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VARIATION IN RESPONSE TO EXPERIMENTAL PAIN ACROSS THE MENSTRUAL CYCLE IN WOMEN COMPARED WITH ONE MONTH RESPOSE IN MEN

MANOJ KUMAR[1], JAGDISH NARAYAN, NAR SINGH VERMA[2] AND INDU SAXENA[3]

Departments of [1]Physiology and [3]Biochemistry, SRMS Institute of Medical Sciences, Bareilly – 243 202 and *[2]Department of Physiology, CSM Medical University, Lucknow – 226 003*

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Abstract : Gender differences in pain perception have been reported in literature. However, most such studies have ignored the role of female sex hormones in influencing pain response across menstrual cycle (MC). In this study, we have investigated the variation in pain response on different days of the menstrual cycle. Ninety subjects (60 females) were subjected to experimental pain of cold pressor task, on days 1, 7, 14, and 21 of the MC (females), and on four consecutive Mondays of a month (males). Male subjects showed no variation in pain response. Females reported higher pain sensitivity on days 7 and 14 of MC. We suggest that experimental pain studies involving female menstruating subjects should be carried out only during a particular phase of the cycle, and this phase should be reported in literature to increase the reproducibility of the experiment.

Key words : Cold pressor task, experimental pain, menstrual cycle, pain response

INTRODUCTION

Sex differences in the perception of noxious experimental stimuli have been reported by various groups, with women exhibiting higher pain sensitivity than men (1-3). Contradictory reports, however, exist. Fillingim and Maixner (2) reviewed 34 human experimental studies and found sex-related differences in only two-thirds of them. One factor that can explain the discrepancies observed is the variation of female hormone levels across the menstrual cycle. The authors have not specified the menstrual phase of female subjects at the time of conducting the experiment. Leutinizing hormone increases pain sensitivity in rats (4). Estradiol and progesterone have been stated to produce analgesia that is modulated through the spinal cord k-opiate receptor analgesic system (5, 6). However, greater opioid-mediated stress induced analgesia has been reported in male rats compared with female rats (7, 8); and estrogen is believed to cause this difference by suppressing stress-induced analgesia (9). A typical menstrual cycle of 28 days can be divided into three phases. The follicular phase begins on the first day of menses and lasts 10-14 days. About 22-36 h before ovulation, a peak in estradiol level occurs, followed by a peak in leutinizing hormone level 10-12 h before ovulation. The phase after ovulation is called the luteal phase, which lasts for 14 days. Progesterone peak and a secondary estradiol peak occur 8 days after ovulation, i.e. on the 18th-22nd day of the menstrual cycle. The levels of estrogen and progesterone in blood start falling rapidly 9-11 days after ovulation and reach

*Corresponding Author : Dr. Manoj Kumar, Department of Physiology, Teerthanker Mahaveer Medical College and Research Centre, Theerthanker Mahaveer University, Bagarpur, Delhi Road (NH–24) Moradabad–244 001 (U.P.)

their lowest levels at the start of the menstrual period (10).

On the basis of the above facts, pain sensitivity should decrease on the 13th day when estradiol peak appears, and after 17th day when both estradiol and progesterone levels are high. Goolkasian (11) reviewed the literature and reported a consistent pattern of highest pain sensitivity during days 15-22 of a 28-day cycle, contrary to what is expected. However, Hellstrom and Lundberg (12) have reported contradictory observations. They performed cold pressor task (CPT) on female subjects in two phases of the menstrual cycle, and found pain sensitivity to be significantly lower in the second phase of the MC (days 20-24). Klatzkin et al (13) have published radically different results. They performed CPT on 49 female and 48 male subjects. Three episodes were conducted on each individual, in case of females at three points in the MC: early follicular, late follicular and luteal phases. They did not find any significant difference in the pain sensitivity in the three menstrual phases.

Most of the pain related studies have been carried out on subjects of western origin. Since pain sensitivity has been shown to vary with genetic (12), racial (13), and cultural (14) factors, our aim was to investigate the pain sensitivity of Indian female subjects across the menstrual cycle.

MATERIALS AND METHODS

A total of 126 female and 47 male subjects (students of MBBS I, II and III years, enrolled at SRMS Institute of Medical Sciences, Bareilly) volunteered for this study. They were screened for selection on the basis of the following criteria :

a) The person should not have a history of bone injury in the non-dominant hand.
b) The person should not be taking medicines for pain relief.
c) Female volunteers should report a regular, 28 day menstrual cycle.

Sixty-nine female and 43 male subjects were initially recruited for the study, of which 9 female and 13 male subjects dropped out during the course of the study due to various reasons. Final analysis was carried out on data obtained from 60 female and 30 male subjects.

Written informed consent was obtained from the subjects before beginning the study. Protocol for the study was approved by the Ethics Committee at SRMS- Institute of Medical Sciences.

Method of cold pressor task

A circulating water bath with pump and thermometer (designed locally) was used to immerse the non–dominant hand of the subject (palm down, up to 5 cm above wrist level). Water was maintained at 0-2^0 C using crushed ice. Pain threshold (time after which subject reported feeling pain) and tolerance (time for which the subject tolerated the pain) were measured in seconds using two separate stop watches. Pulse and blood pressure were recorded manually before and immediately after the cold pressor task (CPT). Pain rating (the intensity of pain felt during CPT, on a scale of 0-10) was obtained from the subject on a visual analog scale (VAS) (15) after the experiment. CPT was performed on four separate occasions with each subject; on days 1,7,14, and 21 of the menstrual cycle in case of female subjects (the date on which the menses began was noted and considered day 1), and on four consecutive Mondays of a month in case of male subjects.

Dexter and Chestnut (16) have reported the t-test to be a reliable method of data analysis in VAS measurements. We have, therefore, analyzed the data obtained in our experiments by this method. Day 1 readings were taken as reference and observations made on days 7, 14, and 21 were individually compared with them. Similarly, in case of male subjects, the readings taken on the first Monday were taken as reference and the observations made on all other days were compared separately with the respective reference values.

RESULTS

Pulse and blood pressure readings were taken before and immediately after performing the cold pressor task. For convenience, we have presented here only the differences in pulse (dPulse), systolic (dSBP), and diastolic (dDBP) blood pressures. The differences were obtained by subtracting the resting values of each parameter from the respective values obtained immediately after the CPT.

Table I presents the base-line values of different parameters of female and male subjects. The comparison of the base-line values of the various parameters showed a significant difference between ages and body weights. Males were slightly older, and weighed more, but there was no significant difference in the body mass indices of the two groups.

Table II shows the statistical analysis of data obtained from 30 male subjects taken as control. No statistically significant differences were observed in any of the six parameters studied (dPulse, dSBP, dDBP, pain threshold, pain tolerance, and pain rating) in the four episodes of CPT.

TABLE I : Base-line values (mean+SD) of different parameters of female and male subjects

Parameter	*Female*	*Male*	*P value*
Age (years)	19.72+1.67	21.43+2.22	0.001
Body Weight (kg)	59.23+10.70	68.87+12.95	0.001
BMI	24.35+4.35	23.11+4.51	0.219
Resting Pulse (min)	88.7+10.76	87.3+7.90	0.497
Resting SBP (mm Hg)	107.33+12.77	103.27+12.02	0.144
Resting DBP (mm Hg)	72.63±9.87	76.40±12.58	0.158

TABLE II : Mean ± SD values of dPulse, dSBP, dABP Pain threshold(s), Pain tolerance(s) and Pain rating obtained in case of male subjects. CPT was performed on 4 consecutive mondays of a month.

Parameters	*Week*			
	*1**	*2**	*3**	*4**
d Pulsed	8.93 ± 8.00	8.13 ± 7.13	8.93 ± 8.07	8.33 ± 8.00
d SBP	5.2 ± 3.00	5.33 ± 2.22	4.67± 4.12	6.53 ± 3.96
d DBP	3.73 ± 3.92	5.47 ± 5.96	5.87 ± 3.74	4.93 ± 5.01
Pain threshold	18.27 ± 8.89	19.33 ± 6.85	19.06 ± 8.88	20.67 ± 10.39
Pain Tolerance	143.00 ± 162.59	138.07 ± 154.65	136.33 ± 163.01	129.93 ± 145.88
Pain rating (VAS)	5.27 ± 1.10	5.47 ± 0.83	5.53 ± 0.92	5.47 ± 1.46

No significant different was obtained amongs the different days (P value $\leq$ 0.05)

*Depicts comparison with respective values obtained on day 1.

Data obtained from the sixty female volunteers is summarized in Table III. A significant increase in dPulse value was observed on day 21 of the menstrual cycle. The mean value of dPulse increased on days 7 and 14 also (in comparison to day 1) but the increase was not significant. The mean value of dSBP decreased significantly in comparison to day 1 on the 14th day of the cycle. The change in the mean values of dDBP was not significant (P > 0.05).

TABLE III : Mean ± SD values of dPulse, dSBP, dDBP, Pain threshold(s), Pain tolerance(s) and Pain rating obtained in case of female subjects, on days 1, 7, 14, and 21 of the menstrual cycle.

Parameters	*Day of menstrual cycle*			
	1*	**7***	**14***	**21***
d Pulse	6.73 ± 4.82	7.57± 5.94	7.53 ± 6.21	10.27 ± 8.27*
d SBP	8.07 ± 6.76	9.00 ± 4.75	5.00 ± 4.13	6.33 ± 4.93
d DBP	5.00 ± 3.39	4.47 ± 3.92	5.60 ± 5.74	6.73 ± 6.38
Pain Threshold	22.43 ± 36.39	18.47 ± 23.38	13.13 ± 18.11*	20.5 ± 28.13
Pain Tolerance	109.07 ± 152.19	69.43 ± 107.56*	53.77 ± 73.3**	99.60 ± 131.53
Pain Rating (VAS)	5.67 ± 1.58	5.53 ± 1.89	5.50 ± 1.59	5.17 ± 1.62

*P < 0.05 ; ** P < 0.005.

*Depicts comparison with respective value obtained on day 1.

The mean pain threshold values were highest on days 1 and 21 of the cycle. A significant decrease (in comparison to day 1) occurred on day 14 of the menstrual cycle. Similarly, pain tolerance showed a significant decrease on days 7 and 14 of the cycle. Lowest pain rating was obtained on day 21. Decreases in the mean values of pain rating observed on days 7 and 14 of the cycle were not significant.

Values of each parameter (e.g. dPulse) recorded for all female subjects on different days of the menstrual cycle were compared. The number of subjects showing the highest value of the particular parameter was counted for each day. (For example, highest dPulse values were recorded in 4 subjects on day 1, and in 22 subjects on day 21 of the menstrual cycle.) The numbers of subjects showing the lowest value of each parameter on different days were also counted. The data are summarized in Table IV.

TABLE IV : Number and percentage of female subjects showing maximum and minimum values of different parameters (dPulse, dSBP, dDBP, pain threshold, pain tolerance and pain rating) on different days of menstrual cycle.

S.N.	*Parameters*	*Subjects showing highest values*			*Subjects showing highest values on 2/more days*		*Subjects showing lowest values*		*Subjects showing lowest values on 2/more days*	
		Day	No.	%	No.	%	No.	%	No.	%
		1	4	6.67			8	13.33		
a	dPulse	7	10	16.67			12	20.00		
		14	18	30.00	6	10	12	20.00	18	30.0
		21	22	36.67			10	16.67		
		1	10	16.67			6	10.00		
d	dSBP	7	22	36.67			4	6.67		
		14	8	13.33	14	23.3	20	33.33	24	40.0
		21	6	10.00			6	10.00		
		1	6	10.00			6	10.33		
c	dDBP	7	8	13.33			6	10.33		
		14	12	20.00	22	36.7	16	26.67	26	43.3
		21	12	20.00			6	10.33		
		1	18	30.00			4	6.67		
d	Pain	7	16	26.67			6	10.00		
	Threshold	14	6	10.00	4	6.7	26	43.33	20	33.3
		21	16	26.67			4	6.67		
		1	18	30.00			6	10.00		
e	Pain	7	16	20.00			2	3.33		
	Tolerance	14	2	3.33	10	16.7	46	76.67	6	10.0
		21	18	30.00			0	0.00		
		1	6	10.00			4	6.67		
f	Pain	7	6	10.00	38	63.3	6	10.00	36	60.0
	Rating	14	6	10.00			2	3.33		
		21	4	6.67			12	20.00		

Highest dPulse values were recorded in maximum number of subjects on day 21, highest values of dSBP on day 7, and highest values of dDBP were recorded in maximum number of subjects on days 14 and 21 of the menstrual cycle. Maximum number of subjects showed lowest values of dPulse on days 7 and 14, and lowest values of dSBP and d DBP on day 14 of the cycle (see Table IV, parts a, b, c). The highest values of pain threshold were exhibited by maximum number of subjects on day 1, but only 6 subjects showed highest pain threshold on day 14 of the menstrual cycle. Twenty six subjects showed lowest pain threshold values on day 14 (Table IV, part d). A total of 36 subjects showed highest pain tolerance on days 1 and 21 of the menstrual cycle. Only 2 subjects showed highest pain tolerance on day 14, while 46 subjects (76.67 %) showed lowest pain tolerance on day 14 (Table IV, part e). Lowest value of pain rating was given by 12 subjects (20% of the total) on day 21 of the menstrual cycle (Table IV, Part f).

DISCUSSION

This study examined the variation of pain response across the menstrual cycle in Indian females. The pain response of subjects was studied in terms of cardiovascular reactivity (differences in pulse, systolic, and diastolic blood pressure observed upon performing cold pressor task) and pain sensitivity (values of pain threshold, pain tolerance, and pain rating). A high pain sensitivity is indicated when pain threshold and pain tolerance values are low and pain rating is high.

Our results can be summarized into the following points: 1) The group of 30 male subjects taken as control did not show any significant variation in any of the parameters studied in the four separate episodes of CPT, indicating that pain variation in females is not a chance variation. 2) Female subjects showed significant variation in both parameters for cardiovascular reactivity as well as pain sensitivity. The cardiovascular reactivity was relatively high on the 7th and 21st days of the menstrual cycle (apparent from the significantly high values of dPulse on day 21, Table III; highest values of dPulse recorded for 22 subjects on day 21 and highest values of dSBP recorded for 22 subjects on day 7, Table IV a, b). A relatively low cardiovascular reactivity was observed on day 14 of the cycle (apparent from significantly less value of dSBP on day 14, Table III; 20 and 16 subjects showed lowest values of dSBP and dDBP, respectively, on day 14, Table IV, b, c).

Pain sensitivity was high on days 7 and 14 of the menstrual cycle. A significantly low value of mean pain threshold was obtained on day 14. Highest pain threshold was observed in 6 subjects on day 14 while 26 subjects (43% of total) reported lowest pain threshold on this day (Table IV, d). Mean pain tolerance was significantly less on days 7 and 14 of the menstrual cycle. This difference was highly emphasized on day 14 when only 2 subjects showed highest pain tolerance and 46 subjects (76.7% of total) showed lowest pain tolerance (Table IV, e).

We conclude from the above findings that cardiovascular reactivity is less on the 14th and 21st day of the cycle while pain sensitivity is highest on the 7th and 14th days of the menstrual cycle. In our study, 76.7% subjects showed highest pain sensitivity on day 14.

Pain rating values were not significantly different, suggesting that the intensity of pain perceived by the subjects did not vary across the cycle. A particular intensity of pain appeared in less time on the 14th day, it occurred after a greater time interval on the 1st or 21st day of the cycle. Most subjects recorded identical pain ratings on two or more days of the cycle, indicating that a subject did not prefer to bear pain beyond certain intensity, time duration for attaining that pain intensity did not matter.

The high pain sensitivity on the day 14 can be attributed to the effect of leutinizing hormone during the ovulatory period. The peak in leutinizing hormone level occurs 10-12 h before ovulation, but its effect on pain sensitivity probably lasts for a longer duration.

Dawson-Basoa and Gintzler (5) have reported that estrogen and progesterone produce analgesia. The levels of both the hormones are high on days 19-23 of a typical 28-day menstrual cycle, and may be responsible for the decreased pain sensitivity on day 21. However, decreased pain sensitivity on day 1 can not be due to these hormones as they are at their lowest levels on days 28 to 5.

Mogil et al (9) reported that estrogen suppresses stress- induced analgesia and is therefore responsible for the higher pain sensitivity demonstrated by females. This could explain the fact that pain sensitivity was high on day 7 when estrogen level had started rising while progesterone level was still low. On day 14, pain sensitivity was highest due to increased levels of estrogen and leutinizing hormone. On day 21, the analgesic effect of progesterone masked the effect of estrogen, causing a decrease in pain sensitivity.

Forty-eight of the total sixty female subjects selected for this study were dysmenorrheic. It is possible that pain sensitivity was reduced on day 1 of the cycle due to mental distraction to experimental pain by dysmenorrhea. This can be investigated further by comparing the pain response of dysmenorrheic and non-dysmenorrheic females.

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