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Does Premedicatıon wıth Mıdazolam Reduce Preoperatıve Anxıety Through Menstrular Cycle Phases?

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ABSTRACT

Aim: In this study, it was aimed to investigate and compare the effects of menstrual cycle phases on preoperative anxiety and postoperative pain scores in patients given midazolam for premedication before anesthesia.

Methods: Septorhinoplasty, goiter surgery and laparoscopic cholecystectomy 126 female patients, aged 21-45, with American Society of Anesthesiologists (ASA) score I-II and with regular menstrual cycles, were included. Of the cases; The phase of the menstrual cycle was recorded according to the last menstrual period (SAT) and accordingly the patients were divided into 3 groups as Follicular phase, the Ovulatory phase, and the Luteal phase. Anxiety assessment was performed using the State-Trait Anxiety Inventory (STAI FORM TX-1) test. Anxiety scores were evaluated by performing a preoperative test 3 minutes before and 1 hour after intravenous (IV) administration of 0.02 mg/kg midazolam. Visual analog scale (VAS) was used for postoperative pain assessment.

Results: Midazolam was found to decrease STAI FORM TX-1 scores the most during the ovulatory phase of the menstrual cycle, but there was no significant difference between the groups in terms of VAS scores.

Conclusion: It has been observed that premedication with midazolam reduces preoperative anxiety in all phases of the menstrual cycle in women of reproductive age, but is most effective in the ovulatory phase. The effect of premedication with midazolam on postoperative pain does not change according to the phases of the menstrual cycle.

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Introductıon

Anesthesia and surgical applications are sources of stress and trauma for the body [1]. Previous studies have reported that 60-80% of patients are anxious in the preoperative period [2,3]. Preoperative anxiety negatively affects the intraoperative and postoperative process, it is known that it causes a higher dose of the anesthetic drug during anesthesia induction and higher analgesic requirement due to postoperative pain. Therefore, the anxiety levels of patients should be reduced. In our study, in patients who were given midazolam for premedication before anesthesia; was aimed to investigate and compare the effects of menstrual cycle phases on preoperative anxiety and postoperative pain scores.

Materıal and Method

Approval for our study was obtained from Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Clinical Research Ethics Committee on 26/05/2014 with protocol number 96.126 female patients between the ages of 21-45 and with ASA score I-II, scheduled for elective surgery between January 2015 and March 2017, were included in the study. Patients with a history of allergic reactions to the drugs used, with cardiac, pulmonary, hepatic or renal failure, obese (BMI> 35), pregnant and epileptic patients who did not agree to participate in the study were not included in the study. Besides, patients with irregular menstrual cycles, psychiatric and neurological diseases, preoperative chronic pain, psychiatric drugs, and chronic alcohol use were not included in the study. Of the cases; According to the anamnesis, physical examination and laboratory test results; The age, height and weight, ASA scores, medications (if any) used, menstrual cycle order, last menstrual cycle date and the day of the cycle, the type of operation to be performed, the type of anesthesia to be given were recorded. Body mass indexes of the cases were calculated according to the weight / height2 (kg / m^2) formula. The demographic characteristics (age, gender) and body mass index (BMI) of the patients are shown in Table 4. Also, the last menstrual period (LMP) was recorded to calculate the menstrual phases of the patients. According to the LMP record, patients within the first 1-8 days of the menstrual cycle were evaluated as the follicular phase, those between 9-15 days in the ovulatory phase, and those between the end of the 16th day-cycle phase were evaluated as in the luteal phase. In the clinical evaluation, the State-Trait Anxiety Inventory (STAI FORM TX-1) was applied to each patient to measure their anxiety levels and the Visual Analogue Scale (VAS)

for postoperative pain assessment.

In our study, to apply the STAI FORM TX-1 test, the participants were asked to mark the most appropriate one among the options of 'nothing', 'a little', 'a lot' or 'completely' for each statement numbered from 1 to 4 on the scale. . The scores obtained from the scale theoretically vary between 20 and 80. A high score indicates a high anxiety level, a low score indicates a low anxiety level. The same is true when interpreting scores according to percentage order. That is, a low rank indicates that there is less anxiety [3-6]. STAI FORM TX-1 test was performed preoperatively one hour ago. Midazolam IV at 0.02 mg/kg was given to all patients 3 minutes after the test. One hour after premedication, the STAI FORM TX-1 test was repeated, and then the patients were taken to the operating room. All patients were administered Propofol at a dose of 2.5 mg/kg as an intravenous anesthetic, rocuronium Bromide at a dose of 0.6 mg/kg as a muscle relaxant, and Fentanil at a dose of 1mcg / kg as an analgesic. 120 seconds after the administration of muscle relaxant, the patients were intubated with an appropriate-sized endotracheal tube. In the maintenance of anesthesia, all patients were given 2% Sevoflurane, 50% air, and 50% O2, and continued with 0.1 mcg/kg/hr Remifentanil. In all patients, 15 mg/kg Paracetamol and 1 mg/kg Tramadol were administered intravenously as a standard, for postoperative analgesia approximately 30 minutes before the end of the operation. 0.01 mg/kg Atropine and 0.05 mg/kg Neostigmine IV were administered to all patients to remove the muscle relaxant effect. Visual Analogue Scale (VAS) was used in the postoperative period. VAS scores were calculated 5 times for each patient in postoperative 15 minutes, 1 hour, 2 hours, 4 hours, and 6 hours.

Statistical Analysis

For the sufficiency of the sample size, GPower was calculated with the 3.1 version. According to the analysis results, the PartialEtaSquared value for 2-replicate STAI measurement was 0.124 and our Post Power value calculated for N = 126 was 99.9%. SPSS 22.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) programs were used in the analysis of variables. The compatibility of univariate data to normal distribution was evaluated with the Shapiro-Wilk test and multivariate normal distribution with Mardia (Dornikand Hansenomnibus) test, and variance homogeneity was evaluated with the Levene test. One-way ANOVA test, one of the parametric methods, was used to compare multiple independent groups with each other according to quantitative data, while the Kruskal-Wallis H Test, one of the nonparametric tests, was used with the results of the Monte Carlo simulation technique.

The General Linear Model-RepeatedAnova test, one of the parametric tests, was used to examine the interaction of repeated quantitative measurements of the dependent quantitative variables according to the groups, while the Fisher'sLeastSignificantDifference (LSD) test was used for post hoc analysis. Among the nonparametric tests, while using Friedman's Two-Way test together with the result (Monte Carlo), Dunn's test was used for post ad hoc analysis. In the comparison of categorical variables with each other, PearsonChi-Squaretest was tested with the Monte Carlo Simulation technique. Quantitative variables were shown as mean ± std. (Standard deviation) and median range (Maximum / Minimum), and categorical variables as n (%). Variables were analyzed at a 95% confidence level and a p-value of less than 0.05 was considered significant.

The demographic data (age, weight, height, BMI) of the patients included in the study, the ASA groups and the distribution of the menstrual cycle to the follicular, ovulatory, and luteal phases of the menstrual cycle, and their total values, distribution by operation types are shown in Table 1.

Table 1: Demographic Data

	phase				
	Follicular phase	**Ovulatory phase**	**Luteal phase**	**Total**	**P Value**
	Mean ± SD.	me Mean ± Sd	Mean ± Sd	Mean ± Sd	
Age	28,34±7,29	28,46±7,77	29,85±8,98	28,87±7,99	0,635
Size	163,93±5,63	162,80±3,82	162,29±4,73	163,03±4,81	0,275
Weight	57,91±7,05	59,22±8,95	57,66±9,72	58,25±8,57	0,677
BMI *	21,64±2,89	22,43±3,77	21,91±3,70	21,98±3,45	0,565
	Median(Max./Min.)	Median(Max./Min.)	Median(Max./Min.)	Median(Max./Min.)	
Cycle time	28(30/24)	28(30/24)	28(30/24)	28(30/24)	0,280
ASA	n (%)	n (%)	n (%)	n (%)	
I	31(70,45)	31(75,61)	25(60,98)	87(69,05)	0,354
II	13(29,55)	10(24,39)	16(39,02)	39(30,95)	
Operation					
Goiter operation	3(6,82)	2(4,88)	9(21,95)	14(11,11)	-
Laparoscopic cholecystecto	4(9,09)	2(4,88)	5(12,20)	11(8,73)	
Septorhinoplasty	37(84,09)	37(90,24)	27(65,85)	101(80,16)	

OneWay ANOVA Test - Kruskal Wallis Test(Monte Carlo) - PearsonChiSquare Test(Monte Carlo) / SD : Standard deviation - Max. :Maximum - Min.:Minumum* BMI: Body mass index

The distribution of the patients' VAS 15 minutes, 1st, 2nd, 4th, and 6th-hour scores according to the phases of the menstrual cycle and the change accordingly over time are shown in Table 2. Accordingly, VAS scores showed a significant decrease in all groups from the 15th minute to the 6th-hour values ($p < 0.001$). However, when VAS changes in follicular, ovulatory, and luteal phase groups were compared, no significant difference was found between them ($p > 0.05$).

Table 2: Menstrual Cycle Distribution of Vas Scores According to Phase Groups

	phase			
	Follicular phase (I)	**Ovulatory phase (II)**	**Luteal phase (III)**	**P value**
	Median (Max./Min.)	Median (Max./Min.)	Median (Max./Min.)	
VAS15.min	=A 0,75(6/0)	1,10(5/0)	1,36(6/0)	0,303
VAS1.hr	=B 0,38(6/0)	0,46(6/0)	0,88(6/0)	0,121
VAS2.hr	=C 0,18(2/0)	0,25(4/0)	0,29(2/0)	0,174
VAS4.hr	=D 0(0/0)	0(0/0)	0(0/0)	1
VAS6.hr	=E 0(0/0)	0(0/0)	0(0/0)	1
variation				
15min – 1hr	0(4/-4)	1(3/-4)	1(3/-2)	0,704
15min – 2hr	0(6/-2)	1(4/-2)	1(5/-2)	0,457
15min – 4hr	0(6/0)	1(5/0)	1(6/0)	0,300
15min – 6hr	0(6/0)	1(5/0)	1(6/0)	0,300
1hr – 2hr	0(4/0)	0(2/0)	0(4/-1)	0,664
1hr – 4hr	0(6/0)	0(6/0)	1(6/0)	0,115
1hr – 6hr	0(6/0)	0(6/0)	1(6/0)	0,115
2hr – 4hr	0(2/0)	0(4/0)	0(2/0)	0,170
2hr – 6hr	0(2/0)	0(4/0)	0(2/0)	0,170
4hr – 6hr	0(0/0)	0(0/0)	0(0/0)	1
P value	<0,001	<0,001	<0,001	
A – B	1	0,332	0,749	
A – C	0,010	0,001	0,001	
A – D	0,002	<0,001	<0,001	
A – E	0,002	<0,001	<0,001	
B – C	0,919	0,642	0,361	
B – D	0,310	0,098	0,006	
B – E	0,310	0,098	0,006	
C – D	1	1	1	
C – E	1	1	1	
D – E	1	1	1	

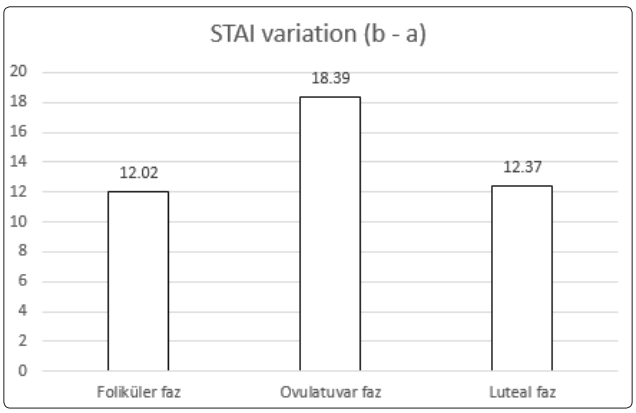
Friedman Test(Monte Carlo) Post Hoc Test : Dunn's Test - Kruskal Wallis Test(Monte Carlo) / - Max.:Maximum - Min.:Minumum

The data of the STAIFORM-TX-1 scale administered before and after premedication with midazolam and the data of its distribution among follicular, ovulatory, and luteal phase groups are shown in Table 3. Accordingly, the group with the highest initial STAIFORM-TX score is the Luteal phase group and the lowest in the Follicular phase group. When STAIFORM-TX scale total scores before premedication were compared with STAIFORM-TX scale scores after premedication, the values showed a statistically significant decrease in all 3 groups ($p = 0.001$). While the mean scale score before premedication was 46.84 ± 10.13 in the follicular phase, it decreased to an average of 34.82 ± 8.31 after premedication and decreased by $24.30 \pm 14.70\%$ in total. In the ovulatory phase, the score before premedication decreased from 49.34 ± 8.55 to 30.95 ± 5.44 after premedication (a total change of $36.34 \pm 11.42\%$). In the luteal phase, it decreased from 50.17 ± 10.73 to 37.80 ± 8.46, and a total decrease of $23.52 \pm 13.49\%$ was observed. According to these values, the most statistically significant difference between STAIFORM-TX values before and after premedication in all 3 groups was observed in the ovulatory phase group (graph 1 and graph 2).

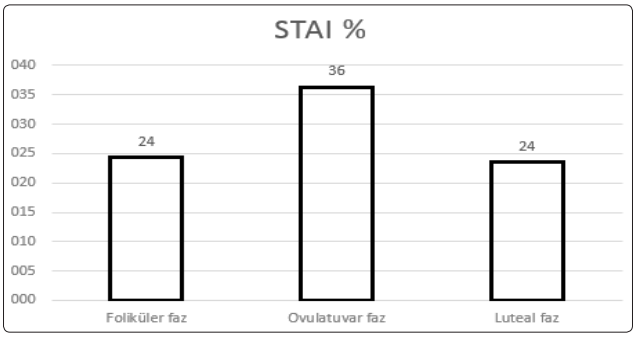
Table 3: STAIFORM-TX values before and after premedication and its distribution among Follicular, Ovulatory and Luteal Phase Groups

	STAIFORMTX1 before midazolam	STAIFORMTX1 after midazolam	STAI change (b - a)	STAI % (100* (b - a)/b)	P value
	Avarage±SD.	Avarage±SD.	Avarage±SD.	Avarage±SD.	
Follicular phase	=I 46,84 ± 10,13	34,82 ± 8,31	12,02 ± 8,00	24,30±14,70	0,001
Ovulatuar phase	=II 49,34 ± 8,55	30,95 ± 5,44	18,39 ± 7,34	36,34±11,42	0,001
Luteal phase	=III 50,17 ± 10,73	37,80 ± 8,46	12,37 ± 8,09	23,52±13,49	0,001
P value	0,269	<0,001	<0,001	<0,001	
I – II	0,733	0,060	<0,001	<0,001	
I – III	0,366	0,212	0,840	0,789	
II – III	1	<0,001	0,001	<0,001	

General Linear Model RepeatedAnova Test - OneWay ANOVA Test - Post Hoc Test: Fisher'sLeastSignificantDifference (LSD) / SD.: Standard deviation



Graph 1: Changes in STAIFORM-TX scores before and after premedication in Follicular, Ovulatory and Luteal phase groups (numerical value)



Graph 2: Change in STAIFORM-TX scores before and after premedication in Follicular, Ovulatory and Luteal phase groups (%)

Dıscussıon

In addition to preoperative concerns, anesthesia and surgical applications are also sources of stress and trauma for the body [7]. Midazolam used for premedication has been found effective in reducing the negative effects of preoperative anxiety. Studies are reporting that it has minimal effect on respiratory and hemodynamic parameters and that it can be used safely in terms of patient comfort, therefore it is frequently preferred in the routine [8-10].

In our study, we found that midazolam administered for premedication reduces anxiety in every phase of the menstrual cycle, especially in the ovulatory phase. When the STAIFORM-TX-1 scale total scores before and after premedication were compared, the values showed a statistically significant decrease in all 3 groups, but the most statistically significant difference was with a decrease of approximately 1/3 (49% -31%) in the scores before and after premedication. observed in the ovulatory phase group.

Estradiol, whose level is high in the preovulatory and postovulatory periods, causes an increase in the sensitivity of the pituitary and hypothalamus [11]. Similarly, fluctuations in estradiol and progesterone balance lead to changes in the hypothalamus and pituitary sensitivity. In women of reproductive age, the blood levels of progesterone in the preovulatory phase are at the lower limits of immunoassay sensitivity (less than 100ng / dl). However, the progesterone level varies between 500-2000 ng / dl during the luteal phase. Premenstrual syndrome with symptoms such as anxiety, tension, fatigue, etc. is observed in many people in the luteal phase of the cycle even if no operation is performed. One of the theses put forward in the etiopathogenesis of this syndrome is the decreased estrogen and endogenous opiate levels [12]. Midazolam is a highly protein-bound agent (96-98%) whose mechanism of action is through GABA-A and glycine receptors [13]. Some studies have reported that its anxiolytic effect is related to its affinity for glycine receptors in the brainstem [14].

Accordingly, it can be thought that midazolam exerts an anxiolytic effect by possibly increasing glycine-like neurotransmitters and its potency is related to its affinity for glycine receptors. According to this mechanism, it can be accepted that estradiol levels that increase in the ovulatory phase contribute to the effect of increasing sensitivity and receptor affinity in the hypothalamus. Halbreich et al. reported that dysphoria is seen in the premenstrual phase (luteal phase) of the cycle in women of reproductive age are due to a decrease in endogenous opiates [12]. In our study, we found that midazolam has stronger anxiolytic activity in the ovulatory phase. We think that this is due to the synergistic effect of midazolam with endogenous endorphins that increased estradiol levels in the preovulatory and postovulatory periods. Although the study of Halbreich et al. covered only the luteal phase, it supports our results in terms of the relationship between endogenous opiates and estradiol.

On the other hand, the fact that the synthesis of hepatic enzymes is suppressed in the ovulatory phase compared to other cycle phases may delay the degradation of midazolam and increase its

half-life and be more efficient. The bioavailability of midazolam in oral administration is 44%. Its clearance depends on hepatic blood flow [15,16]. Midazolam is largely (94%) bound to plasma proteins. A small change in the plasma protein amount can lead to large changes in the free portion of midazolam in plasma. Since increased estradiol levels from the follicular phase to ovulation reduce the level of Sex hormone-binding globulins, the free portion of estradiol increases, suggesting that it will increase the free amount of midazolam and consequently its anxiolytic effect. However, further studies are needed to prove this issue by measuring the half-life of midazolam and its free levels in plasma according to the phases of the menstrual cycle.

Unlike our study, Kharasch et al. examined the pharmacokinetics of midazolam in different phases of the menstrual cycle and found no significant difference in the clearance of midazolam compared to the phases of the menstrual cycle [17]. The limitation of this study is that the amount of free midazolam in plasma and the half-life of midazolam was not taken into account. Besides, the sample size (n: 11) in this study was small, and hepatic CYP3A4 activity was evaluated only on certain days of the menstrual cycle. However, since the clearance of midazolam is dependent on hepatic blood flow [15,16]. it is necessary to measure hepatic blood flow and free plasma protein levels in the phases of the menstrual cycle. On the other hand, suppression of the synthesis of hepatic enzymes in the ovulatory phase increases the half-life and efficiency of midazolam.

Yalınay et al. and Güz et al. both reported that patients with high preoperative anxiety levels had higher postoperative pain scores and decreased pain tolerance [18,19]. Considering these studies, we would have expected that the anxiolytic effect of midazolam would be more in the ovulatory phase, and consequently, postoperative pain scores in patients would be lower. However, we could not find a significant difference between pain scores in different menstrual cycle phases. In the progressive measurement values (from the 15th minute to the 6th hour), we found a decrease in the postoperative pain scores in all groups. In our opinion, the probable reason for this may be that the pain scoring used is subjective, the pain threshold is different between the patients and the surgeries are not the same type. The fact that the expected postoperative pain level was not high and the use of adequate analgesics may have clouded the difference between the groups.

Son et al. reported that midazolam exerts an anti-inflammatory effect by inhibiting the activation of macrophages in oligosaccharides and, as a result of this effect, decreases pain [20]. However, there is more than one preoperative factor affecting postoperative pain. Therefore, activation of macrophages alone is not sufficient to explain postoperative analgesia. In our study, we determined the phases of the menstrual cycle according to the information obtained from the patients. If menstrual cycle phases were determined according to estradiol, progesterone, and pituitary gonadotropin results and ultrasound folliculometry follow-up, more effective results could be obtained. Measuring endogenous opiate and plasma protein levels by phases and determining the half-life of midazolam by hepatic clearance would have been more descriptive. We believe that it will be more beneficial to consider these issues in future studies. It is known that different types of surgery affect preoperative anxiety and postoperative pain at different levels [21]. Considering these factors in future studies, we think that it would be more beneficial to perform it in a single type operation group.

According to the results of this study, the preoperative dose of midazolam used for anxiolytic purposes in women scheduled for surgery in the reproductive age can be adjusted according to the phases of the menstrual cycle. Of course, further studies are needed to support this assumption.

Result

Although premedication with midazolam reduces preoperative anxiety in all phases of the menstrual cycle in women of reproductive age who will undergo elective surgery, it has been observed that it mostly affects the ovulatory phase. The effect of premedication with midazolam on postoperative pain does not change according to the phases of the menstrual cycle.

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