

The Relationship between Menstrual Cycle Phases with Postoperative Nausea and Vomiting after Open Cholecystectomy Surgery

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Abstract

Background: Postoperative Nausea and Vomiting (PONV) is one of the common and unpleasant complications after surgery. The menstrual cycle may be one of the factors which affect the incidence of PONV.

Objectives: This study aimed to determine the relationship between different phases of the menstrual cycle and PONV.

Methods: The present study was a cross-sectional descriptive study and involved 70 women, 15-45 years old, ASA (American Society of Anesthesiologists) class I and II and were candidates for elective open cholecystectomy. The first day of the previous menstrual period was considered the first day of the cycle, and the patients were divided into two phases: days one to 14 constituted the proliferative and the follicular phases and days 14 to the last day of the cycle constituted the luteal phase. The patients' general anesthesia was accomplished in a standard way. After the end of operation and the transfer of patients to the recovery room, their rate of nausea and vomiting during recovery, within the first two hours, and the first two to six hours of their transfer to the department was examined and recorded. The Rhodes index was used to determine the severity of nausea and vomiting. The data were analyzed using of descriptive statistics, chi-square test, and independent t-test using SPSS 17 software.

Results: Based on the results of this study, the severity of PONV during recovery, the first two hours, and the first two to six hours after the transfer of participants to the department did not significantly differ among the different phases. Moreover, there was not a significant difference between the occurrence of nausea and vomiting and the menstruation phases regardless of its severity in the mentioned periods. The received amount of anti-nausea or anti-vomiting medication (i.e. Plasil in this study) was higher in the proliferative-follicular phase in the first 24 hours (p value=0.011).

Conclusion: This study showed that menstrual phase does not affect the incidence and severity of PONV.

Keywords: *cholecystectomy, menstrual cycle, postoperative nausea and vomiting*

Introduction

Postoperative Nausea and Vomiting (PONV) is one of the most serious complications after surgery and has been examined in various studies [1-3]. Although PONV is self-limiting in most cases, it is an unpleasant complication and can lead to the patient's discomfort and dissatisfaction. Moreover, it prolongs the recovery time, increases the patient's care costs, results in the aspiration of the contents of the stomach, opens up the stitches, and rarely leads to dehydration and electrolyte disturbances [4-9]. Each episode of vomiting causes a 20-minute delay in discharging the patient from the recovery

section [10]. Despite progress in anti-vomiting treatments, the prevalence of PONV is 20% to 30% and reaches 70% in people with specific risk factors. These risk factors include: being female, having a history of PONV, having a history of motion sickness, being a non-smoker, being at lower age groups, being anaesthetized with inhaled medications, using drugs, and undergoing breast, middle ear, and gynecologic surgeries in women [11-14]. Various studies have shown that the menstrual cycle in women has an effect on the incidence of PONV [15-18]. The rate of PONV in women is two to four times higher than its rate in men [10]. During the menstrual cycle, the change

in blood levels of sex hormones in women is three times higher than this change in men [19]. There is a controversy over the effects of menstrual phases on PONV. Some studies have shown that its risk increases in the follicular phase [20-22]. Other studies have revealed that its rate increases in the luteal phase [23]. Finally, the results of a number of studies have shown that the menstrual cycle does not affect its rate [24-25]. Moreover, Apfel and Gratz's study highlighted the fact that there was not a relationship between menstrual phases and PONV [11,24]. Another study revealed that hormonal changes (especially estrogen) play a role in vomiting syndromes. Moreover, it showed that changes in the concentration of progesterone or 17-beta-estradiol may result in the sensitivity of the vomiting center [19]. These findings are clinically important due to the fact that surgical planning can be effective in preventing or reducing PONV levels. Considering the complications and the importance of preventing and treating PONV, the fact that the female gender is a well-known and important risk factor, and the existence of few studies with contradictory results about this issue (especially in Iran), we made an endeavor to examine the differences in PONV among the women's menstrual cycle phases. The results of this study can help us to determine the time of elective surgery in women accurately and to provide an effective way to prevent this serious complication.

Methods

The present study was a cross-sectional descriptive study and obtained the zums.rec.1392.63 permission number from the Ethics Committee. It was conducted in the 2013-2014 time period and involved 70 women 15-45 years old, ASA (American Society of Anesthesiologists) class I and II and were candidates for elective open cholecystectomy in the operating room of Ayatollah Mousavi Hospital in Zanjan. They had specific characteristics including: giving consent, having regular menstrual cycles (28-35 days), passing a minimum of an eight-week time period after the end of pregnancy (Considering the fact that according to gynecologic's references, there is the possibility of nausea and vomiting due to hormonal changes until two months after delivery, patients who had undergone surgery before the

end of eight weeks were excluded from the study in order to remove the aforementioned factor), not using medications that reduce or stimulate PONV such as antipsychotics and corticosteroids, being non-pregnant or non-breast feeder, knowing the last day of the period, having a minimum of an eight-hour of fasting time period, not having no history of surgery on the stomach or esophagus, not having a previous history of PONV, being a non-smoker, and undergoing a surgery which took less than two hours.

The first day of the previous menstrual cycle of the patients who had the required criteria was considered to be the first day of the cycle and the patients were divided into two groups: the first group consisted of women who were in the proliferative-follicular phase (days one to 14), and the second group comprised the women who were in the luteal phase (days 15 to the last day of the cycle). Purposive sampling was utilized to select 35 participants for each of these groups in the 2013-2014 time period. After the patients' entrance into the operating room, intravenous access was secured with 18-G cannula and 20 ml ringer serum per kilogram of body weight per hour was administered for all patients. Standard monitoring included electrocardiography, pulse oximetry, and arterial blood pressure measurements. All of the patients received two mg midazolam and 100 micrograms fentanyl as premedication. After pre-oxygenation, anesthesia induction was performed with sodium thiopental 5mg/kg and atracurium 0.5 mg/kg and the patients were intubated after three minutes. Anesthesia was administered to the patients with 50% O₂+50% N₂O, iso-fluoranes 1 to 1.5%, Atracurium 0.1 mg/kg repeated every 20 minutes until the end of operation. At the end of the operation and after the beginning of the patients' spontaneous respiration, the effects of muscle relaxation medications including neostigmine 0.04 mg / kg and atropine 0.02 mg / kg were reversed and the patients were extubated and transferred to the recovery room after the examination of the stability of their respiratory status. The severity of patients' nausea and vomiting in the recovery room and during the first two hours and two to six hours after their transfer to the department were examined and recorded. The Rhodes index was used to determine the severity of nausea and vomiting. Accordingly, nausea or vomiting was

classified into four categories based on the degree of severity: degree 0=lack of nausea and vomiting; degree 1: nausea only irritates the patient; degree 2=patient vomits less than two times; and degree 3=patient vomits more than two times. Moreover, the complication with the higher degree of severity was emphasized in the classification of the severity of these complications. For instance, if the patient had moderate vomiting and severe nausea, the researcher would place them in the severe nausea and vomiting category. Similarly, if the patient had severe nausea without vomiting, the researcher classified them in the same category. Subsequently, the severity of postoperative nausea and vomiting was analyzed based on the collected data. Rodex index was used to determine the severity of nausea and vomiting [26]. The data were analyzed by means of descriptive statistics, chi-square test, and independent t-test using SPSS 17 software. In this study, $p < 0.05$ was considered to be statistically significant.

Results

In the present study, the mean age of the participants of the first group, who were in the proliferative-follicular phase, was 28 ± 0.6 . Furthermore, this age was 29 ± 5.9 for the participants of the second group who were in the luteal phase. Based on the results of the independent t-test, there was not a significant difference between the age of the participants who were in the proliferative-follicular phase and the ones who were in the luteal phase ($p = 0.463$). Table 1 provides the results of the comparison in regard to the severity of nausea and vomiting at the time of recovery, the first two hours, and the first two to six hours after the operation. The results of chi-square showed that the difference between the severity of nausea and vomiting in these time periods and the menstrual phases was not significant ($p\text{-value} = 0.206$, $p\text{-value} = 0.143$, & $p\text{-value} = 0.112$) (Table 1).

Table 1: Comparison of severity of nausea and vomiting in different postoperative time periods based on menstrual phase

After Surgery	Menstrual Phase	Nausea & Vomiting Severity				P value	
		0	1	2	3		
In Recovery	Luteal	22(%62.9)	13(%37.1)	0(%0)	0(%0)	0.206	
	Proliferative-Follicular	16(%45.7)	16(%45.7)	2(%5.7)	1(%9.2)		
In Ward	2h	Luteal	8(%22.9)	17(%48.6)	8(%22.9)	2(%5.7)	0.143
		Proliferative-Follicular	5(%14.3)	5(%42.9)	6(%17.1)	9(%25.7)	
	2-6h	Luteal	4(%11.4)	22(%62.9)	9(%25.7)	0(%0)	0.112
		Proliferative-Follicular	9(%25.7)	17(%48.6)	6(%17.1)	3(%8.6)	

Moreover, the results of the comparison regarding the existence or lack of nausea and vomiting without the examination of the severity of nausea

in the aforementioned two phases highlighted the lack of a significant difference (Table 2)

Table 2: Comparison of the presence or absence of nausea and vomiting in different time periods after the operation based on the menstrual phase

After Surgery	Menstrual Phase	Nausea & Vomiting Status			P value	
		NO	YES	TOTAL		
		recovery	Luteal	22		13
Proliferative-Follicular	16		19	35		
In Ward	2h	Luteal	8	27	35	0.540
		Proliferative-Follicular	5	30	35	
	2-6h	Luteal	4	31	35	0.218
		Proliferative-Follicular	9	26	35	

Furthermore, in this study, the amount of the received anti-nausea or anti-vomiting medication

(i.e. Plasil in this study) was compared between the two groups during the first 24 hours. The

results showed that, this amount was larger in the proliferative-follicular phase (p-value=0.011)

(Table 3)

Table 3: The relationship between the total received Plasil and the menstrual phase

	Zero time N=28	One time N=25	Two to three times N=14	More than three times N=3
Luteal Phase	18(%51.4)	14(%40)	2(%5.7)	1(%2.9)
Proliferative-Follicular Phase	10(%28.6)	11(31.4)	12(%34.3)	2(%5.7)
P value=0.011				

Discussion

The present study showed that the menstrual phases did not have an effect on the severity of nausea and vomiting during recovery, the first two hours, and the first two to six hours after the transfer of the participants to the department. Moreover, it revealed that, the difference between the severity of nausea and vomiting in these time periods and menstrual phases was not significant. There is controversy over the effect of menstrual phases on nausea and vomiting. In some studies the risk of PONV increases in the follicular phase [22-25]. Nonetheless, in other studies this risk increases in the luteal phase [23].

These results are in line with the results of a number of previous studies [11,19,24,25]. Nevertheless, the results of the study by Honkavara et al. showed that nausea and vomiting after gynecological laparoscopic surgery depended on the phase of the menstrual cycle and its most severe state occurred in the luteal phase [17]. The findings of another study, which was conducted by Beattie, showed that the menstrual cycle had a noticeable predictive effect on PONV. In this study, patients were examined only for the presence or absence of nausea and vomiting regardless of their severity for 24 hours. Based on the findings, the rate of nausea and vomiting increased for the participants who were in the first eight days of the menstrual cycle [18]. The reason behind the difference between the results of this study and the results of our study may be its longer follow-up of patients. In the study by vahhabi et al., PONV and the requirement for metoclopramide had the highest rate in the first 24 hours after surgery in women who were in the luteal and follicular phases. On the other hand, they had the lowest rate in the menstrual and premenstrual phases [27]. In this study, menstrual phases were defined as follows: follicular

phase=days eight to 12, ovulation phase=days 13 to 15, luteal phase=days 20 to 24, and the next cycle of the premenstrual phase=days 25 to six. The highest intensity degree of PONV was in luteal and follicular phases. On the other hand, its lowest intensity degree was in the premenstrual phase. It appears that, the difference between our results and the results of this study stems from their different ways of classification of menstrual cycle.

In another study Vahhabi et al. showed that there was not a difference between the incidence of nausea and vomiting in women before and after menopause [9]. Notwithstanding, Leksowski showed that there was a high incidence of PONV in women after menopause [28].

The findings of the study which was carried out by Simurina showed that, PONV rates were lower in participants who were in the luteal phase in comparison with the other participants. These findings are in line with the results of our study. Nonetheless, based on our results, this difference was not significant [22]. One of the important issues in the study of the effect of menstrual phases on PONV is the various and incompatible definitions of menstrual cycle phases and menstrual cycle changes from woman to woman and from cycle to another cycle. This issue may lead to the differences among the findings of the relevant studies.

This study was limited due to its short (six hours) follow-up of the patients. It is suggested that the future studies monitor the patients' nausea and vomiting for 24 hours. The high prevalence of PONV in women at the beginning of pregnancy and during pregnancy highlights the role of sex hormones in this mechanism [29]. Studies on PONV have not measured the amount of sex hormones. This issue may be a cause of controversy surrounding the results. The result of

a study revealed that high levels of estradiol increased the risk of PONY [30]. The findings of another study showed that its low levels increased this risk [31]. Finally, based on the results of a certain study estradiol did not affect PONV [32]. Consequently, it is suggested that, future studies examine the sex hormones levels.

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Conflict of interest

There is no conflict of interest in this study.

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References

- 1- Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999; 91: 693–700.
- 2- Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. *Anaesthesia*. 1997; 52: 443–49.
- 3- Stadler M, Bardiau F, Seidel L, Albert A, Boogaerts JG. Difference in risk factors for postoperative nausea and vomiting. *Anesthesiology*. 2003; 98(1): 46–52.
- 4- Rüsç D, Eberhart LH, Wallenborn J, Kranke P. Nausea and Vomiting After Surgery Under General Anesthesia. *Dtsch Arztebl Int*. 2010; 107(42): 733–41.
- 5- Eberhart LH, Hogel J, Seeling W, Staack AM, Geldner G, Georgieff M. Evaluation of three risk scores to predict postoperative nausea and vomiting. *Acta Anaesthesiol Scand*. 2000; 44(4): 480–88.
- 6- Visser K, Hassink EA, Bonsel GJ, Moen J, Kalkman CJ. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: postoperative nausea with vomiting and economic analysis. *Anesthesiology* 2001; 95(3): 616–26.
- 7- Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but

not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth*. 2002; 88: 659–68.

8- Scuderi PE, Conlay LA. Postoperative nausea and vomiting and outcome. *Int Anesthesiol Clin*. 2003; 41(4): 165-74.

9- Vahabi S, Abaszadeh A, Yari F, Yousefi N. Postoperative pain, nausea and vomiting among pre- and postmenopausal women undergoing cystocele and rectocele repair surgery. *Korean J Anesthesiol*. 2015; 68(6): 581-85.

10- Gan TJ, Meyer TA, Apfel CC, et al. Society of ambulatory anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2007; 105: 1615-28.

11- Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth*. 2012; 109(5): 742-53.

12- Harmon D, Ryan M, Kelly A, Bowen M. Acupressure and prevention of nausea and vomiting during and after spinal anaesthesia for caesarean section. *Br J Anaesth*. 2000; 84(4):463-67.

13- Van den Bosch J, Moons K, Bonsel G, Kalkman CJ. Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting. *Anesth Analg*. 2005; 100(5): 1525-32.

14- Mraovic B, Simurina T, Sonicki Z, Skitarellic N, Gyan TJ. The dose response of nitrous oxide used in postoperative nausea in patients undergoing gynecologic laparoscopic Surgery – A preliminary study. *Anesth Analg*. 2008; 107(3): 818-23.

15- Morino R, Ozaki M, Nagata O, Yokota M. Incidence of and risk factors for postoperative nausea and vomiting at a Japanese Cancer Center: first large-scale study in Japan. *J Anesth*. 2013; 27: 18–24.

16- Kitamura A, Kon T, Kamiyama M, Ogawa R. Menstrual stage influences postoperative nausea and Vomiting following epidural buprenorphine. *Acta anaesthesiol scand*.1996; 40(3): 368-71.

17- Honkavara P, Lehtinen AM, Hokava S, Korttila K. Nausea and Vomiting after gynecological laparoscopy depends on the phase of the menstrual cycle. *Can J Anaesth*. 1991; 38(7): 876-79.

18- Beattie WS, Hidbland T, Buckley DN, Forrest JB. Menstruation increases the risk of nausea and

- vomiting after laparoscopy, A prospective randomized study. *Anesthesiology*. 1993; 78: 272-76.
- 19- Sener EB, Kocamanoglu S, Cetinkaya MB, Ustun E, Bildik E, TurA. Effects of Menstrual cycle on postoperative Analgesic Requirements, Agitation, Incidence of Nausea and vomiting after Gynecological laparoscopy. *Gynecol Obstet Invest*. 2005; 59 (1): 49-53.
- 20- Beattie WS, Lindblad T, Buckley DN, Forrest JB. Menstruation increases the risk of nausea and vomiting after laparoscopy. *Anesthesiology*. 1993; 78(2): 272-76.
- 21- Beattie WS, Lindblad T, Buckley DN, Forrest JB. The incidence of postoperative nausea and vomiting in women undergoing laparoscopy is influenced by the day of menstrual cycle. *Can J Anaesth*. 1991; 38(3): 298-302.
- 22- Simurina T, Mraovic B, Skitarelic N, Andabaka T, Sonicki Z. Influence of the menstrual cycle on the incidence of nausea and vomiting after laparoscopic gynecological surgery: a pilot study. *J Clin Anesth*. 2012; 24(3): 185-92.
- 23- Honkavaara P, Lehtinen AM, Hovorka J, Korttila K. Nausea and vomiting after gynaecological laparoscopy depends upon the phase of the menstrual cycle. *Can J Anesth*. 1991; 38(7): 876-79.
- 24- Gratz I, Allen E, Afshar M, Joslyn AF, Buxbaum J, Prilliman B. The effects of menstrual cycle on the incidence of emesis and efficacy of ondansetron. *Anesth Analg*. 1996; 83(3): 565-69.
- 25- Green G. Levels of estradiol but not phase of menstrual cycle influences the incidence of post-operative nausea and vomiting among fertile women. *Acta anaesthesiologica scandinavica*. 1997;41(suppl 110):173.
- 26- Zhou Q, O'Brien B, Soeken K. Rhodes index of Nausea and vomiting form 2 in pregnant women: a confirmatory factor analysis. *Nurs Res*. 2001. 50(4): 251-57
- 27- Vahabi S, Ghafarzade M, Lorzade N, Moradkhani M R, Frazan B, Geranghadr P. The effect of menstrual cycle phase on the meperidine and metoclopramide consumption rate for controlling postoperative pain, nausea and vomiting. *yafta*. 2007; 9 (1):15-22
- 28- Leksowski K, Peryga P, Szyca R. Ondansetron, metoclopramid, dexamethason, and their combinations compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a prospective randomized study. *Surg Endosc*. 2006; 20(6): 878-82.
- 29- Gan TJ. Risk factors for postoperative nausea and vomiting. *Anesth Analg*. 2006; 102(6): 1884-98.
- 30- Lindblad T, Forrest JB, Buckley DN, Beattie WS. Anaesthesia decreases a hormone mediated threshold for nausea and vomiting. *Anesth Analg*. 1990; 70: S242.
- 31- Harmon D, Connor PO, Lennon M, Hamilton V, Moran C, Gardiner J. The effects of the menstrual cycle and oestradiol concentration on postoperative nausea and vomiting. *Eur J Anaesthesiol*. 2000; 17(sup 19): 13.
- 32- Lee JW, Kim SK, Kim DC, Han YJ, Ko SH. The effects of female hormones on postoperative nausea and vomiting. *Korean J Anesthesiol*. 2008; 54: 58-62.