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SCIENTIFIC ARTICLE

The influence of the menstrual cycle on acute and persistent pain after laparoscopic cholecystectomy

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Acute pain;
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Abstract
Background and objectives: Fluctuations of female sex hormones during menstrual cycle influence pain perception. Endogenous pain inhibition is impaired in follicular phase of menstrual cycle. We tested the primary hypothesis that the women having surgery during their follicular phase have more acute pain and require higher opioids than those in the luteal phase, and secondarily we tested that women who have surgery during their follicular phase have more incisional pain at 3 month postoperatively.
Methods: 127 adult females having laparoscopic cholecystectomy were randomized to have surgery during the luteal or follicular phase of their menstrual cycle. Standardized anesthesia and pain management regimen was given to all patients. Pain and analgesic consumption were evaluated in post-anesthesia care unit and every 4 h in the first 24 h. Adverse effects were questioned every 4 h. Time to oral intake and ambulation were recorded. Post-surgical pain, hospital anxiety, depression scale, SF-12 questionnaire were evaluated at 1 and 3 month visits.
Results: There was no difference in acute pain scores and analgesic consumption through the 24 h period, Visual Analog Scale at 24 h was 1.5 ± 1.5 cm for follicular group 1.4 ± 1.7 cm for luteal group ($p = 0.57$). Persistent postoperative pain was significantly more common one and at three month, with an incidence was 33% and 32% in the patients at follicular phase versus 16% and 12% at luteal phase, respectively. The Visual Analog Scale at one and at three month

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was 1.6 ± 0.7 cm and 1.8 ± 0.8 cm for follicular group and 2.7 ± 1.3 cm and 2.9 ± 1.7 cm in the luteal group ($p = 0.02$), respectively. There were no significant differences between the groups with respect to anxiety and depression, SF-12 scores at either time. Nausea was more common in follicular-phase group ($p = 0.01$) and oral feeding time was shorter in follicular phase (5.9 ± 0.9 h) than in luteal phase (6.8 ± 1.9 h, $p = 0.02$).
Conclusions: Although persistent postoperative pain was significantly more common one and three months after surgery the magnitude of the pain was low. Our results do not support scheduling operations to target particular phases of the menstrual cycle.

PALAVRAS-CHAVE
Ciclo menstrual;
Dor aguda;
Dor crônica;
Colecistectomia;
Laparoscopia;
Dor pós-operatória

A influência do ciclo menstrual na dor aguda e persistente após colecistectomia laparoscópica

Resumo
Justificativa e objetivos: As flutuações dos hormônios sexuais femininos durante o ciclo menstrual influenciam a percepção da dor. A inibição endógena da dor é prejudicada na fase folicular do ciclo menstrual. Testamos a hipótese primária de que cirurgias em mulheres durante a fase folicular têm mais dor aguda e precisam de mais opioide que aquelas na fase lútea e a hipótese secundária testada foi que as cirurgias em mulheres durante a fase folicular têm mais dor incisional aos três meses de pós-operatório.
Métodos: No total, 127 mulheres adultas submetidas à colecistectomia laparoscópica foram randomizadas para serem operadas durante a fase lútea ou folicular de seus ciclos menstruais. Um regime padronizado para anestesia e tratamento da dor foi administrado a todas as pacientes. A dor e o consumo de analgésico foram avaliados na sala de recuperação pós-anestésica e a cada quatro horas nas primeiras 24 horas. Efeitos adversos foram avaliados a cada quatro horas. Os tempo para ingestão oral e deambulação foram registrados. Dor pós-cirúrgica, ansiedade hospitalar, escala de depressão e questionário SF-12 foram avaliados em visitas feitas no primeiro e terceiro meses.
Resultados: Não houve diferença nos escores de dor aguda e no consumo de analgésicos durante o período de 24 horas, Escala Visual Analógica em 24 horas foi de 1,5 ± 1,5 cm para o grupo folicular e 1,4 ± 1,7 cm para o grupo lúteo ($p = 0,57$). A dor persistente no pós-operatório foi significativamente mais prevalente no primeiro e terceiro mês, com incidência de 33% e 32% nas pacientes em fase folicular *versus* 16% e 12% na fase lútea, respectivamente. A Escala Visual Analógica no primeiro e terceiro mês foram 1,6 ± 0,7 cm e 1,8 ± 0,8 cm no grupo folicular e 2,7 ± 1,3 cm e 2,9 ± 1,7 cm no grupo lúteo ($p = 0,02$), respectivamente. Não houve diferença significativa entre os grupos em relação à ansiedade e à depressão, escore SF-12 em ambos os tempos. Náusea foi mais comum no grupo na fase folicular ($p = 0,01$) e o tempo para alimentação oral foi menor na fase folicular (5,9 ± 0,9 horas) que na fase lútea (6,8 ± 1,9 horas, $p = 0,02$).
Conclusões: Embora a dor persistente no pós-operatório tenha sido significativamente mais prevalente no primeiro e no terceiro mês após a cirurgia, a magnitude da dor foi baixa. Nossos resultados não apoiam o agendamento de cirurgias tendo como alvo fases específicas do ciclo menstrual.

Introduction

Acute postoperative pain is complex and affected by multiple factors including sex. Sex seems to play an important role in the perception and interpretation of pain.[1,2] With comparable stimuli, for example, women report more pain than men. Women also have lower pain thresholds. Fluctuations of female sex hormones during the menstrual cycle also influence pain sensitivity, possibly via interaction with serotoninergic and noradrenergic neurons, which effect inhibitory pain pathways and sensory neurons.[3–5] Furthermore, there appear to be increases in opioid receptor expression prompted by higher circulating concentrations of estrogen and progesterone.[5,6] Another potential mechanism is that estrogen enhances activity of N-methyl-D-aspartate receptors, which are important modulators of both acute and chronic pain.[6]

Sex differences also play important roles in chronic pain; women are more likely than men to report chronic pain syndromes.[7,8] Animal models have also demonstrated

significant increase in chronic pain in ovariectomized animals.[2,9] The potential importance of sex hormones was illustrated in a clinical study in which menstrual cycle disorders were associated with development of complex regional pain syndrome.[10]

Poorly controlled acute post-operative pain is strongly associated with development of persistent pain syndromes.[11] It is thus plausible that factors that reduce acute postoperative pain will also reduce the risk of persistent surgical pain. Many are unmodifiable; but most surgery could be scheduled at specific phases of the menstrual cycle if doing so resulted in less postoperative pain. Published studies of menstrual cycle and acute postoperative pain are scarce, and there are essentially none on persistent surgical pain. We therefore evaluated the theory that endogenous pain inhibition is impaired in the follicular phase when the level of estradiol is high and progesterone is relatively low. Specifically, we tested the *primary hypothesis* that the women having surgery during their follicular phase have more acute pain and require higher opioids than those in the luteal phase. Our *secondary hypothesis* was that women who have surgery during their follicular phase have more incisional pain 3 month postoperatively than those who have surgery during their luteal phase.

Methods

This study was permitted and approved by the Local Ethics Board. After written consent, 127 adult females having laparoscopic cholecystectomy were enrolled in this randomized, blinded study in Traning and Research Hospital.

We included women who were American Society of Anesthesiologists physical status I-III, had no significant cardiovascular or central nervous system disease, had regular and predictable menstrual cycles lasting 25–35 days, no irregularities or major gynecological problems, and who knew the date of their last menstruation. Menses onset was self-reported by the patient. The phase of menstrual cycle was determined by counting days from the first day of the last menstrual period. We considered days between 6 and 12 as follicular and days 20–24 as luteal. Women who were between 13 and 19 days of their cycles were not included because neither luteinizing nor progesterone hormones predominant during this period.

Patients with pre-existing pain syndromes or routinely using opioids were excluded. Participants were further excluded for use of hormone preparations in the last 6 months; hysterectomy; breastfeeding in the previous 6 months; or body mass index >35 $kg.m^2$. Only women with a negative urine pregnancy test were included.

Protocol

Participating women were randomized to have surgery during the luteal or follicular phase of their menstrual cycle. The randomization was computer-generated and allocation was concealed until after consent was obtained. During the preoperative evaluation and on the day of surgery before anesthetic premedication, Visual Analog Scale (VAS) pain reporting was explained to participating women. The research staff involved in post-operative assessments was blinded to menstrual cycles. For premedication, 0.07 $mg.kg^{-1}$ midazolam and 0.01 $mg.kg^{-1}$ atropine were given intramuscularly 45 min before surgery. Fentanyl, 1 $mcg.kg^{-1}$ IV, was given before the surgical incision, and thereafter as clinically indicated by attending anesthesiologists who were blinded to menstrual cycle.

Anesthesia was induced with 2–2.5 $mg.kg^{-1}$ propofol and 0.6 $mg.kg^{-1}$ rocuronium. Mechanical ventilation was maintained to keep end-expiratory CO_2 partial pressure between 34 and 42 mmHg. During laparoscopy, intra-abdominal pressure is set at 10–12 mmHg, and residual carbon dioxide was carefully evacuated at the end of the surgery via open trocars. Patients were given sevoflurane for maintenance of anesthesia, titrated to clinical needs with the general goal of keeping BIS between 40 and 60. Before skin closure, 0.1 $mg.kg^{-1}$ morphine was given IV and residual neuromuscular blockade was antagonized by neostigmine 1.5 mg and atropine 0.5 mg. Four mg ondansetron was given before extubation for postoperative nausea and vomiting prophylaxis.

Patients were given 75 mg diclofenac intramuscularly if VAS pain scores exceeded 4 or when patients requested analgesic. Meperidine (0.5 $mg.kg^{-1}$) was given intravenously if pain scores remained >4 cm on a 10 cm visual analog scale 1 h after diclofenac administration. Starting 24 h after surgery, 75 mg diclofenac was given orally every 12 h. Ondansetron, 4 mg, was given intravenously when patients reported nausea or vomited.

Measurements

Morphometric and demographic parameters (age, sex, height, and weight) were recorded preoperatively. Pain scores, on a 10 cm Visual Analog Scale (VAS), were evaluated while patients were lying in bed, while sitting 30 and 60 minutes after arrival in the post-anesthesia care unit, and thereafter on the ward every 4 h for 24 h by an investigator blinded to menstrual status. At each interval, an investigator also recorded heart rate, oxygen saturation, mean blood pressure, respiratory rate, Ramsey sedation scale, and meperidine and diclofenac use. Investigators blinded to the women's menstrual phase conducted all postoperative measurements.

Patients were questioned every 4 h through the postoperative 24 h. About the occurrence of any adverse effects, such as nausea and vomiting, constipation, respiratory depression, dizziness, urinary retention, somnolence, peripheral edema, diarrhea, headache, and pruritus. Patient's satisfaction overall with their treatment was recorded at 24 h, and then 1 and 3 months after surgery. Time to oral intake and ambulation were recorded.

One and three months after surgery, participating women were seen at clinic and post-surgical pain was evaluated dichotomously (yes/no). Patients with pain were asked to rate its severity on a VAS scale. The 14 item Hospital Anxiety and Depression Scale (HADS) was also used to evaluate the anxiety and depression at 1 and 3 month visits. Patients were also evaluated for their quality of life using the SF-12 questionnaire one and three months postoperatively.

Table 1 Baseline characteristics of the patients.

Characteristics	Group F ($n=63$)	Group L ($n=64$)	p-value
Age (years)	35 ± 8	35 ± 8	0.99[b]
ASA status			
1	65%	60%	0.6[a]
2	33%	40%	
3	2%	0	
Weight (kg)	71 ± 13	71.9 ± 12	0.71[b]
Height (cm)	163 ± 6	160 ± 6	0.19[b]
Surgical time (min)	46 ± 12	48 ± 15	0.28[b]
Received postoperative Diclofenac	43	34	0.10[a]
Received postoperative Ondansetron	16	11	0.29[a]
Received postoperative Meperidine	8	3	0.13[a]

Data are represented as mean $\pm$ SD, and patient percentage (%).
[a] Chi-square.
[b] *t*-test.

Statistical analysis

In retrospective analysis of 4 laparoscopic cholecystectomy patients, we observed a mean VAS pain score of 4.6 cm, with a standard deviation of 2.1 cm. Thus 59 patients per group were expected to provide an 80% power for detecting a 30% reduction in pain scores at an alpha value of 0.05.

Demographic and morphometric characteristics were summarized as means and standard deviations. Pearson's Chi squared test was used to compare nausea and consumption of diclofenac, ondansetron, and meperidine among the follicular and luteal phase groups at the collected time points. All other outcomes were compared among the follicular and luteal phase groups with Student *t* tests. The Bonferroni multiple comparison correction was used to control the multiple comparisons. Bonferroni corrected *p*-values are reported. A significance criterion of $p < 0.05$ was used. JMP Pro 9.0.00 (SAS Institute, Cary, NC) was used for statistical analysis.

Results

A total of 216 patients screened, 137 patients were consented for the study, and 10 were dropped from study participation because of scheduling conflicts. All 127 remaining patients were included, and no patient data were excluded. None of the planned laparoscopic procedures was converted to open surgery. There were no significant differences between the groups with respect to age, weight, height, ASA physical status, number of patients who received postoperative ondansetron, diclofenac, and meperidine, or surgical/anesthesia duration (Table 1). Additionally, patients in both groups received the same dose of fentanyl (1 mcg.kg^{-1}) at the start of surgery. Immediate postoperative pain scores were similar at all times (Fig. 1). Diclofenac and meperidine consumption at 0–2 h were similar in women assigned to surgery during the luteal and follicular phases of the menstrual cycle (Table 1). In the ward none of the patients required diclofenac and meperidine.

Patient satisfaction with pain treatment did not differ significantly; furthermore time to ambulation was similar

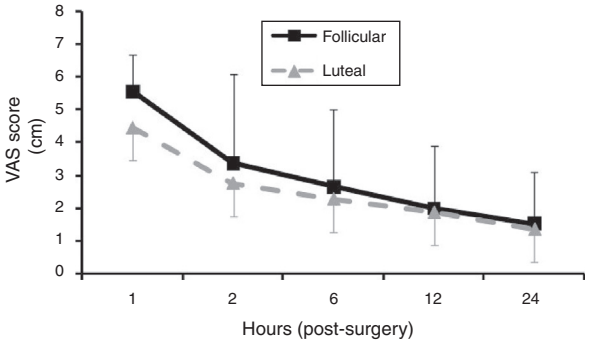

Figure 1 Acute postoperative pain.

in each group. Nausea was more common 6 h after surgery in the follicular-phase group (21 out of 63 women in the follicular group vs. 7 out of 64 in the luteal group, Bonferroni adjusted $p = 0.01$). Oral feeding time was shorter in the follicular phase (5.9 ± 0.9 h) than in the luteal phase (6.8 ± 1.9 h, Bonferroni adjusted $p = 0.02$) (Table 2). Other side effects occurred at similar frequencies in each group.

Persistent postoperative pain was significantly more common one month after surgery conducted during the follicular than luteal phase of the menstrual cycle: $n = 21$, 33% vs. $n = 10$, 16% (Bonferroni adjusted $p = 0.04$). At that time, VAS pain scores among those reporting pain were 1.6 ± 0.7 cm for follicular group vs. 2.7 ± 1.3 cm for luteal group (Bonferroni adjusted $p = 0.049$). Persistent postoperative pain was also significantly more common three months after surgery conducted during the follicular than luteal phase of the menstrual cycle: $n = 20$, 32% vs. $n = 8$, 12% (Bonferroni adjusted $p = 0.02$). At that time, VAS scores among those reporting pain were 1.8 ± 0.8 cm in the follicular group and 2.9 ± 1.7 cm in the luteal group (Bonferroni adjusted $p = 0.2$).

There were no significant differences between the groups with respect to anxiety and depression one or three months after surgery. Furthermore there were no differences in satisfaction or SF-12 scores at either time (Table 2).

Table 2 Oral feeding and ambulation times, SF-12, and Hospital Anxiety and Depression Scores.

	Group F ($n = 63$)	Group L ($n = 64$)	Bonferroni adjusted p-value
Oral feeding (h)	5.9 ± 0.9	6.8 ± 1.8	0.02
Ambulation time (h)	5.5 ± 0.8	5.9 ± 1.7	0.5
SF 12			
1 Month	29 ± 3	29 ± 3	1
3 Month	29 ± 3	29 ± 3	1
HAD			
Anxiety component			
1 month	16 ± 3	17 ± 2	1
3 month	16 ± 3	16 ± 3	1
Depression			
1 month	19 ± 4	19 ± 3	1
3 month	19 ± 4	20 ± 3	1

Discussion

Our primary results demonstrated that pain scores were similar at all measured times in first 24 h; nor was there any significant difference in analgesic consumption. That acute pain scores and analgesic consumption were similar after surgery in the luteal and follicular phases of the menstrual cycle was surprising given that most non-surgical reports suggest that consequent hormonal variations play important roles in pain perception. Ribeiro-Dasilva et al.,[12] Craft,[13] and others have all demonstrated hormonal associations with pain sensitivity in volunteers, and even suggest that menstrual hormones influence opioid sensitivity.[3,14] In contrast, a recent study was unable to demonstrate any difference in response to experimental pain during the follicular and luteal phases of the menstrual cycle in volunteers.[15]

Perioperative results are also controversial. Sener et al.[16] evaluated women having diagnostic laparoscopy and determined that those in the luteal phase required slightly more analgesic. However this study was designed to evaluate postoperative nausea and vomiting not pain scores. In contrast, Ahmed et al.[17] evaluated 60 patients scheduled for hysterectomy and determined that pain scores, although generally similar, were slightly greater at 12 h when patients were in the luteal phase; analgesic consumption was similar irrespective of menstrual cycle. Taken together, our results and previous literature suggests that hormonal changes have minimal effect on acute pain, which is apparently largely determined by other factors. Among these is certainly degree of surgical injury, incision location, genetic variation in responds to pain medications, the rate at which analgesic drugs are metabolized, and pain expression. Certainly, available data do not support scheduling operations to target particular phases of the menstrual cycle, which appears to have little or no effect on postoperative pain.

We found that the incidence of persistent surgical pain after cholecystectomy, independent of menstrual phase, was 24% after one month and 22% after three months. This incidence is similar to multiple previous studies, including a recent meta-analysis, which demonstrated 18%-33% persistent pain after cholecystectomy.[18] Pain intensity in our patients, though, was mild, averaging only about 2 cm on a 10 cm visual analog scale.

Associations between menstrual cycle and chronic pain been reported in various pain conditions including complex regional pain syndrome, migraine, fibromyalgia, temporomandibular joint and chronic back pain.[3,19] Furthermore, these data are supported by animal studies, although inconsistently with regard to pattern and direction of the association. We are unaware of previous studies that evaluated persistent surgical pain as a function of menstrual phase. The observed difference in the incidence of persistent pain was potentially clinically important, being almost 50% greater in the follicular group. However, magnitude of the pain was low and similar in each phase. Another important outcome of our study was that there was significant higher incidence of nausea in follicular group. This is unsurprising since there are several studies suggesting role of menstrual cycle and female sex hormones on nausea and vomiting. Changing concentrations of progesterone and/or estradiol seems to be responsible from increased emetic syndromes. Consistent with our findings, Sener et al.[16] demonstrated significantly more postoperative nausea and vomiting in women during the follicular phase.

This study has some important limitations. Firstly participants menstrual cycle phase was divided into functionally phases, based either on the ovarian or endometrial cycle instead of plasma or serum sex hormone assessments in the present study, similarly with the majority of studies investigating pain across the menstrual cycle.[20] Estrogen and progesterone during each phase may vary among womens and also if ovulation does not occur gonodal hormonal environment in the second half of the menstrual cycle will differ from that which occurs in a normal ovulatory menstrual cycle. Therefore we may not effectively capture the cyclical changes in the gonadal hormones during each phase. Secondly severe premenstrual mood changes such as premenstrual dysphoric disorder or dysmenorrhoea which may impact pain responses were not evaluated.

We considered days between 6 and 12 as follicular and days 20–24 as luteal. It is possible — although unlikely — that difference with these ranges influences responses,

or those responses are more impressive during excluded periods.[20] The surgical model we used certainly produces more intense pain than human experimental models, but equally certainly produces far less pain than larger procedures. It thus remains possible, although again probably unlikely, that phase differences in pain sensitivity are more impressive at other stimulus levels.

Conclusion

Acute pain scores and opioid consumption were similar when women were randomized to cholecystectomy during the follicular or luteal phases of their menstrual cycle. The overall incidence of persistent surgical pain after cholecystectomy, independent of menstrual phase, was 24% after one month and 22% after three months, which is consistent with previous reports. Persistent postoperative pain was significantly more common one and three months after surgery conducted during the follicular than luteal phase of the menstrual cycle. However, pain scores among those reporting pain were low, typically about 2 cm on a 10 cm-long visual analog scale, and did not much differ as a function of phase. Our results do not support scheduling operations to target particular phases of the menstrual cycle, which appears to have no effect on acute postoperative pain, and only minimal influence on persistent pain.

Key-messages:

- Female sex hormones during the menstrual cycle influence pain perception.
- Endogenous pain is impaired in the follicular phase of the menstrual cycle.
- Follicular phase have no effect on acute postoperative pain.
- Follicular phase only minimal influence on persistent pain.

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Contribution

Sinem Sari: This author helped to designing of the study and preparation of the manuscript. She also helped to data collection and to conduct to the study.

Attestation: This author attests to the integrity of the original data and the analysis reported in this manuscript.

Betul Kozanhan: This author helped to data collection and to conduct to the study. She also helped for designing of the study.

Attestation: This author is the archival author.

Ayse Ilksen Egilmez: This author helped to data collection and to conduct to the study. She also helped for designing of the study.

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Aykut Soyder: In our study, this author helped to data collection and to conduct to the study. He also helped for designing of the study.

Attestation: This author approved the final manuscript.

Osman Nuri Aydin: This author helped to data collection and to conduct to the study. He also helped for designing of the study.

Attestation: This author is the archival author.

Fabrizio Galimberti: This author helped to data analysis, writing and design in our study.

Attestation: He attests to the integrity of the original data and the analysis reported in this manuscript.

Daniel Sessler: This author helped to designing of the study and preparation of the manuscript.

Attestation: This author is the archival author.

Alparslan Turan: This author helped to designing of the study and preparation of the manuscript.

Attestation: This author is the archival author.

Conflicts of interest

The authors declare no conflicts of interest.

Notes: The trial is registered as NCT02137135 at clinicaltrials.gov.

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