39 μg/mL. Ce-OBS was 3.80 ± 0.69 μg/mL, 3.25 ± 0.68 μg/mL, and 2.90 ± 0.57 μg/mL. In three other instances, Ce was decreased by remifentanil. Generalized linear model analysis revealed that remifentanil had no influence on the relationship between the three Ces.

Conclusion During propofol anesthesia, even low concentrations of remifentanil shifted concentration-related electroencephalographic changes.

Keywords Pharmacodynamics · Interindividual variation · Propofol · Opioid

Introduction

For maintenance of anesthesia, plasma concentrations (Cp) or effect-site concentrations (Ce) of propofol widely vary among patients [1]. TCI (target-controlled infusion) systems and electroencephalographic (EEG) monitoring enable us to adjust and maintain adequate concentrations of propofol. Even using these devices, however, it is sometimes difficult to assess what concentrations are adequate for maintenance.

We previously reported that propofol Ce at loss of response (Ce-LOR) closely correlates both with Ce when alpha power is highest (Ce-alpha) and with Ce when burst waves first emerge (Ce-OBS, onset of burst suppression) [1]. In that study, only propofol was administered. In daily clinical practice, however, we routinely administer opioids. Previous reports [2–10] have shown that opioid dose-dependently decreases Ce-LOR. For example, Lysakowski, et al. [2] reported that fentanyl, alfentanil, remifentanil and sufentanil decrease Ce-LOR; Schraag, et al. [3] have shown that remifentanil dose-dependently decreases Ce-LOR of

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propofol; and Scott, et al. [4] have also shown, at Ce of 3.0 ng/mL, remifentanil decreases Ce-LOR. We set out to further investigate the influence of remifentanil on the relationship between Ce-LOR, Ce-alpha, and Ce-OBS.

Materials and methods

Patients

Before study commencement, the protocol was approved by the Research Ethical Committee of Kansai Medical University (Hirakata, Japan. #2,020,188) on 25, Nov 2020, and registered in UMIN Clinical Trial Registry on 18, Dec 2020, (ID: UMIN000042785, URL: https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000048836) prior to patient enrollment.

After obtaining written informed consent from each participant, we enrolled 90 patients (age 31–69, American Society of Anesthesiologists physical status I or II) who were scheduled for elective mammectomy or elective laparoscopic cholecystectomy. We set the number of cases in each group as 30, because 26 cases had been shown enough in the previous study [1]. Exclusion criteria included serious liver dysfunction, renal dysfunction, or psychological disorders, pregnancy, lactation or receipt of psychotropic drugs, and allergy to propofol or remifentanil.

In the current study, as pharmacokinetic and pharmacodynamic models, we used Marsh model [11] for propofol and Minto model [12] for remifentanil. Using computer-generated random block tables (block size; 3 × 3), patients were randomly allocated to one of three groups according to predicted Ce of remifentanil: that is, 0 ng/mL (Remi_0); 1 ng/mL (Remi_1); and 2 ng/mL (Remi_2).

Anesthetic protocol

The anesthetic protocol was very similar to our previous study [1], the only difference being before propofol administration, we infused remifentanil to maintain the target Ce in each of the three groups.

No premedication was applied. Through intravenous catheter in the forearm or dorsal hand, Ringer's solution was infused at arrival in the operating room. Besides standard monitors including three-lead electrocardiogram, pulse oximetry, non-invasive blood pressure, bladder temperature, and capnography, we used a BIS-VISTA™ monitor (software version 4.1; Covidien Boulder, CO). As recommended by the manufacturer, after mildly abrading sensor-contact sites using Skinpure™ (Nihon Koden, Tokyo, Japan), a BIS-QUATRO™ sensor was attached to the patient's forehead. Throughout the study, electrode impedance was kept at 5 kΩ or less.

Using Bispectrum Analyzer for BIS-XP/A2000/VISTA (BSA: URL http://www7.kmu.ac.jp/anesthw/software-library), a freeware application developed by one of the authors (SH) [13], via an RS232C interface, all binary data packets, including raw-wave data along with BIS and other processed parameters were collected, analyzed, and recorded onto a personal computer (IdealPad S340, Lenovo, Japan). Using BSA, at 10 s intervals, the power spectrum was continuously calculated from the preceding 30 s of EEG data.

Using our original software TE371 Logger and Controller Ver 1.10 (http://www7.kmu.ac.jp/anesthw/software-library), we made an infusion schedule table to maintain the Ce of remifentanil at the proposed concentrations for 30 min using 'off-line TCI' mode based on the Minto model [12]. The infusion schedule table comprised time from the start and infusion rate pairs. We infused remifentanil via an infusion pump (TE–371; Terumo, Tokyo, Japan) in mL/h mode controlled by the software using 'online scheduled mode', which controlled infusion according to the infusion schedule table. After achieving remifentanil Ce equilibrium at the randomly assigned proposed concentration, anesthesia was induced with propofol, which was infused through another infusion pump (TE–371; Terumo, Tokyo, Japan) using the target-controlled infusion mode with pharmacokinetic parameters, including k_{e0}, identical to the Diprifusor™ [14].

Initially, the target blood propofol concentration was set at 2.0 μg/mL, as in our previous study. When the estimated Ce of propofol reached below the target concentration by 1.0 μg/mL, we increased the target blood concentration by 0.2 μg/mL. This adjustment was repeated until burst suppression was observed. All adjustments were logged on the computer with time stamps. Loss of response (LOR) was defined as lack of response when the patient was addressed by name and shaken gently by the shoulder, that is, exhibited criteria for level 1 of the Observer's Assessment of Alertness/Sedation Scale (OAA/S) [15]. OAA/S was assessed by one anesthesiologist (SA) every 10 s and we recorded Ce-LOR. After LOR was confirmed, the patient received 0.6 mg/kg of rocuronium and, to maintain normocapnia, mask ventilation was started. When the EEG burst-suppression pattern was observed, the protocol of this study was complete; however, to acquire data for another study, we continued recording EEG data and made pump adjustments until the end of anesthesia.

During the study protocol, we added phenylephrine 0.1 mg when systolic blood pressure decreased below 80 mmHg or mean blood pressure was lower than 50 mmHg, and we added atropine 0.5 mg when heart rate was lower than 40 bpm. A warming blanket was employed to maintain patient body temperature at 36.0°–37.5°C.

Electroencephalographic processing and PK/PD estimation

As in our previous study, raw EEG data were processed offline after data acquisition. The power spectrum was calculated from the most recent 30 s of EEG signal.

To detect burst suppression, we first applied a finite impulse response (FIR) filter, which was designed to pass frequencies between 3.0 and 47.0 Hz. After filtering, each local peak was determined, and EEG amplitude was calculated as the half height between adjacent peaks. Finally, as a refinement of Rampil's definition [16], we defined suppression as mode periods of 0.5 s during which EEG amplitude did not exceed 5 μV.

We calculated propofol Ce values using TIVATrainer (Ver 9.0; Frank Engbers, Leiden, The Netherlands) simulation. Based on this calculation, we determined Ce at Ce-LOR, Ce-alpha, and Ce-OBS. During the period when propofol Ce was continuously increased and 30 s periods of EEG power spectrum were averaged, Ce-alpha was defined as the Ce at the midpoint of power spectrum calculation, that is, at 15 s from the beginning of the calculation period.

Statistics

Statistical results were regarded as parametric when Shapiro–Wilk testing revealed normality of distribution, and non-parametric if otherwise.

Demographic data, including age, weight, and height, were analyzed by one-way ANOVA using R (Ver 4.1.3; R Foundation for Statistical Computing) [17]. To analyze to effect of remifentanil on the relationships between Ce-LOR, Ce-alpha, and Ce-OBS, we applied a generalized linear model. We also applied this model to analyze the relationships between the three Ces in each group. Comparing the averages of the three Ces between Remi_0 and Remi_1, and between Remi_1 and Remi_2, we applied Student's *t* test with Holm's correction. *P* values of less than 0.05 were considered significant for all data.

Results

For 90 participants, we successfully completed the protocols; three cases (one in each group), however, were excluded owing to accidental loss of data. Figure 1 shows the typical EEG patterns in each checked point observed in Case#11 (49 years, female) of Remi_2 group. We were able to analyze the data of 87 participants. Table 1 shows the demographic data for the three groups, in which no significant differences were found in age, height and weight. No differences in ratio of gender or types of operation were found. Furthermore, no electromyographic contamination was observed in any of the obtained EEG data used for determining Ce-alpha and Ce-OBS. Shapiro–Wilk testing revealed that all variables could be handled as parametric.

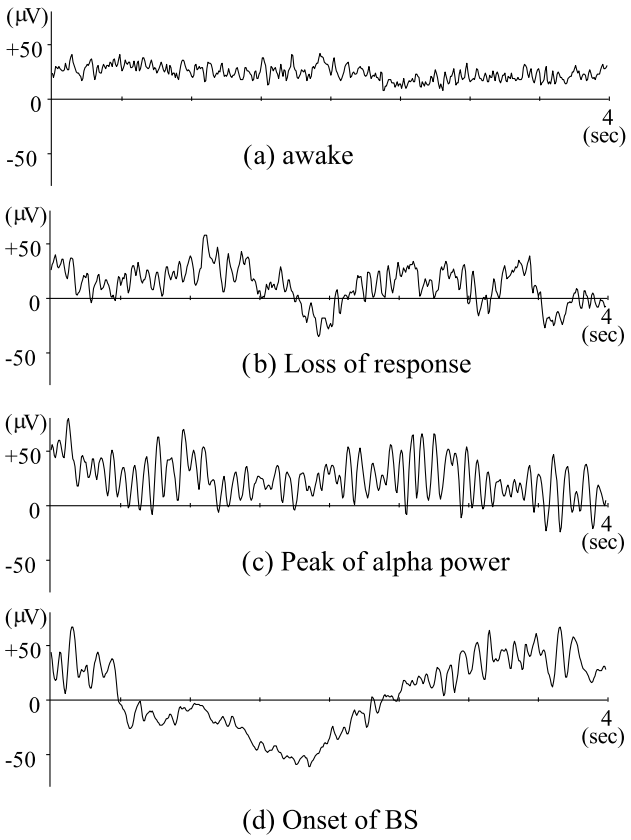

Fig. 1 Typical EEG patterns at (**a**) awake, (**b**) loss of response, (**c**) when alpha power became maximum, and (**d**) onset of burst suppression in a 49-year-old female (Remi_2 group)

Table 1 Demographic data

Remifentanil	Remi_0	Remi_1	Remi_2
Age (years)	53.9 ± 9.5	53.4 ± 11.1	54.5 ± 7.9
Gender (M/F)	2/27	2/27	1/28
Height (cm)	158.6 ± 6.1	158.6 ± 6.8	157.2 ± 7.2
Weight (kg)	62.4 ± 13.3	59.8 ± 12.6	55.7 ± 8.0
Operation (M/F)			
Mammectomy	0/26	0/25	0/26
Cholecystectomy	2/1	2/2	1/2

Data are expressed as mean ± SD

Considering the influence of remifentanil concentration and associations between Ce-LOR and remifentanil concentration, we applied a generalized linear model analysis and obtained the following equation;

$$\text{Ce-alpha}, \quad \text{Ce-OBS} = 0.78 \times \text{Ce-LOR} + 1.38 + \text{Dummy} \times 0.87 \quad (\text{Ce-alpha};\ \text{Dummy} = 0,$$

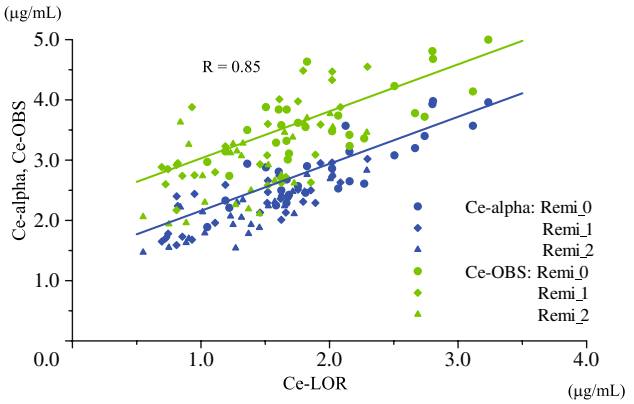

Fig. 2 Linear regression-derived correlations, Ce-alpha, Ce-OBS = 0.78×Ce-LOR + 1.38 + Dummy×0.87 (Dummy = 0 for Ce-alpha, Dummy = 1 for Ce-OBS, adjusted r = 0.85,) (dummy = 0 for Ce–LOR, and = 1 for Ce–alpha; adjusted $r = 0.90$, $p < 2.2e\text{-}16$). Ce, effect-site concentration; Ce-LOR, Ce at loss of response; Ce-alpha, when electroencephalographic alpha power becomes highest; and Ce-OBS, Ce at onset of burst suppression

Ce-OBS; Dummy = 1), which reveals that remifentanil concentration had no influence on the relationship between the three Ces. Sub-group analyses also showed that two regression curves, Ce-LOR–Ce-alpha and Ce-LOR–Ce-OBS, were sufficiently parallel in each group. In sub-group analyses, we obtained the following equations: Ce-alpha, Ce-OBS = 0.81×Ce-LOR + 1.29 + Dummy×0.88 (R = 0.81) for Remi_0, Ce-alpha, Ce-OBS = 0.75×Ce-LOR + 1.23 + Dummy×0.95 (R = 0.82) for Remi_1, and Ce-alpha, Ce-OBS = 0.74*Ce-LOR + 1.11 + Dummy×0.78 (R = 0.81) for Remi_2 (Ce-alpha; Dummy = 0, Ce-OBS; Dummy = 1). Figure 2 shows the relationship between Ce-LOR – Ce-alpha and their regression curve (blue line). Figure 2 similarly shows the regression curve for Ce-LOR – Ce-OBS (green line).

Figure 3 shows the cumulative probability plots for loss of response in the three remifentanil groups. Curves were obtained by probit regression. For the three groups, Fig. 4 shows the cumulative probability for EEG α power reaching its maximum, and Fig. 5 shows probability plots for emergence of burst and suppression patterns. These figures demonstrate that increasing remifentanil concentrations shift the regression curves to the left.

Table 2 shows the values of the Ces for each group. Ce-LOR in Remi_1 was significantly lower than Ce-LOR in Remi_0. Ce-LOR in Remi_2 was also lower than in Remi_1, but the difference was not significant. Ce-Alpha in Remi_1 was significantly lower than that in Remi_1. Ce-alpha in Remi_2 was also lower than that in Remi_1, but the reduction was not significant. Ce-OBS in Remi_1 was significantly lower than in Remi_0, and Ce-OBS in Remi_2 was also significantly lower than in Remi_1.

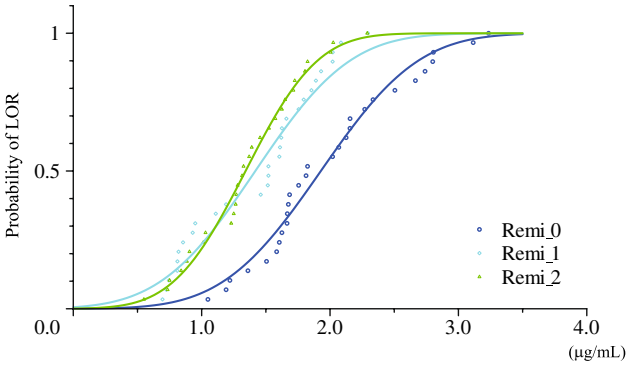

Fig. 3 Cumulative probability plots of loss of response in three remifentanil groups. Fitted curves were obtained by probit regression. Blue indicates Remi_0, light blue indicates Remi_1, and green indicates Remi_2. Remifentanil dose: Remi_0, constant Ce 0 ng/mL; Remi_1, Ce 1 ng/mL; and Remi_2, Ce 2 ng/mL

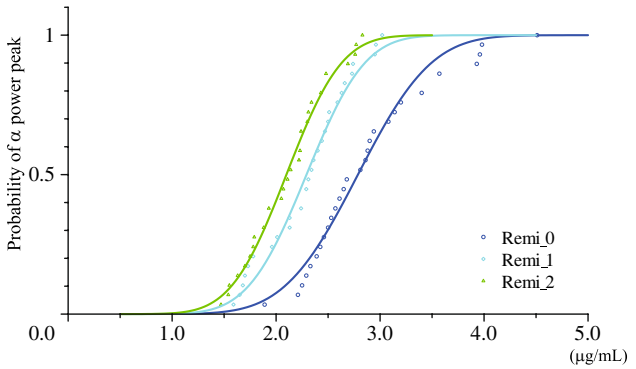

Fig. 4 Cumulative probability plots of α power reaching its highest in three remifentanil groups. Fitted curves were obtained by probit regression. Blue indicates Remi_0, light blue indicates Remi_1, and green indicates Remi_2. Remifentanil dose: Remi_0, constant Ce 0 ng/mL; Remi_1, Ce 1 ng/mL; and Remi_2, Ce 2 ng/mL

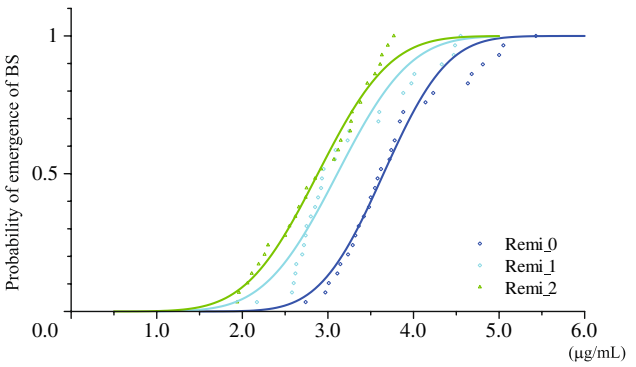

Fig. 5 Cumulative probability plots of emergence of burst suppression in three remifentanil groups. Fitted curves were obtained by probit regression. Blue indicates Remi_0, light blue indicates Remi_1, and green indicates Remi_2. Remifentanil dose: Remi_0, constant Ce 0 ng/mL; Remi_1, Ce 1 ng/mL; and Remi_2, Ce 2 ng/mL

Table 2 Observed Ce-LOR, Ce-alpha, and Ce-OBS values

(μg/mL)	Ce-LOR	Ce-alpha	Ce-OBS
Remi_0	2.00 ± 0.58	2.91 ± 0.63	3.80 ± 0.69
Remi_1	1.43 ± 0.49	2.30 ± 0.41	3.25 ± 0.68
Remi_2	1.37 ± 0.42	2.12 ± 0.39	2.90 ± 0.57

Data are expressed as mean ± SD in each group.

Ce-alpha, when electroencephalographic alpha power becomes highest; and Ce-OBS, Ce at onset of burst suppression

Ce effect-site concentration, *Ce-LOR* Ce at loss of response

Discussion

In the current study, we found that the relationships between the three Ces were not influenced by remifentanil concentration. Namely, the relationships between the three Ces were unchanged when concentration of remifentanil was kept constant. We had speculated because low concentrations of opioid have little effect on electroencephalograms, only Ce-LOR would significantly decrease when remifentanil concentration increases. Our results revealed, however, that Ce-alpha and Ce-OBS decreased when remifentanil was co-administered, which is a new finding: even a low concentration of remifentanil significantly decreased Ce both when EEG α power was at its maximum and at onset of burst and suppression. Steriade et al. [18, 19] have reported electroencephalogram rhythm during anesthesia/sleep is determined by the membrane potential of thalamo-cortical relay (TC) neurons, with spindle rhythms occurring when the membrane potential of TC neurons is between –55 mV and –65 mV [19] and, further, changing to burst and suppression when the membrane potential of TC neurons decreases below −90 mV.[20]. Considering this, there is a possibility that opioids might hyperpolarize the membrane potential of TC neurons. Of course, to clarify this, further research is required.

All three Ces significantly decreased after 1 ng/mL of remifentanil was administered, but Ce-LOR and Ce-alpha were not further decreased by 2 ng/mL of remifentanil. On Fig. 2, for Remi_1, several points are plotted above the regression curve at 0.8–1.0 μg/mL. This seems to indicate that several patients lost response in advance of expectation. Using TCI, initially propofol is infused so that the agent in the central compartment reaches the target concentration. When target concentration is set at 2.0 μg/mL, Diprifusor initially administers 0.46 mg/kg of propofol at 1200 mL/h. The drawback is that the compartment model ignores the dilution phase, which, in the real world, takes about 3 min to complete. Consequently, plasma concentration (Cp) and Ce calculated by the pharmacokinetic model, even when using a TCI, becomes inaccurate within about 3 min of initial infusion.

It is known that propofol Cp can become unexpectedly high soon after propofol bolus administration [21]. Of course, this is only transient and the increase of Ce may be only slight; even so, it could affect Ce-LOR. Our interpretation of the results is that this problem did not affect Ce-LOR in Remi_0, but that it might have caused unexpectedly low Ce-LOR in some Remi_1 patients. In Remi_2, Ce-LOR was too low to have been affected by remifentanil. Continuous propofol infusion at a constant rate of 10–12 mg/kg/h would likely solve this problem. Since we were unaware of this before completing data collection and analysis, it remains something for further study. For now, we can say that all three Ces decreased when remifentanil concentration increased, although some rises were not significant.

Previous reports [2–8] have shown that 0–8 ng/mL of remifentanil dose-dependently decreases propofol Ce-LOR. If so, Ce-LOR would probably decrease as remifentanil concentration increases. So far, we have found no previous reports investigating Ce-alpha or Ce-OBS: our results clearly show that remifentanil decreases Ce-alpha and Ce-OBS, and that relationships between the three Ces were independent of remifentanil concentration.

Since mask ventilation might have been required to maintain normocapnia, which would influence Ce-LOR, we did not investigate the influence of remifentanil doses higher than 2.0 ng/ml. In routine ventilation, the maintenance concentration of remifentanil is usually higher than 2.0 ng/ml, so it is necessary to observe whether the relationship between the three Ces is similar when remifentanil concentration is higher than 2.0 ng/ml.

Because the regression curve in the Remi_0 group was almost identical to that obtained previously [1], measurements were considered to be adequately performed.

Whereas, in the previous study, we investigated the relationship between the same three Ces in female patients only, in the current study we were able to include both genders. Unfortunately, however, we could recruit only few male patients. This means we cannot conclude that our findings are also valid for males. This may eventually be resolved as studies progress.

In conclusion, we found that while remifentanil decreased Ce-LOR, Ce-alpha, and Ce-OBS, it had no influence on the relationship between the three Ces. During propofol anesthesia, concentration-related changes in electroencephalography were shifted to the left by remifentanil.

Author contributions SA: helped in data acquisition, analysis, interpretation and writing of manuscript. SH: helped in study conception and designing, data acquisition, and writing manuscript. RU: helped in data acquisition and writing of manuscript. TK: helped in study conception and designing, data analysis, and writing manuscript.

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Data availability The datasets used in the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest. The authors declare no conflicts of interest associated with this manuscript.

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