Inter-individual Variation in Pain Sensitivity among Healthy Young Indian Adults- a pilot study

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ABSTRACT

Background

Pain perception, with inter-individual variability, is a challenge for both patients and clinicians. Distribution of pain sensitivity parameters being less explored in Indian population can vary with reports from outside India.

Objective

To describe distribution of pain sensitivity parameters using cold pressor test in healthy adults and to explore relationship of pain sensitivity with gender, vascular reactivity and parental history of hypertension.

Method

Pain was induced with non-dominant hand immersed in cold water (3^0C to 5^0C) in 150 subjects (75 males and 75 females) selected as per inclusion and exclusion criteria. Pain sensitivity (pain threshold, tolerance and unpleasantness), vascular reactivity (Δ change in blood pressure and pulse rate) were measured.

Result

Subjects demonstrated pain threshold [17.6 s (10.7, 26.6)], tolerance [40.2 s (30.0, 59.2)] and unpleasantness [7.0 (6.1,8.0)]. Pain unpleasantness showed a weak negative correlation with pain threshold and tolerance ($p < 0.001$). Pain threshold had moderate positive correlation with tolerance ($p < 0.001$). Males had significantly higher pain threshold and tolerance than females ($p=0.004$). Significant rise in post-test systolic and diastolic blood pressure ($p < 0.001$), decrease in pulse rate ($p=0.007$) were found compared to resting values. Pain tolerance showed a weak positive correlation with Δ systolic blood pressure ($p=0.039$). Subjects with positive parental history of hypertension showed higher pain unpleasantness scores ($p=0.02$).

Conclusion

The study demonstrated a wide range of pain sensitivity for narrow age and body mass index. Gender difference was observed for pain threshold and tolerance. Vascular reactivity was demonstrated. Subjective pain perception was higher in subjects with parental history of hypertension.

KEY WORDS

Cold pressor test, Pain threshold, Tolerance, Parental history of hypertension, Vascular reactivity

INTRODUCTION

Pain is a distressing sensation that varies with the quality, location, intensity, duration of stimulus and tolerance of the person. Subjective responses to a painful stimulus and varying measurement methods, are challenges for clinicians to determine pain sensitivity and to treat pain.[1-4]

Pain perception is measured in terms of pain sensitivity. Inter-individual variability in pain sensitivity is relevant as it influences the individual's response to the course of a disease, quality of life and analgesic dosage.[5] Experimental laboratory-based pain models have induced pain, using various stimuli (mechanical, chemical, electrical and thermal) and can mimic clinical pain. Thermal pain induced by ice application causes the activation of A-delta and C-fibres.[2,6] Previous studies done outside India on pain sensitivity using experimental pain models have reported its association with age, gender, body mass index, resting blood pressure, cardiovascular reactivity and parental history of hypertension.[7-17] It is also largely influenced by ethnicity and genetic factors.[1,18,19] Given that the inter-individual variability of pain sensitivity could be different from that reported elsewhere in the world, this study was conducted using the cold pressor test to induce pain and characterise pain sensitivity, mimicking ischemic clinical pain in young healthy Indian adults.[2,3,20]

METHODS

The study is a descriptive, cross-sectional study approved by the Institutional ethics committee (IEC Study Ref No. 262/2018, Dated 9/10/2018) conducted in the laboratory of the Physiology department of the institution. The required sample size with 95% confidence intervals and 5% precision to evaluate pain sensitivity of healthy young Indian adults, was 148, rounded off to 150.[21] Young healthy Indian subjects n = 150 (75M; 75F), between 18 to 35 years with body mass index (BMI) 18.5 to 24.9 kg/m^2, and resting blood pressure < 130/85 mmHg were recruited following written informed consent.[12,22] There were no dropouts. Subjects with a h/o chronic/acute painful condition, impaired cognition, pregnant and any skin abnormalities like callus, dermatitis, recent cut or burns, recent bone injury in the upper limbs at the time of experiment, h/o smoking, tobacco chewing, alcohol consumption, and analgesic intake were excluded from the study.[7,16,21,23] Females with regular menstrual cycles were studied during the pre-ovulatory phase (5th to 11th day) of the menstrual cycle, which was based on menstrual history provided by the subjects.[24] CPT was performed in the evening and at same laboratory on all the subjects. On the test day, subjects were requested to wear light comfortable clothes, avoid strenuous physical activity, consume a normal vegetarian meal before 1.30 pm, to refrain from fatty foods, added salt intake and beverages for at least 12 hours, as various foods are known to increase pain sensitivity soon after consumption.[25]

Prior to the test were recorded- age, gender, occupation, parental history of hypertension (P h/o HTN), room temperature and humidity using digital recorder, weight in kilograms (using weighing machine, TANITA), height in cm (using stadiometer) converted to metres. BMI was calculated using the formula [weight (kg)/height^2 (m)].[12] The subject's hand was inspected for any redness, dermatitis, callus, cuts and burns.[26] They were instructed to empty their bladder, sit comfortably with a back rest, feet on the ground and arm supported at the level of heart and three resting blood pressure (BP) measurements were taken and deflated BP cuff is left around the arm The CPT procedure (supporting file : image) was explained to each subject before the experiment.[15] They immersed their non-dominant hand (palm down and fingers spread out) up to 5 cm above the level of the wrist in ice cold water.[27] The water was maintained between 3^{0}C to 5^{0}C throughout the test, by adding the necessary quantity of ice and ice-cold water to the container. This was stirred with a glass rod to dissipate the heat generated by the hand as this could alter pain perception and the temperature noted using a laboratory thermometer.[9,16,21,28] Two stop watches were started when the subjects immersed their hand. They were instructed to say the word 'pain' when they started feeling pain, then one of the stop watches was stopped. This represented the 'pain threshold' in seconds. Subjects continued to immerse their hand in cold water until they were unable to tolerate pain at that point, they removed their hand from the water. The second stopwatch was stopped at this point and the 'pain tolerance' in seconds noted. Immediately after CPT, room temperature, humidity, pulse rate (PR) and BP were recorded on the dominant hand. Cardiovascular reactivity was assessed as the change in systolic BP, diastolic BP and PR (Δ SBP, Δ DBP and Δ PR), calculated as the difference between post-test and pre-test values. The intensity of pain (pain unpleasantness) experienced by the subject was assessed using a visual analog scale (VAS)-'zero as no pain' and '10 as unbearable pain'.[7,16,29,30]

Data analysis was done with the R version 3.6.1 software. Based on statistical analysis, the normally distributed values were expressed as Mean ± SD and not normally distributed values were represented as Median (IQR). Pain threshold, pain tolerance and pain unpleasantness (pain rating) were the primary outcome parameters of this study. The association between pain sensitivity and quantitative health parameters were explored by Spearman Correlation test. Test of Significance for parametric data was obtained by Paired t-test and for non- parametric data, Mann Whitney U test. $P < 0.05$ was considered statistically significant.

RESULTS

The Mean ± SD values of the baseline parameters of the study: age (20.4 ± 2.9) years, BMI (21.7 ± 2.2) kg/m^2, average resting SBP (108.3 ± 9.9) mmHg, average resting DBP (64.6 ± 7.5) mmHg and average resting PR (77.6 ±

11.8) bpm were within the range considered for inclusion criteria. Humidity (60.2 ± 9.1)% and room temperature (25.7 ± 0.9) ^{0}C at the beginning of the experiment were not significantly different from the humidity (60.2±9.1)%, and room temperature (25.7 ± 0.8) ^{0}C at the end of the experiment. Water temperature was maintained between 3^{0}C to 5^{0}C at the beginning (3.5 ± 0.4) ^{0}C, middle (3.8 ± 0.4) ^{0}C and end of the experiment (4.2 ± 0.4) ^{0}C as per the protocol.

The median (Interquartile range) values of pain threshold (s) are 17.6 (10.7, 26.6) with a wide range of 2 to 240 seconds, tolerance(s) are 40.2 (30.0, 59.2) with a wide range of 9.8 to 300 and unpleasantness using VAS are 7.0 (6.1, 8.0) with a wide range of 2 to 9.5 (table 1).

Table 1. Pain sensitivity parameters of the study population

Parameter	Median (Interquartile range [Q1, Q3])	Range
Pain threshold (s)	17.6 (10.7,26.6)	2.0 to 240.0
Pain tolerance (s)	40.2 (30.0,59.2)	9.8 to 300.0
Pain unpleasantness (VAS score)	7.0 (6.1,8.0)	2.0 to 9.5

Data are presented as median (interquartile range= Q1: 1st quartile; Q3: 3rd quartile) for pain threshold, pain tolerance; and pain unpleasantness; s: seconds; VAS: visual analog scale.

Hundred and two (68%) subjects out of 150 had pain threshold between 1 to 24 seconds; 40 (26.7%) subjects between 24.1 to 48 seconds; Remaining 8 (5.3%) were between 48.1 to 240 seconds (figure 1 (a)). Out of 150 subjects, around 38 (25.3%) of them could tolerate pain in the range between 1 to 30 seconds; 77 (51.3%) subjects were between 30 to 60 seconds; remaining 35 (23.3%) were between 60 to 300 seconds (figure 1 (b)). Subjects demonstrated a wide range of pain unpleasantness with a median of 7.0 and IQR of 1.9 with a wide range of 2 to 9.5. Seventy-eight subjects (52%) rated their perception of pain on the scale between 4.1 to 7; 70 subjects (46.7%) rated between 7.1 to 10; 2 subjects (1.3%) rated their unpleasantness between 1 to 4 (figure 1 (c)).

A significant weak negative correlation was found between pain threshold and unpleasantness (ρ = -0.29; p < 0.001*), pain tolerance and unpleasantness (ρ = -0.35; p < 0.001*). A significant moderate positive correlation was seen between pain threshold and tolerance (ρ = 0.68; p < 0.001*).

Pain threshold and tolerance of males were significantly higher than females (p=0.004*). Subjects with P h/o HTN demonstrated significantly higher scores of pain unpleasantness compared to subjects with negative P h/o HTN (p = 0.02*) (table 2).

A significant rise in post-test SBP and DBP were found compared to the pre-test values (p < 0.001*). There was a significant decrease in post-test PR compared to the pre-test values (p=0.007*) (table 3). Vascular reactivity is the Δ change (post-test values minus resting values) of SBP, DBP and PR. Δ SBP showed a significant weak positive correlation with pain tolerance (ρ = 0.17; p=0.039*).

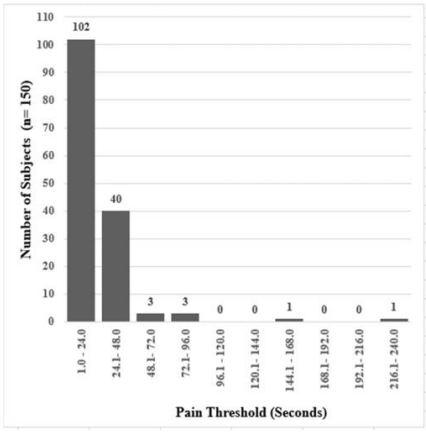

Figure 1a. Distribution of pain threshold.

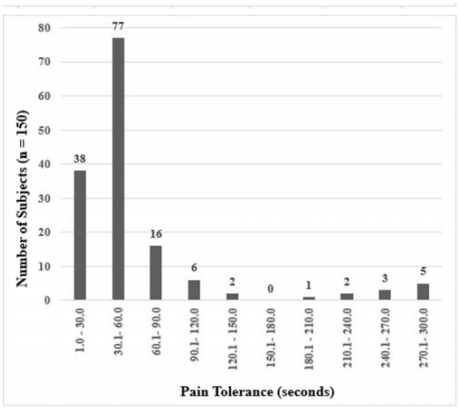

Figure 1b. Distribution of pain tolerance.

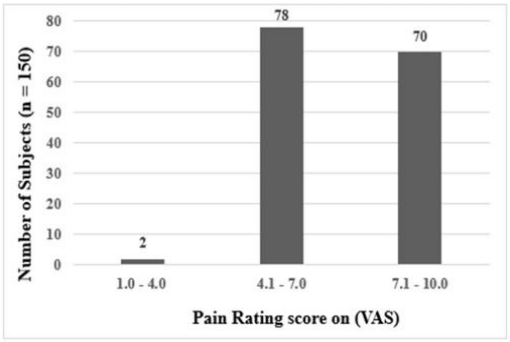

Figure 1c. Distribution of pain unpleasantness (rated on visual analog scale).

DISCUSSION

Pain is an unpleasant experience with inter-individual variability ranging from mild or moderate distress. It is a challenge for both researchers and clinicians due to interference with the standard of health, until treating root cause.[31,32] This pilot study was an attempt to provide a baseline data for the pain sensitivity parameters

Table 2. Gender differences and comparison of pain sensitivity parameters with positive and negative parental history of hypertension in response to cold pressor test:

Objectives	Category	Pain threshold (s)		Pain tolerance (s)		Pain unpleasantness (VAS)	
		Median (IQR= Q1, Q3])	p value	Median (IQR= Q1, Q3])	p value	Median (IQR= Q1, Q3])	p value
Gender differences	Males (n = 75)	**20.0 (13.2,30.5)**	**0.004***	**46.3 (33.6,64.5)**	**0.004***	7.0 (6.0,8.0)	0.013
	Females (n = 75)	14.3 (9.8,21.0)		35.7 (25.1,46.2)		7.5 (6.5,8.0)	
Parental history of hypertension	Positive parental history of hypertension (n = 48)	17.3 (10.4,25.6)	0.623	41.3 (30.1,59.1)	0.966	**8.0 (6.5,8.0)**	**0.02***
	Negative parental history of hypertension (n = 102)	17.6 (11.0,29.1)		40.2 (29.4,59.6)		7.0 (6.0,8.0)	

Data are presented as median (IQR: interquartile range= Q1: 1st quartile; Q3: 3rd quartile); s: seconds; VAS: visual analog scale. p value calculated using Mann Whitney U test. * $p < 0.05$ was considered statistically significant.

Table 3. Change in systolic blood pressure, diastolic blood pressure and pulse rate in response to cold pressor test.

Parameter	Resting values (Mean ± SD)	Post-test values (Mean ± SD)	Δ change [post -test value minus pre-test value] (Mean ± SD)	p value
SBP (mmHg)	**108.3 ± 9.9**	117.7 ± 12.0	9.5 ± 7.8	**p < 0.001***
DBP (mmHg)	**64.6 ± 7.5**	70.3 ± 8.8	5.7 ± 7.4	**p < 0.001***
PR (bpm)	**77.6 ± 11.8**	75.7 ± 12.8	-1.9 ± 8.3	**p = 0.007***

Data are presented as mean ± SD (standard deviation); SBP: systolic blood pressure; DBP: Diastolic blood pressure; PR: pulse rate; mmHg: millimetres of mercury; bpm: beats per minute. p value calculated using paired t-test. *$p < 0.05$ was considered statistically significant.

distribution between age group of 18 to 35 years among young adults of South India.

The pilot data showed that with a narrow range of age limits of the study population, subjects demonstrated a wide range of pain threshold, tolerance and unpleasantness measures. Pain unpleasantness showed a weak negative correlation with both pain threshold and tolerance. There was moderate positive correlation between pain threshold and tolerance ($p < 0.001$). Studies, mostly from other countries, have demonstrated different ranges of pain sensitivity values when compared to the present study using this model.[20] Studies on distribution of pain sensitivity have several implications. This study provides experimental evidence to the common notion that not only the subjective but also objective measures of pain sensitivity have inter-individual variability. This could be applied in a clinical setting while assessing the extent of injury and pain sensitivity reported by individuals to arrive at a diagnosis. Further, knowledge of the fact that there exists a wide range of pain sensitivity (objective and subjective measures) helps in titration of analgesic dosage.

Exploration of gender difference demonstrated that pain threshold and tolerance of males were significantly higher than females (p=0.004), whereas pain unpleasantness was found to be not statistically significantly different between males and females. In previous studies, women reported lower pain threshold compared to men, though the mechanisms underlying this concept were however unclear, one of the possible reasons is with biological, psychological, socio-cultural expectations where men are expected to suppress and tolerate more pain and are motivated not to complain or express early about pain because of the masculine gender, when compared to females.[8,9,21] Contradictory to this, another study demonstrated women with higher pain threshold than men within the age groups of 18 to 35 years which is the same age group of this study.[33] Subjects with P h/o HTN demonstrated significantly higher scores of pain unpleasantness compared to subjects with negative P h/o HTN (p=0.02), while same not observed with objective measures. Few studies reported increase in pain sensitivity parameters among subjects with positive P h/o HTN.[14,17] Contradictory to study findings, France, et al 1995 reported that positive P h/o HTN is associated with decrease in pain unpleasantness. Few other studies demonstrated that normotensives with positive P h/o HTN had higher pain threshold and tolerance. Hypoalgesia is reported as a potential predictor of future hypertension in subjects with a positive P h/o HTN.[14] The probable reason for varied results is testing different sets of people, age groups and laboratory setups.

Our study reported a significant increase in the post-test SBP, DBP ($p < 0.001$) and decrease in PR ($p = 0.007$), when compared to their resting values. Few studies have reported similar findings.[34-36] The probable mechanism behind significant increase in BP after immersing hand in cold water is due to release of norepinephrine with increased sympathetic stimulation. Arteriolar constriction, increased heart rate and cardiac contractility in turn causing increased cardiac output are the cardiovascular responses provoked by the stimulation of sympathetic nervous system. Increase in SBP, DBP is explained with an increase in cardiac output and the arteriolar constriction leading to increased peripheral resistance.[34] The decrease in PR is secondary to increase in BP.[37]

Response to pain was studied in terms of cardiovascular reactivity which was the Δ change. In this study, Δ SBP

exhibited a significant weak positive correlation with pain tolerance (ρ = 0.17; p = 0.039), whereas no significant correlation with pain threshold and unpleasantness. Also, no significant correlation found between Δ DBP and Δ PR with pain sensitivity parameters. Similar findings were reported by few other studies. Decreased pain unpleasantness scores and increased pain tolerance were reported among subjects with exaggerated cardiovascular response to stress, which is a future predictor of hypertension.[13,14,36]

Applying the findings of this study to all age groups and occupations can be a limitation due to involvement of narrow age group, student's population and a difference in pain reactivity and perception in a real-life scenario compared to the laboratory settings. Minute to minute BP and PR were not recorded during the CPT. Preovulatory phase of the menstrual cycle was considered based on recall of subjects without any laboratory investigations. P h/o HTN was noted with the history given by the subjects and not cross checked with the parents. Confounders of pain sensitivity like habitual levels of physical activity with physical activity questionnaire, anxiety levels with anxiety scores, thermal comfort and administration of pain sensitivity questionnaire before CPT were not performed.

Future direction: The present study being a pilot study, forms the basis for future studies with larger sample size and wider age group and BMI ranges which could have relevance for clinical assessment and management of pain. Thus, future studies need to be directed towards exploring the distribution of pain sensitivity parameters in a larger population and to examine the influence of the factors associated with pain sensitivity in Indian scenario.

CONCLUSION

The present study demonstrated a wide range of pain threshold, tolerance and unpleasantness. Pain unpleasantness showed a weak negative correlation with both pain threshold and tolerance. Pain threshold showed a moderate positive correlation with pain tolerance. Males had significantly higher pain threshold and tolerance than females. Subjects with P h/o HTN demonstrated significantly higher scores of pain unpleasantness compared to negative P h/o HTN. A significant rise in post-test SBP and DBP and a decrease in PR found compared to their resting values. Pain tolerance exhibited a significant weak positive correlation with Δ SBP.

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