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RESEARCH ARTICLE

Pain sensitivity and cardiovascular reactivity to the experimental induced cold pressor pain during different phases of menstrual cycle in young Indian females

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ABSTRACT

Background: Many previous research studies have shown a higher prevalence of chronic pain conditions as well as more pain sensitivity or lesser pain thresholds (PTh) among women as compared to men. It might be related to the effect of female reproductive hormones, as these hormones produce its effect on various aspects of physiological systems. **Aims and Objectives:** The aim of this study is to find the differences in the pain responses as well as cardiovascular reactivity during cold pressor test in different phases of menstrual cycle. **Materials and Methods:** Following physical parameters were measured in 75 apparently healthy young Indian females during the three phases of menstrual cycle and utilized for data analysis: Response to cold-induced experimental pain in the form of PTh, pain tolerance (PTo), pain rating on visual analogous scale, pulse reactivity (PRe), systolic blood pressure reactivity (SBPRe), and diastolic BPRe (DBPRe). **Results:** Mean PRe was significantly higher during luteal phase as compared to menstrual as well as follicular phase. Mean SBPRe and mean DBPRe were found to be significant higher during luteal phase as compared to the menstrual and follicular phase. Mean PTh and mean PTo were significantly higher during follicular phase as compared to menstrual as well as luteal phase. **Conclusion:** This is concluded from above findings that the pain responses vary across the menstrual cycle as shown by higher PTh and tolerance during follicular phase of menstrual cycle. The cardiovascular reactivity to cold pressor pain also varies. The hormonal fluctuation and the differences in the physiological responses, mainly autonomic nervous system reactivity due to these fluctuations, would be the underlying mechanism for these findings.

KEY WORDS: Pain Threshold; Pain Tolerance; Pain Rating; Pulse Reactivity; Systolic and Diastolic Blood Pressure Reactivity

INTRODUCTION

Pain is defined "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] In healthcare settings, pain is the most common symptom for the patients visiting in the emergency department as well as to the family physicians. Pain is no respecter of person, not discriminating on the basis of gender, race, or age.[2] However, many previous research studies have shown higher prevalence of chronic pain conditions as well as more pain sensitivity or lesser pain thresholds (PTh) among women as compared to men, for example, some chronic diseases including fibromyalgia, arthritis, migraine, temporomandibular disorders, and interstitial cystitis are more prevalent in females.[2-6]

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The significant differences due to gender differences also occur in the pain-related behaviors, like utilization of healthcare resources.[7] This led to the understanding that it might be related to the effect of female reproductive hormones such as estrogen and progesterone, as these hormones produce its effect on all the aspect of various physiological systems. The concentration of these hormones varies vastly during different phases of menstrual cycle.[8-11] These differences may lead to the response of the pain perceived as found in many previous studies.[12-14] The female reproductive hormones have been reported to affect cardiovascular system in various ways, during the normal menstrual cycle.[15-19]

The definitive interaction of these physiological characteristics is very meagerly found in literature search, particularly in young Indian females. The results of studies conducted in women, examining the response of experimentally induced noxious stimulation and its variations related to the menstrual phase, did not showed conclusive findings.[20-22] With this existing lacunae and gap in the knowledge, the systematic research study based on these physiological characteristics in young Indian females is justifiable.

The objectives of this study were to find the differences in the pain responses as well as cardiovascular reactivity during cold pressor test (CPT) in different phases of menstrual cycle. The parameters used for the response to cold-induced experimental pain were PTh, pain tolerance (PTo), pain rating (PRa) on visual analogous scale, pulse reactivity (PRe), systolic blood pressure reactivity (SBPRe), and diastolic BPRe (DBPRe).

MATERIALS AND METHODS

This is a cross-sectional (descriptive) study conducted during June 2015–May 2016. The written permission from the Institutional Ethical Committee was obtained before the study. The informed written consent was taken from each participant according to the guidelines.

Sampling Description

The participants in this study included 75 female undergraduate and postgraduate students selected at random from medical and paramedical courses of different constituent Colleges of University. The sample size calculation was done with the help of online software, OpenEpi. This online software module calculated sample sizes after comparing two means as the ratio of sample size of Group 2 to Group 1, mean and standard deviation (SD) of values from the pilot study on 12 females. After using the confidence interval (95%), power (90%), and taking consideration of 10% attrition rate, the sample size obtained for this study was 75.

Inclusion and Exclusion Criteria

Detailed history was obtained from each participant for any significant medical illness or any discomfort in the recent times, and they were excluded accordingly. Females with irregular menstrual cycles, any significant history of dysmenorrhea, menorrhagia, taking any form of hormonal therapy, having undergone any form of reproductive surgery (e.g., hysterectomy and ovariectomy) were excluded from the study. Participants suffering from any known illness affecting or involving the autonomic nervous system (ANS), for example, diabetes mellitus, thyroid disorder, any cardiovascular, or neuropsychiatric disorder were also excluded from the study. Those not willing to participate in study were also excluded from the study.

All the included participants were unmarried, never pregnant, and also had not consumed any form of contraceptive medication in the past 3 months' duration.

The different phases of menstrual cycle were estimated according to the menstrual history related questionnaire and date of last menstrual period, as follows:

- Menstrual phase: During the 1st or 2nd day of the menstrual bleeding;
- Follicular phase: 3–4 days after complete stoppage of bleeding;
- Luteal phase: 2 weeks after the mid-follicular phase.

All the participants were asked to report thrice in the physiology research laboratory according to their phases of menstrual cycle (once in all the three phases of menstrual cycle in the same cycle). The height and weight of each participant were recorded every time, but for data analysis, only the first time measurements were considered. All the other physical parameters were measured during three phases of menstrual cycle and utilized for data analysis.

The body mass index (BMI) was calculated using the formula: BMI = weight (in kg) divided by height^2 (in m^2).

After 15 min of rest in comfortable posture, the pulse rate in radial artery, SBP, and DBP in the arm was recorded, using a standardized mercury sphygmomanometer.

For the CPT, the participant was asked to sit in a chair. A water-bath was filled with ice-cold water (temperature between 4°C and 8°C. The participant was asked to dip her one hand into the water bath (palm down, water up to 5 cm above wrist level). Immediately, two stopwatches were started.

Time when the participant felt pain for the first time, one stopwatch was stopped. This time was noted as PTh (first sensation of pain). Once the pain became intolerable, and the participant removed her hand even after repeated motivation, the second stopwatch was stopped. This time was taken as PTo (the induced pain became unbearable).

The participant was asked to determine the maximum perceived pain intensity during the test and rate it on a scale of 0–10, "0" being no pain at all, while "10" being the worst

possible pain, this was PRa. Immediately, after the CPT, the radial pulse, SBP, and DBP were recorded. The differences between resting and after-test values were taken PRe, SBPRe, and DBPRe, accordingly.

To avoid any possible recording bias, all the measurements related to pain responses were done by 1st author (AK) and measurements related to cardiovascular reactivity were done by 2nd author (RBJ), both working in tandem.

Statistical Analysis

The mean and SD of each parameter were calculated. The analysis of variance was used to compare the means of various parameters in three phases of menstrual cycle. For comparing the means of various parameters in two phases of menstrual cycle, unpaired *t*-test was used. For statistical significant differences, $P < 0.05$ were taken. The statistically significant differences on unpaired *t*-test were expressed as alphabets a, b, and c, as follows: (a) = Significant difference ($P < 0.05$) between menstrual and follicular phase on unpaired *t*-test, (b) significant difference ($P < 0.05$) between follicular and luteal phase on unpaired *t*-test, and (c) significant difference ($P < 0.05$) between menstrual and luteal phase on unpaired *t*-test.

RESULTS

Findings of the present study are depicted in Tables 1–3.

Table 1: Descriptive anthropometric parameters of all the participants in the study

Parameters	Mean±SD	Range
Age (years)	23.64±4.31	18–30
Height (cm)	150.21±12.23	146–169
Weight (kg)	57.23±7.10	48.8–73.3
BMI	21.56±3.68	19.1–24.6
Age at menarche (year)	12.67±1.98	12–15
Average duration of menstrual cycle (days)	29.46±3.84	25–34
Average duration of menstrual bleeding phase (days)	4.76±1.42	3–6

BMI: Body mass index, SD: Standard deviation

DISCUSSION

During the reproductive age of a female, the monthly menstrual cycle is an important physiological phenomenon, which is characterized by different levels of reproductive hormones. The present study has shown significantly higher PTh during follicular phase as compared to menstrual and luteal phase. The pain perception or PRa was not found to be significantly different during the three phases of menstrual cycle. We found increased PRe as well as SBPRe and DBPRe during the luteal phase as compared to the follicular phase.

These results on pain characteristics are in coherence to the study of Teepker *et al*.,[12] they reported similarly that during the follicular phase of the menstrual cycle there occurs increased PTh. Stening *et al*. [20] had shown that there occurs prolonged activation time to the hand cold pressor during the follicular phase when it was compared to the luteal phase. Higher PTo during the follicular phase of the menstrual cycle was also reported by Hapidou and De Catanzaro.[13] However, Kowalczyk *et al*.[21] found no significant changes in cold PTh. Furthermore, in contrast to this present finding, Hellstrom and Anderberg[22] revealed a significantly higher PTh during the second half of the menstrual cycle (luteal phase). Few previous studies demonstrate less pain sensitivity during phases of the menstrual cycle associated with high estrogen which is reported by Hellstrom and Anderberg.[22] Amandusson *et al*. reported that few estrogen receptor-expressing neurons are opioidergic[14] and show increased opioid transcription after taking estrogen.[23] One previous research study also reported the ovarian sex steroid antinociception as being mediated by opioid like mechanism and this might be due to activation of similar receptors in spinal cord.[24] However, another research study using animal experiment shows that estrogen does not modulate opioids sensitivity for analgesic effects every time.[25] Another study using animal models reported that there occurred diminished analgesic response to morphine resulting from desensitization of brain opiate receptors caused by the induction of luteinizing hormone surge during ovulation.[26] Thus, one can speculate that hormonally induced (ovulation) opiate receptor desensitization could enhance luteal phase pain sensitivity among women.

In the present study, we did not found significant differences in the resting heart rate (HR), SBP, and DBP during the three phases, which is also similar to the results of previous studies.[15-17] In the same line, a few studies have also reported insignificant differences in the mean arterial pressure.[16,18] This has been suggested to be because the changes in hypothalamic pituitary ovarian axis functioning over the course of the menstrual cycle are barely reflected in resting parameters and which may become prominent when the system is activated by a potent stressor.[19] A painful stimulus in CPT provokes changes in the ANS as an adaptation response to the stressor.[27] More specifically, the physiologic reactivity to pain is associated with intrinsic adjustments of the sympathetic and parasympathetic divisions of the ANS through autonomic efferent pathways. This adaptive response is done by reciprocal interactions of the sympathetic and parasympathetic systems.[28] These autonomic fluctuations attributable to pain usually result in clinically observable changes, such as a rise in HR or increase in blood pressure. In this study, we found increased PRe as well as SBPRe and DBPRe during the luteal phase as compared to the follicular phase. The hormonal fluctuations during different phases could be the reason behind this.

Table 2: Cardiovascular reactivity in response to experimental pain during menstrual cycle

Parameters	Menstrual phase	Follicular phase	Luteal phase	ANOVA	*t*-test
Resting pulse (beats/min)	73.36±5.18	77.28±9.32	75.40±10.10	0.130	-
PRe (beats/min)	10.46±7.53	11.64±6.67	15.90±4.70	0.042	b, c
Resting SBP (mmHg)	113.31±13.2	111.78±18.56	115.62±14.38	0.093	-
SBPRe (mmHg)	22.84±8.41	23.62±6.17	26.57±8.29	0.008	c
Resting DBP (mmHg)	78.68±8.10	73.56±10.65	75.49±9.13	0.356	-
DBPRe (mmHg)	19.41±5.89	17.60±6.17	22.72±10.35	0.039	b

PRe: Pulse reactivity, SBP: Systolic blood pressure, SBPRe: Systolic blood pressure reactivity, DBP: Diastolic blood pressure, DBPRe: Diastolic blood pressure reactivity, ANOVA: Analysis of variance

Table 3: Pain sensitivity parameters in response to experimental pain during menstrual cycle

Parameters	Menstrual phase	Follicular phase	Luteal phase	ANOVA	*t*-test
PTh (s)	13.3±5.39	18.37±6.19	12.2±5.27	0.0032	a, b
PTo (s)	41.2±13.46	48.24±14.7	38.5±10.29	0.0007	a, b
PRa (0–10)	6.23±4.12	5.94±3.26	6.40±2.75	0.83	-

PTh: Pain thresholds, PTo: Pain tolerance, PRa: Pain rating, ANOVA: Analysis of variance

Estrogen is predominant in follicular and progesterone in the luteal phase. Hence, it increases the parasympathetic tone and progesterone blocks this action resulting in an increased sympathetic activity during luteal phase.[17] Sato *et al.* also reported that sympathetic nervous activities being predominant in the luteal phase as compared with follicular phase.[28] Hence, it can be hypothesized that cardiovascular reactivity to cold-induced stress to be more in luteal phase than the follicular phase of menstrual cycle. Similar observations regarding cardiovascular reactivity to stress were also observed by few previous studies;[15,29,30] although there stimulant stressor was different, i.e., behavioral or mental stress was utilized in these studies, few studies also show that sex hormones have minimal influence on autonomic reactivity.

The main strength of the study is the statistically found sample size before the study and the strictly following the study in the coherence of menstrual cycle phases. In Indian young females, this aspect is very less studied earlier. As the limitations, the correlation of hormonal quantitative analysis is not done, which could yield better predictability, which could be the done in the form of another study.

CONCLUSION

We can conclude from this study that pain responses vary across the menstrual cycle as shown by higher PTh and tolerance during follicular phase of menstrual cycle. The cardiovascular reactivity to cold pressor pain also varies during different phases of menstrual cycle. The hormonal fluctuation and the differences in the physiological responses, mainly ANS reactivity due to these fluctuations, should be the underlying mechanism for these findings.

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