Original Article
Effects of the menstrual cycle on bispectral index and anesthetic requirement in patients with preoperative intravenous dexmedetomidine following propofol induction

Xiaomin Zhou, Tingting Wang, Shaoqiang Huang

Department of Anesthesiology, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China

Abstract: Several studies have suggested that the menstrual cycle has the impact on sedation. No previous study has evaluated the effects of the menstrual cycle on sedation level and propofol requirement with preoperative intravenous dexmedetomidine. Sixty-four adult fertile women receiving general anesthesia for elective gynecologic surgery were included in the study. Patients were classified into four groups on the basis of the phase of menstrual cycle and whether infused dexmedetomidine preoperatively: Group FS: the follicular phase (days 8-12) and preoperative intravenous normal saline; Group FD: the follicular phase (days 8-12) and preoperative intravenous dexmedetomidine; Group LS: the luteal phase (days 20-24) and normal saline; Group LD: the luteal phase (days 20-24) and dexmedetomidine. The patients were infused respectively dexmedetomidine at 0, 1.0, 0 and 1.0 μg/kg over 10 min, and then propofol TCI, which was administered with target plasma concentration at 4.0 μg/ml. BIS, heart rate, MAP were recorded until BIS to 50. In the LD group, the descent range of the BIS values was significantly sharpest among the four groups at loss of eyelash reflex. From propofol administered to loss of eyelash reflex and BIS values reach to 50, propofol requirements were significantly least and duration were shortest in the LD group among the four groups. Menstrual cycle phases affect the sedation of propofol induction with preoperative intravenous dexmedetomidine, which is deeper in the luteal phase. We should cautious of excessive sedation by propofol anesthesia with preoperative dexmedetomidine in the luteal phase.

Keywords: Menstrual cycle, bispectral index, anesthetic i.v., propofol, dexmedetomidine

Introduction

Menstrual cycle is regulated by estrogen and progesterone, which is split into three phases: menstruation, follicular and luteal phases [1]. During the reproductive period, hormonal, psychological and physical changes occur in women due to the menstrual cycle [2]. Female sex hormones and its metabolites are related to sedation, anxiolytic, analgesia and anticonvulsant through action on the γ-aminobutyric acid (GABA) type A receptor [3-8]. For this reason, different phases of the menstrual cycle may have an influence on anesthetic requirements. A previous study showed that propofol requirements were higher in patients in the follicular phase compared with those in the luteal phase reach to the median effective effect-concentration for loss of consciousness, suggesting that the luteal phase could reduce anesthetic requirements [9].

Dexmedetomidine, a highly specific, potent and selective α2-adrenoceptor agonist [10], now has been suitable for perioperative sedation and analgesia. While propofol is a traditional sedation drug that has been widely adopted for induction and maintenance of anesthesia due to its rapid onset. However, to the best of our knowledge, there is no study addressing the effects of the different phases of the menstrual cycle on sedation level and propofol requirements with preoperative intravenous dexmedetomidine.

The hypothesis of our study was that patients during the luteal phase, preoperative intravenous dexmedetomidine results in an increased

sedation level in comparison with that either in the follicular phase or without dexmedetomidine. To test this hypothesis, we chose times during the menstrual cycle at which hormonal levels are different from each other, the follicular and luteal phases. Secondary end points of our study included the comparison of the duration and propofol consumption from propofol administered to loss of eyelash reflex and bispectral index reach to 50 during the different menstrual cycle with or without preoperative intravenous dexmedetomidine.

Materials and methods

This trial is registered at ClinicalTrail.gov, NC-T02035930. After approval by the Ethics Committee of The Obstetrics and Gynecology Hospital, Fudan University, and written informed consent, 64 adult fertile women receiving general anesthesia for elective gynecologic surgery including myomectomy and oophorocystectomy were enrolled. The study was conducted from Nov 2010 to Nov 2012 at the Obstetrics and Gynecology Hospital. Inclusion criteria were ASA physical status 1 and 2, aged 24-40 years and a regular menstrual cycle. A regular cycle was defined as lasting 23 to 35 days, with no more than a 4 day variation between cycles [11]. The day of the cycle on which surgery took place was calculated from the first day of the last menstrual bleeding. Exclusion criteria were pregnancy; those receiving hormones and medications that affected ovulation during the 6 weeks before surgery; breastfeeding; obesity [body mass index (BMI) > 30 kg/m²]; known hypersensitivity to drugs used in the study protocol; use of psychotropic drugs and steroids within 72 hours before the surgery; renal impairment; central nervous system injury; alcoholism and opioid addiction.

Patients were classified into four groups on the basis of the phase of menstrual cycle and whether infused dexmedetomidine preoperatively: Group FS: the follicular phase (days 8-12) and preoperative intravenous normal saline; Group FD: the follicular phase (days 8-12) and preoperative intravenous dexmedetomidine; Group LS: the luteal phase (days 20-24) and normal saline; Group LD: the luteal phase (days 20-24) and dexmedetomidine. Before surgery, a blinded nurse recorded patients' menstrual cycle. If consistent with inclusion criteria and belonged to the follicular or luteal phase, she picked by arbitrary numbers from a bag to decide whether infuse dexmedetomidine or normal saline.

All patients fasted for more than 8 h before the operation. No premedication was given. In the operation room, oxygen 8 l/min was administered via the anesthesia machine through a face mask with a 4-tailed bandage. A 18-gauge intravenous cannula was inserted into a vein on the dorsum of the hand and Ringer's lactate solution, 8 ml/kg, was administered. Standard intraoperative monitoring included electrocardiograph, non-invasive blood pressure, pulse oximetry, capnography and bispectral index (BIS; Aspect Medical Systems, Norwood, MA, USA). A 10-min resting period was allowed before the baseline measurements.

Dexmedetomidine (SFDAH20090248, Jiangsu Hengrui Medicine Ltd., Lianyungang, China; batch No. 13101132) was provided in 2-ml ampoules and the sterile solution was clear and colorless. In groups FD and LD, dexmedetomidine 200 μg were diluted to 50 ml with normal saline, then in group FS and LS, only normal saline 50 ml, by the specified investigator who infused via a Graseby syringe pump model 35-00 with the speed of 1.5* patient weight (kg) for 10 min, resulting in dexmedetomidine loading doses of 1.0, 1.0, 0 and 0 μg/kg, respectively.

After the loading dose of dexmedetomidine, propofol was administered via a Graseby syringe pump model 3500 simulating Marsh pharmacokinetic model with target plasma concentration set at 4.0 μg/ml. At the same time, the speed of fluid instillation increased to 600 ml/h.

Mean arterial blood pressure (MAP), heart rate (HR), BIS and peripheral oxygen saturation (SpO$_2$) were recorded after 10 min rest at the OR (T0), loss of eyelash reflex (T1) and bispectral index reduced to 50 (T2) .The duration and propofol consumption from propofol administered to T1 and T2 were also recorded by a blinded anesthetists to the patient grouping.

Adverse hemodynamic responses were defined as hypotension (systolic arterial blood pressure < 90 mm Hg), tachycardia (heart rate > 100 beats/min) and bradycardia (heart rate < 45 beats/min). The complications (cough and abnormal movements) observed during the procedure were also recorded. Bradycardia below 45 beats/min was treated by atropine 0.01 mg/kg

Table 1. Demographic characteristics for the four groups

	FD group (n=16)	LD group (n=16)	FS group (n=16)	LS group (n=16)
Age (yr)	33.4±7.5	33.9±7.0	31.1±6.2	33.1±6.8
Height (cm)	160.5±5.4	161.8±4.5	161.4±4.6	160.3±4.2
Weight (kg)	57.0±9.0	54.7±5.2	54.3±8.1	55.2±5.8
ASA (I/II)	12/4	12/4	13/3	11/5
Menstrual cycle (day)	10.1±1.2[b,d]	22.3±1.7[c]	10.4±1.3[d]	21.6±1.3

Note: Data are expressed as number or mean (SD); Group FS: the follicular phase (days 8-12) and preoperative intravenous normal saline; Group FD: the follicularphase (days 8-12) and preoperative intravenous dexmedetomidine; Group LS: theluteal phase (days 20-24) and normal saline; Group LD: the luteal phase (days 20-24) and dexmedetomidine; ASA: American Society of Anesthesiologists. [b]$P < 0.05$ vs.group LD; [c]$P < 0.05$ vs. group FS; [d]$P < 0.05$ vs. group LS.

Table 2. Changes in the BIS values and hemodynamic parameters

		T0	T1	T2
BIS	FD group	98.2±1.2	79.1±2.3[a]	50[a]
	LD group	97.8±1.0	68.3±4.9[a,b,c,d]	50[a]
	FS group	97.5±0.6	78.5±3.5[a]	50[a]
	LS group	97.3±1.3	78.5±3.2[a]	50[a]
MAP	FD group	86.1±8.8	79.8±6.4[a]	73.3±8.6[a]
(mm Hg)	LD group	84.6±6.3	79.8±8.0[a]	72.5±8.4[a]
	FS group	85.3±5.3	77.9±4.9[a]	71.3±10.0[a]
	LS group	83.1±9.9	79.1±7.3	73.9±11.1[a]
HR	FD group	76.8±8.2	65.4±7.2[a]	56.9±4.8[a]
(beats•min-1)	LD group	78.6±11.6	62.6±7.4[a]	59.6±6.2[a]
	FS group	75.4±10.9	65.9±9.9[a]	61.1±10.2[a]
	LS group	82.8±11.4	68.6±7.2[a]	63.4±8.6[a]

Data are presented as means ± SD; Group FS: the follicular phase (days 8-12) and preoperative intravenous normal saline; Group FD: the follicular phase (days 8-12) and preoperative intravenous dexmedetomidine; Group LS: the luteal phase (days 20-24) and normal saline; Group LD: the luteal phase (days 20-24) and dexmedetomidine; [a]$P < 0.05$ vs. T0; [b]$P < 0.05$ vs. group FS; [c]$P < 0.05$ vs. group LS; [d]$P < 0.05$ vs. group FD. T0: lie down for 10 minutes after entering OR; T1: loss of eyelash reflex; T2: bispectral index reduced to 50.

until above 50 beats/min. If hypotension persisted, phenylephrine 0.1 mg was infused.

The study was terminated until T2 time point. Sufentanil 0.5 µg/kg was given intravenously, rocuronium 0.6 mg/kg was used for neuromuscular relaxation. Ninety seconds later, tracheal intubation was performed.

The sample size was determined by performing a power analysis based on a previous study [9]. According to the data (the BIS value at which the patient had a 95% probability for loss of consciousness was 44 and 95% CI: 40-47 in the follicular group), we calculated that 11 patients in each group would be required to find a significant difference of 10% or more in BIS values among the groups (α=0.05, β=0.1). In this study, 64 patients were enrolled with 16 in each group.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) 13.0 for Windows. Enumeration data including incidence of hypotension, tachycardia, bradycardia and ASA physical status were compared with χ^2 analysis or Fisher's exact test. Paired *t*-test was used for measurement data within one group. The comparison of continuous variables among the groups was performed using analysis of variance with the post hoc Dunnett test. For all observations, the level of significance was accepted as α=0.05. *P* values less than this level were accepted as statistically significant.

Results

Sixty-four patients were enrolled in this study. Patients' characteristics are presented in **Table 1**. The four groups were similar in terms of age, height, weight, ASA physical status (P > 0.05), where as they differed significantly in terms of menstrual cycle days which were shorter compared the FD and FS groups with the LD and LS groups (P < 0.05).

The BIS and hemodynamics data (MAP and HR) of the patients are shown in **Table 2**. In all groups, the BIS decreased significantly since T1 (P < 0.05) compared with those at baseline. Especially in the LD group, the descent range of the BIS values was significantly sharpest among the four groups at T1 (P < 0.05). MAP decreased to some degree after propofol infusion in all groups. Statistically significant decreases (P < 0.05) were found since T1 in group
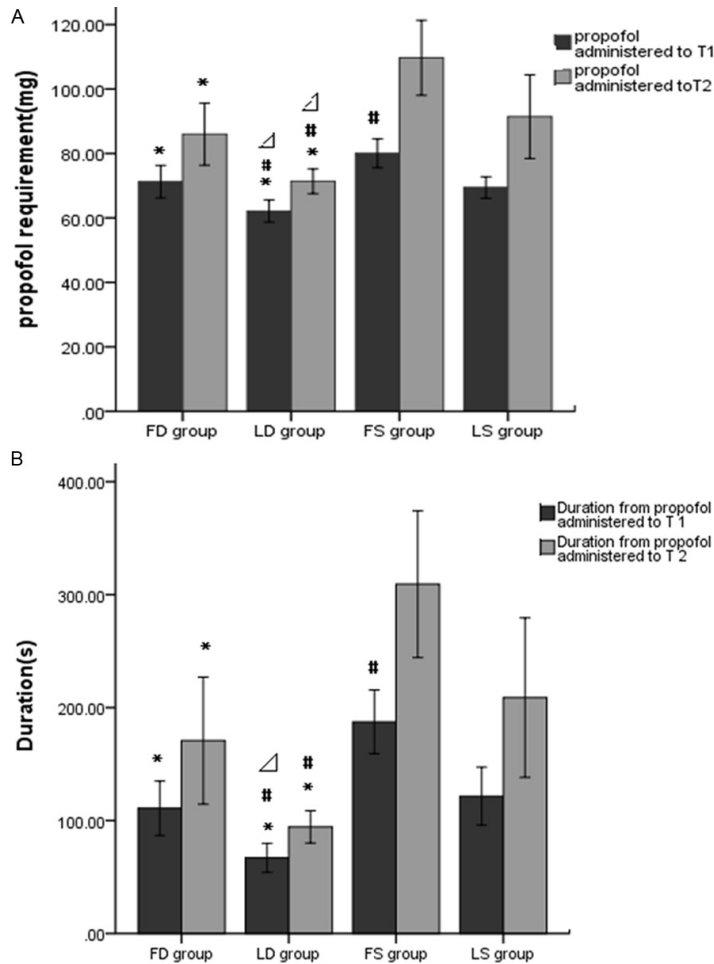
Figure 1. Propofol requirement and duration from T1 and T2. A. Propofol requirement. B. Duration. Group FS: the follicular phase (days 8-12) and preoperative intravenous normal saline; Group FD: the follicular phase (days 8-12) and preoperative intravenous dexmedetomidine; Group LS: the luteal phase (days 20-24) and normal saline; Group LD: the luteal phase (days 20-24) and dexmedetomidine; T1: loss of eyelash reflex; T2: bispectral index reduced to 50. *$P<0.05$ vs. group FS; #$P<0.05$ vs. group LS; ⊿$P<0.05$ vs. group FD.

FD, LD, FS, since T2 in group LS. In four groups, the HR decreased significantly since T1 compared with that at baseline ($P < 0.05$), while the descendent tendency were similar among all groups ($P > 0.05$).

Propofol requirement and duration are shown in **Figure 1**. In group LD, the propofol requirement from propofol administered to T1 and T2 was decreased significantly compared to those in group FS, FD and LS ($P < 0.05$), while the duration from propofol administered to T1 was shortest among four groups and T2 was shorter than the group FS and LS ($P < 0.05$). In group FD, the propofol requirement and duration were

decreased significantly than group FS at T1 and T2 ($P < 0.05$).

There was no incidence of hypotension, tachycardia, bradycardia, cough or abnormal movements in all groups.

Discussion

To our knowledge, this is the first study to investigate the effects of the menstrual cycle on sedation level and propofol requirements with preoperative intravenous dexmedetomidine. Statistically significant differences were observed that the female patients in the luteal phase preoperative intravenous dexmedetomidine 1 μg/kg for 10 min, then administrated propofol TCI induction could lead to more significant sedation effect than those in the follicular phase with or without dexmedetomidine. From propofol administered to loss of eyelash reflex and BIS values reach to 50, propofol requirements were significantly least and duration were shortest in the LD group among the four groups.

During the menstrual cycle, estrogen, progesterone and certain metabolites modulate neurotransmitter and neuropeptide activity in the central nervous system [12]. Progesterone and its metabolites (such as 3α, 5α-tetrahydroprogesterone; allopregnanolone, 3α, 5β-tetrahydroprogesterone; and pregnenolone) have hypnotic effects that are thought to occur via direct action on the GABA$_A$ receptor complex [4, 13]. However, estrogen has the opposite effect by suppressing GABA$_A$ receptor-mediated inhibition [4, 14]. Fu and colleagues [9] compared the adult female patients in follicular phase with those in luteal phase, then showed that not estrogen but progesterone level had a significant difference. Several studies also pointed out that female sex hormones, especially progesterone, may influence the effect of anesthetics [7, 8]. Both animal and human studies [15, 16] demonstrated that the MAC of volatile anesthetics was decreased during pregnancy which there are high levels of progesterone. These findings are in line with

the results of this study that the female patients in the luteal phase preoperative intravenous dexmedetomidine, then administrated propofol TCI induction can lead to more significant sedation effect than those in the follicular phase with or without dexmedetomidine. Propofol and progesterone have a similar central effect via direct action on the GABA receptor complex [17, 18], which is known to be a major substrate for the effects of several general anesthetics. However, dexmedetomidine result in sedation and analgesia effects action on the α2A-adrenoceptors located in the locus ceruleus and the spinal cord, which have been shown that one of its preferred effects is decrease the need for other anesthetics and analgesic drugs [19]. In addition, it was thought that the progesterone could influence the oxidative metabolism of drugs [20]. The potential PK interaction among propofol, dexmedetomidine and progesterone is likely to contribute to the lower propofol requirements for determining sedative level in patients in the luteal phase. Therefore, we could speculate that the menstrual phase changes the sedation level due to progesterone, which is higher in the luteal phase, might enhance propofol and dexmedetomidine's sedative effect and decrease the propofol requirement.

In the current study, menstrual cycle phases affect the sedation of propofol induction with preoperative intravenous dexmedetomidine, which is deeper in the luteal phase. However, oversedation was an independent predictor of increased risk of death at 6 months in critically ill patients because of cognitive impairment or neurohormonal/neurotransmitter derangements [21]. In considering this, we realized that in clinical practice we should cautious of excessive sedation by propofol anesthesia with preoperative dexmedetomidine in the luteal phase. Then the BIS in group LD the duration from propofol administered to BIS reach to 50 was shorter than the group FD, but no statistically significant differences. Meanwhile, the BIS was decreased at loss of eyelash reflex in the group LS but there was no marked differences compared with the group FD and FS. Considering that it was a pilot study and different patient characteristics, we should increase the sample sizes each group to move a forward step. Furthermore, future studies will indicate the optimal dosage or effect site concentration of propofol when preoperative intravenous dexmedetomidine during the different menstrual cycle.

It is worth mentioning specially that in the present study we did not use any clinical sedation scoring system or other electrophysiological variables to measure the depth of sedation. Because BIS correlated best with calculated blood concentrations of propofol than other electrophysiological variables such as 95% spectral edge frequency (SEF), median frequency (MF) and auditory evoked potential index (AEP index) [22]. Furthermore, clinical sedation scoring system, such as the Ramsay Score or the Richmond Agitation-Sedation Scale, involving repetitive verbal or noxious stimuli, would disturb the record of BIS values [19]. In addition, we chose dexmedetomidine as pre-treatment drug because of its analgesic property, shorter recovery profile, less cognitive impairment and respiratory depression. Meanwhile, the bolus of 1 μg/kg dexmedetomidine given over 10 min, which was in line with clinical conventional practice. In the current study, the findings reminded us that when dexmedetomidine administered preoperatively then propofol induced, we should cautious of the effect of different phases of the menstrual cycle on sedative level, therefore decrease propofolrequirements.

In the present study, we did not measure estrogen or progesterone levels while evaluating different menstrual cycle effects, which was also done in other research [23, 12]. Luteinizing hormone peaks on the 13th day, then progesterone starts to increase at the 18th day during the cycle [24]. With this in mind, we excluded the patients who were at the 13th to 19th days of the menstrual cycle so that we might better distinguish between the luteal and follicular phases.

In summary, patients during the luteal phase, preoperative intravenous dexmedetomidine 1 μg/kg for 10 min, then administrated propofol TCI induction could lead to more significant sedation effect than those in the follicular phase with or without dexmedetomidine. From propofol administered to loss of eyelash reflex and BIS values reach to 50, propofol requirements were significantly least and duration were shortest in the LD group among the four groups.

Disclosure of conflict of interest

None.

Address correspondence to: Tingting Wang, Department of Anesthesiology, Obstetrics and Gynecology

Hospital, Fudan University, 128# Shenyang Road, Shanghai 200090, China. Tel: +86-21-63455050-6868; Fax: +86-21-63455090; E-mail: ti3wt@163.com

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