Study Objective: To investigate the effect of the menstrual cycle on rocuronium injection pain.

Design: Prospective, randomized, double-blinded study.

Setting: Academic medical center.

Patients: 80 ASA physical status 1 and 2 women scheduled for elective surgery with general anesthesia.

Measurements: Patients were divided into two groups according to their time in the menstrual cycle. Forty patients at days 8 to 12 of the menstrual cycle were considered to be at the follicular phase (Group F), and 40 patients at days 20 to 24 of the menstrual cycle were considered to be at the luteal phase (Group L). Withdrawal movements were recorded.

Main Results: Overall frequency of withdrawal movements was significantly higher in Group L than Group F ($P<0.001$). The mean withdrawal movement score was $1.77\pm0.76$ in Group L and $0.52\pm0.67$ in Group F.

Conclusion: Menstrual cycle phases affect the severity of rocuronium injection pain. Women exhibit greater pain sensitivity from rocuronium injection in the luteal phase than the follicular phase.

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1. Introduction

Rocuronium bromide is a steroidal nondepolarizing neuromuscular blocking agent [1,2]. Pain due to injection of rocuronium is a common adverse effect and occurs in 50% to 80% of patients [3,4]. A large proportion of women report...
increases in pain-related symptoms at certain stages of the menstrual cycle [5]. Anesthetic, analgesic, and antiemetic requirements also change across the menstrual cycle [6–8]. Several factors have been suggested to explain this situation. Findings from several animal studies indicated that gonadal hormones may influence responses to nociceptive stimuli among female rats. The effects of menstrual cycle still have not been investigated fully in humans [9,10]. There is no study regarding the influence of menstrual cycle on the rocuronium injection pain. The aim of this prospective, randomized, double-blinded study was to evaluate the effects of the follicular and luteal phases of the menstrual cycle on rocuronium injection pain.

2. Materials and methods

After obtaining Kecioren Training and Research Hospital’s Ethical Committee approval and informed consent from patients, 80 women between 18 and 49 years of age were enrolled in the study. Patients who were ASA physical status 1 and 2 and were scheduled for elective gynecologic surgery were studied. Exclusion criteria included neurological or psychiatric diseases, irregular menstrual cycle, history of combined oral contraceptive use, amenorrhea, pregnancy, renal and/or hepatic dysfunction, and hysterectomy and/or bilateral salpingo-oophorectomy.

None of the patients was premedicated in the present study. On patient arrival at the operating room (OR), a 20-gauge intravenous (IV) cannula was inserted into a vein on the dorsum of the hand for infusion of the crystalloid solutions and other premedications.

All patients were allocated to two groups according to the phase of their menstrual cycle. Forty patients who were at day 8 to 12 after the first day of their last menstruation were considered to be in the follicular phase of the menstrual cycle (Group F). Another 40 patients, who were at day 20 to 24 after the first day of their last menstruation, were considered to be in the luteal phase of the menstrual cycle (Group L).

Mean arterial blood pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO2) were recorded on arrival at the OR (baseline) and before, then one minute after endotracheal intubation. Anesthesia was induced with 5 mg/kg of IV thioental sodium 2.5%. Rocuronium 0.5 mg/kg at room temperature was injected over 10 to 15 seconds after loss of consciousness. Withdrawal movement of patients from the injection of rocuronium was assessed by anesthesiologist who was blinded to study group assignment. Withdrawal movement was graded on a 4-point scale, where 0 = no response, 1 = movement at the wrist only, 2 = movement involving the arm only (elbow or shoulder), and 3= generalized response (movement/withdrawal in more than one extremity, cough, breath holding) (Table 1). Before tracheal intubation, fentanyl 1 μg/kg was administered to all patients after assessment of withdrawal movement. Anesthesia was maintained with sevoflurane in 50% oxygen/nitrous oxide.

2.1. Statistical analysis

Statistical analysis was performed using the statistical package SPSS, version 15.0 for Windows (SPSS, Chicago, IL, USA). Based on an estimated incidence of 50% (grades 1, 2, or 3 vs grade 0), a power analysis (sample size calculation) indicated that 38 patients per group would be sufficient to detect a 30% difference in frequency of withdrawal movement between the groups, with a power of 80% at the significance level of 0.05. Descriptive statistics for continuous variables were given as means ± standard deviation and analyzed using Student’s t test. Withdrawal movements were analyzed by χ² test. A P-value < 0.05 was considered statistically significant.

3. Results

There were no significant differences between groups in patient characteristics (P>0.05) (Table 2). Patients’ hemodynamic parameters such as MAP, HR, and SPO2 were comparable between the two groups before and after tracheal intubation (Table 3).

The overall frequency of withdrawal movements was significantly higher in Group L than Group F (P<0.001) (Fig. 1). The mean withdrawal movement score was 1.77 ± 0.76 in Group L and 0.52 ± 0.67 in Group F. No patient in

<table>
<thead>
<tr>
<th>Group L</th>
<th>Group F</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31.4 ± 7.7</td>
<td>32.4 ± 6.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.1 ± 12.2</td>
<td>65.7 ± 10.1</td>
</tr>
<tr>
<td>Menstrual cycle (day)</td>
<td>21.8 ± 1.8</td>
<td>9.8 ± 1.7</td>
</tr>
<tr>
<td>Menstrual duration (day)</td>
<td>27.2 ± 1.2</td>
<td>27.5 ± 1.1</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviation.

Group L patients were at the luteal phase of the menstrual cycle, Group F patients were at the follicular phase of their menstrual cycle.

* Student t test.
Group F showed generalized movement, unlike 10% of Group L patients, who had such movement. A significant difference was noted between Groups F and L according to the frequency and degree of withdrawal movement after rocuronium injection ($P_{b} < 0.001$). Comparison of withdrawal responses during rocuronium injection between the two groups is shown in Table 4.

### Table 3  Hemodynamic parameters in both study groups

<table>
<thead>
<tr>
<th></th>
<th>Group L (n=40)</th>
<th>Group F (n=40)</th>
<th>$P$-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>BI 94.4 ± 10</td>
<td>92.4 ± 11.2</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td>AI 107 ± 15.6</td>
<td>109 ± 13.3</td>
<td>0.586</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>BI 84.7 ± 13.5</td>
<td>85.7 ± 15.2</td>
<td>0.881</td>
</tr>
<tr>
<td></td>
<td>AI 96.3 ± 14.2</td>
<td>102.7 ± 14.4</td>
<td>0.727</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>BI 98.6 ± 0.9</td>
<td>98.3 ± 1.3</td>
<td>0.320</td>
</tr>
<tr>
<td></td>
<td>AI 99.3 ± 0.7</td>
<td>99.4 ± 0.8</td>
<td>0.376</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviation.

Group L patients were at the luteal phase of the menstrual cycle, Group F patients were at the follicular phase of their menstrual cycle.

MAP=mean arterial pressure, BI=before intubation, AI=after intubation, HR=heart rate, SpO₂=peripheral oxygen saturation as measured by pulse oximeter.

* Student’s $t$ test.

### 4. Discussion

This study determined that withdrawal movement from rocuronium injection varies across the menstrual cycle in ASA physical status 1 and 2, healthy, normally menstruating women. Withdrawal movement scores were higher in the luteal phase than the follicular phase.

Pain related to administration of rocuronium is a common adverse effect and a distressing situation for the patients. The rocuronium injection causes hand or limb withdrawal in 80% of patients, even after induction of anesthesia with propofol or thiopental sodium, suggesting the presence of intense nociception. Several theories have been proposed to explain the injection pain due to rocuronium, including direct activation of C-nociceptors by the osmolality or low pH of the rocuronium solution or activation by the release of endogenous mediators such as histamine or bradykinin causing inflammation [3,11,12].

Mencke et al reported that women experienced more severe pain than did men on injection of rocuronium. They explained this finding as a gender-related difference of pain perception [13]. In the present study, we aimed to compare the effect of the menstrual cycle on injection pain from rocuronium; we found that women had higher withdrawal movements scores in the luteal phase than the follicular phase.

Most studies have used experimental pain when evaluating the effect of menstrual cycle on pain perception, but there are limited data for clinical pain. Kowalczyk et al reported no significant differences in cold pressure pain threshold or tolerance according to the phases of the menstrual cycle [14]. Similarly, Vignolo et al showed that different phases of the menstrual cycle did not influence the pressure pain threshold [15]. However, previous studies have reported that thermal pressure, ischemic venipuncture, and propofol injection pain appeared to be higher during the luteal than the follicular phase [16–19]. Riley et al suggested that electrical stimulation differed from the other stimulus modalities that showed a higher pain threshold during the luteal phase [16]. Consideration of the stimulation method and the site of stimulation is important when evaluating the effects of the menstrual cycle on pain [20].

Gonadal hormones may influence the responses to nociceptive stimuli among women. Exogenous administration of luteinizing hormone may lead to diminished analgesic responses to morphine; desensitization of brain opioid receptors has been observed in animal studies [10,11]. Estradiol plays a critical role in the pain modulation system of female mice [21]. Administration of estradiol induced a reduction of nociceptive responses in rats [22]. Furthermore, elevated estrogen and progesterone levels as seen during pregnancy produce analgesia that is modulated through the spinal cord $\kappa$-opioid receptor analgesic system [23].

Increased pain sensitivity correlates with elevated progesterone levels and decreasing estrogen levels. While estrogens influence mood and well-being, progesterone has

### Table 4  Frequency and degree of withdrawal movements associated with rocuronium injection pain

<table>
<thead>
<tr>
<th>Withdrawal movements</th>
<th>Group L (%)</th>
<th>Group F (%)</th>
<th>$P$-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4 (10.0)</td>
<td>23 (57.5)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>1</td>
<td>5 (12.5)</td>
<td>13 (32.5)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>2</td>
<td>27 (67.5)</td>
<td>4 (10.0)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>3</td>
<td>4 (10.0)</td>
<td>0 (0.0)</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

Data are expressed as numbers (%).

Group L patients were at the luteal phase of the menstrual cycle, Group F patients were at the follicular phase of their menstrual cycle.

* Chi-square test.

**Fig. 1**  Comparison of withdrawal movements between patients from Group L (luteal phase of the menstrual cycle) and Group F (follicular phase of the menstrual cycle).
an inhibitory effect on neuronal activities [24]. Specifically, temporomandibular pain and migraine and tension types of headache are more likely to occur – and more intensely – at times of low estrogen levels [25,26]. In the present study, rocuronium injection pain was significantly lower in the follicular phase than the luteal phase (P<0.001). Ninety percent of patients showed withdrawal movements ≥ 1 in the luteal phase, which may be explained by the higher levels of progesterone. Mood changes and decreased β endorphin levels in the late luteal phase also may affect the perception of pain [24]. Spontaneous movements associated with rocuronium injection may be the direct consequence of intense noiception on injection by releasing mediators such as bradykinin, calcitonin gene-related peptide (CGRP), and prostaglandin E2 (PGE2) [12]. Rocuronium injection may cause severe pain with a burning sensation [4]. This type of pain may cause increased response to nociceptive stimuli during the luteal phase with the low estrogen levels.

In the present study, we did not measure estrogen or progesterone levels while evaluating menstrual cycle effects, as was done in other studies [7,8,15,19]. Luteinizing hormone peaks on the 13th day, and progesterone starts to increase at the 18th day, of the cycle [27]. For this reason, patients who were at the 13th to 19th days of their menstrual cycle were excluded so that we might better distinguish between the luteal and follicular phases.

Hancı et al reported that menstrual cycle phases affect the hemodynamic response to tracheal intubation [28]. In the present study, there were no differences in HR or noninvasive arterial blood pressure before or after tracheal intubation, as fentanyl 1 μg/kg was administered before intubation.

The menstrual cycle phases also affect the severity of rocuronium injection pain. Women may exhibit greater pain sensitivity from rocuronium injection in the luteal phase than the follicular phase.

Reference