Effect of stress on contextual pain sensitivity in the preoperative period- A proof of concept study

Shibani Padhy, Ruhi Fatima[1], Shubhranshu Jena[2], Akhya Kumar Kar, Padmaja Durga, Vishal Kumar Neeradi

Departments of Anaesthesiology and Critical Care and [2]Surgical Oncology Nizam's Institute of Medical Sciences, Hyderabad, Telangana, [1]Department of Anaesthesiology and Critical Care, ESI Medical College and Hospital, Hyderabad, Telangana, India

Abstract

Background and Aims: The importance of non-noxious contextual inputs in the interplay of pain with neurophysiologic and behavioral factors is gaining recognition. Stress of impending surgery can act as a negative context, leading to a decrease in pain threshold in patients. This study was conducted to assess the influence of stress conferred by the imminent and other contextual inputs such as anxiety, socioeconomic status, prior painful experience, and the effect of gender on modulation of pain perception in patients undergoing elective surgery.

Material and Methods: In total, 120 patients aged between 18 and 60 years of either gender posted for elective gastrointestinal surgery under general anesthesia were recruited. Data were collected on preoperative anxiety level, socioeconomic status, education, and any prior painful experience. A pressure algometer was used to measure the pressure pain thresholds and pain tolerance on the day before surgery and on the morning of surgery in the preoperative suite.

Results: There was a statistically significant decrease in both pain threshold ($P < 0.0001$) and pain tolerance in the immediate preoperative period in comparison to the baseline readings taken the day before surgery ($P = 0.048$). The magnitude of change in pain scalars was greater in females ($P < 0.001$), those with a high anxiety score, and a history of severe painful experience in the past.

Conclusion: Preoperative surgical stress lowers the pain threshold and pain tolerance. Contextual modulation of pain by factors such as anxiety and memory of prior painful experience, especially in the female gender, could influence postoperative patient outcomes and warrants further research.

Keywords: Anxiety, pain, stress, surgery

Introduction

Pain is a multidimensional process with substantial modulation produced by diverse non-noxious contextual inputs such as stress, emotional and psychological states, expectations, and prior painful experiences.[1,2] In the present era of pain research, such psychological factors have been identified as key factors determining debilitating pain. Context is defined as the collection of cues that signal the probable outcome of a given response. These cues or contexts shape the way one perceives pain so that an identical noxious stimulus will be painful in one situation, while it will not be perceived as painful in a different context. The term *context sensitivity* refers to whether a response is in tune with the social context.[3] Recognition of this newer concept of "contextual pain" has unwrapped new trails to understand the modulation of pain in

Address for correspondence: Dr. Akhya Kumar Kar,
B-503, Gem Ascentia, Hitex Road, Khanamet, Near Meenaxi Sky Lounge Hyderabad - 500 084, Telangana, India.
E-mail: karakshay@gmail.com

diverse situations. Contextual factors can have a direct impact on the quality of therapeutic outcomes. Positive contexts have been shown to decrease pain by creating a placebo effect, whereas negative contexts exacerbate pain by producing nocebo effects.[2]

Stress due to the impending surgery can act as a negative context, leading to a decrease in pain threshold in patients. Surgery is a major stressor that triggers anxiety in patients. Stress by itself modulates pain perception, resulting in either analgesia or hyperalgesia.[4] Although the preoperative period is known to be a significant stressor evoking negative emotions and anxiety, the impact of context sensitivity on pain dynamics has not been explored in the field of anesthesia and preoperative environment.

Prior studies have been conducted only in simulated conditions by using diverse stimuli,[5,6] and few have pointed toward an increased sensitivity to negative psychological cues and increased pain perception in the female gender.[7] Thus, this study was conducted to assess the influence of stressful environment conferred by the imminent surgery on modulation of pain perception in patients undergoing elective surgery.

The primary objective of the study was to assess the change, if any, and the magnitude of such change in pain scalars (pain threshold and tolerance) in patients in the preoperative period prior to elective surgery. Secondary objectives were to identify the influence of gender and contextual factors, namely age, type of surgery, prior painful experiences, level of education, and preoperative anxiety score, on the pain scalars.

Material and Methods

This prospective observational study was initiated after approval from the institutional ethics board and obtaining written informed consent from each participant. We recruited 120 patients aged 18–60 years of either gender posted for elective gastrointestinal surgery under general anesthesia. Pregnant females, those with associated pain syndromes, or those receiving analgesic, anxiolytic, or psychiatric medications affecting pain threshold or anxiety were excluded from the study.

The study consisted of two stages. A preoperative session on the day before scheduled surgery was carried out by one investigator. In this stage, after a detailed history, ASA grade was decided, and the following parameters were recorded using specific questionnaires:

1. Patients were asked to fill in the "Amsterdam Preoperative Anxiety and Information Scale" (APAIS) presented to them as a printed questionnaire. This tool provided a reliable and valid measure of the baseline anxiety score of the patients.[8,9] A score of 13 or more was used to identify clinically significant preoperative anxiety.

2. Socioeconomic status of the participants was recorded as per the modified Kuppuswamy scale updated for 2019.[10]

3. Education level was recorded and classified as Illiterate or less than 10th/10th+/Graduate and above.

4. Prior painful experience was noted in the form of any prior surgery/prior injury, and pain at that time was categorized as mild to moderate or severe by the NRS scale.[11]

In the second stage, an aFPIX50 pressure algometer (WAGNER Instruments) was used to measure the pressure pain thresholds and pain tolerance by applying pressure on the root of the nail.[12,13] The device was used to apply measured pressure perpendicularly on the root of the nail of the ring finger [Figure 1] by a second investigator who was not involved in obtaining the history and other parameters related to the study. The following observations were noted:

A. Pain threshold (PT): The minimum pressure that induces pain at the tissue trigger point.

B. Pain tolerance (PTOL): Maximum pressure the patient tolerates.

The readings were taken in Newton (N), and an average of three measurements was taken as the final readings of PT and PTOL. Repeat measurements of PT and PTOL were taken on the day of surgery in the preoperative suite.

Statistical analysis was conducted using SPSS software version 20.0. Based on the data analysis of the pilot study conducted on 20 patients, the mean baseline pain threshold score was 46, and the presurgical PT score changed to 42 with a standard deviation of 12. This resulted in an effect size of 0.5. Thus, a sample size of 86 was calculated with an alpha error of 0.05 and a power of 95%. This sample size allowed >90% power to detect a correlation of at least 0.5 between the baseline pain threshold value and the preoperative pain threshold value at an α level of 0.05. Considering the possibility of dropout during the study, failure

Figure 1: FPIX50 pressure algometer

to elicit a response and improper history by the patient, and postponement of cases related to COVID-19 positivity, we planned to enroll 120 patients.

Analysis by descriptive statistics was calculated for all variables (*i.e.* mean, SD, median, and range) as appropriate. Nonparametric Spearman correlation was used to investigate the relationship between contextual factors and pain scalars. Shapiro–Wilk test was used to assess the normality of the data distribution. Students *t* test was used to analyze changes in pain scalars from the baseline to preoperative period. $P < 0.05$ was considered significant. The relationship between gender and preoperative psychosocial variables with the change in pain threshold and tolerance values from the baseline was explored using ANOVA and Pearson correlation test, and correlation coefficients were calculated. The unadjusted relationship between the APAIS value and changes in pain threshold scores from the baseline to immediate preoperative period was explored using Spearman rank correlation.

Results

A total of 100 patients were finally able to complete the study, and 20 patients were excluded due to a variety of reasons [consort flow diagram; Figure 2]. Patients of both genders had a comparable demographic profile with regards to age, height, weight, BMI, type of surgery ASA grades, socioeconomic status, education level, and history of past surgery [Table 1]. The recorded algesiometer pain measurements when analyzed using student's *t* test revealed a statistically significant lowering in pain threshold and pain tolerance values in the immediate preoperative period in comparison to the baseline readings taken the day before surgery [Table 2a]. Furthermore, gender analysis revealed that females exhibited a marked lowering in pain threshold

and tolerance in the preoperative period as compared to their male counterparts [Table 2b]. Corroboratively, the magnitude of changes in pain threshold and pain tolerance scores from the baseline was larger and achieved statistical significance in females as compared to males [Figure 3].

The APAIS score in patients who exhibited significant lowering of pain scalars was significantly more than in those who did not (mean ± SD: 18.61 ± 3.94 vs. 10.99 ± 2.83; $P = 0.002$). The correlation of preoperative patient parameters to the change in pain scores was analyzed by Spearman correlation analysis. A high APAIS score (a score of 13 or more points was termed high), history of previous surgery, and a severely painful experience during that period were the factors identified to be associated with a significant decrease in pain scores in the preoperative period. There was no significant association of age, socioeconomic factors, level of education, ASA grade, or type of surgery for which the patient was posted on the change in pain scores [Table 3].

Discussion

The chief findings of this study are that preoperative stress lowers pain threshold and tolerance in patients regardless of the type of surgery. Female gender, a high preoperative anxiety score, and past severely painful experience are the factors associated with a marked lowering in pain scalars and increased pain perception in the preoperative scenario.

Psycho-physiological predictors for postoperative acute or chronic pain have been the focus of extensive perioperative research. This research is novel in that it gives the anesthesiologist an insight into the negative influence of preoperative stress of the imminent surgery on perioperative pain tolerance.
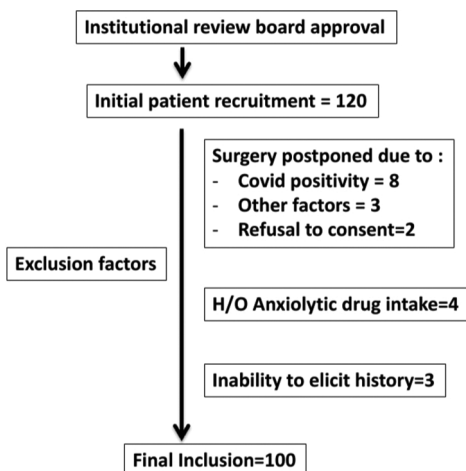

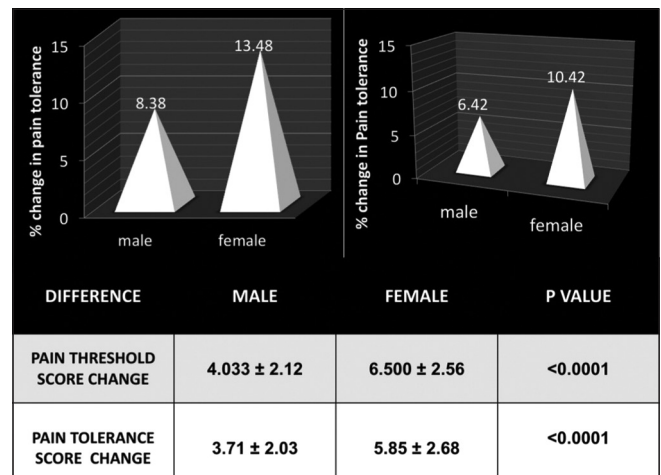**Figure 2:** Consort flow diagram for patient recruitment

Figure 3: Change in pain scores from the baseline

Table 1: Demographic profile

Parameter	Total (*n*=100)	Male (*n*=53)	Female (*n*=47)	*P*
Age (years)	51.42±12.15	54.50±13.74	54.36±11.82	0.306+
Height (cm)	159.47±8.84	164.13±5.66	154.67±4.49	0.446+
Weight (kg)	62.84±9.11	62.00±7.74	60.10±10.16	0.472+
BMI (kg/m²)	22.49±3.71	23.11±3.76	25.10±2.71	0.317+
Type of surgery				
Intermediate	14	8	6	0.39*
Major	86	45	41	
ASA grade				
1	34	18	16	0.33*
2	66	35	31	
Socioeconomic status				
Low	64	31	33	0.66*
Intermediate	32	19	13	
Good	4	3	1	
Education				
Illiterate	54	22	32	0.36*
Matric	26	17	9	
Above SSC	20	14	6	
Prior Surgery				
No	37	17	20	0.40*
Yes	63	36	27	
Patients with severe past painful experience (NRS score ≥8)	51	27	24	0.91*

Table 2a: Pain scalars

Pain parameter	Baseline value*	Presurgical value*	*P*
Pain threshold (PT)#	48.165±5.43	43.00±5.84	<0.0001
Pain tolerance (PTOL)#	56.97±6.48	52.27±6.68	0.048

Table 2b: Gender distribution of pain scalars

Parameter	Male (*n*=53)*	Female (*n*=47)*	*P*
PT baseline#	48.12±5.34	48.22±5.59	0.932
PT presurgical#	44.08±5.92	41.72±5.53	0.035
PTOL baseline#	57.71±6.50	56.10±6.42	0.200
PTOL presurgical#	53.99±6.84	50.25±5.94	0.003

Values depicted as Mean±SD; P derived by t test; P<0.05: statistically significant. #Measured in Newton

Preeminently, this research suggests that a particular prototype of patient, typically female, with a high preoperative APAIS score and with a positive history of severe past painful surgical experience exhibit an increased pain sensitivity and decreased tolerance to acute pain. This could elevate them into a higher risk category for developing persistent postoperative pain after surgery. Identification of such patients would enable the institution of tailored perioperative psychological interventions such as cognitive-behavioral therapy as well as pharmacological measures such as preemptive and multimodal analgesia.

Surgery is a significant external stressor triggering a cascade of physiological and psychological reactions.[14] Stress in both acute and chronic forms has been shown to produce hyperalgesia by an increase in the pain threshold in numerous behavioral models.[3,15] The adrenergic neurotransmission pathway is touted to be involved in the regulation of response to both pain and stress. Increased pain perception in response to stress is often associated with increased adrenergic sensitivity of the primary afferent nerve.[4,14]

Our study finding of the direct relationship between anxiety as measured by the APAIS questionnaire and pain perception can be explained by various experimental studies. Functional neuroimaging studies have conclusively shown anxiety to exacerbate pain through activation in the entorhinal cortex of the hippocampus.[16,17] We observed that the PT and PTOL values and their magnitude of decrease from baseline were lower in females than in males. Providentially, studies have shown that females are more sensitive to threat-related stimuli and experience higher negative affect than males, leading to increased pain perception.[18] We found that females are more sensitive to pain-related contextual factors, leading to increased pain perception. Existing research points toward specific biological mechanisms as an explanation for such gender differences in pain perception. These occur in the form of differences in the underlying structure and physiology of neural systems in the female gender as well as effects of phasic changes, such as fluctuations in the hormonal milieu.[19-22]

Table 3: Correlation of preoperative factors with pain threshold

Parameters	Change in threshold score*	*P*
Age	−0.18	0.853
S/E status	−0.125	0.196
Education	−0.188	0.051
ASA	−0.182	0.41
Type of surgery	0.058	0.552
Previous surgery/painful experience	0.194	0.043
Severe pain at prior painful experience	0.317	0.001
Apais score #	0.734	<0.0001

Change in threshold score depicted by Spearman rho correlation coefficients.
#APAIS Score: Amsterdam Preoperative Anxiety and Information Scale

Prior painful experience: We found that patients reporting a previous severe painful experience had a marked lowering in pain threshold and tolerance.

Such a relationship between pain and memory has been demonstrated by Biedma-Velázquez *et al.*[1] in their study.

Anatomically, the areas of the brain involved in encoding and consolidation of memory, namely the hippocampus, amygdala, and anterior cortex, are also implicated in various aspects of pain.[23] The authors surmise that common neurotransmitters and the phenomenon of neural plasticity such as central sensitization can explain the mechanistic overlap between chronic pain and memory.

Our study is veritable in that it is the only study to have used an objective measure of pain by the algesiometer to study the modulation of pain in the preoperative period and its influence by cognitive and emotional cues. Prior studies have been conducted only in simulated conditions using diverse stimuli.[5,24] The reliability and validity of a pressure algometer similar to the one used in our study for eliciting a pressure-pain threshold have been conclusively demonstrated by experimental research.[12,13]

It is well known that poorly managed postoperative pain significantly interferes with activities of daily living, emotions, and sleep, culminating in delayed recovery.[25] Our study has amassed evidence for the cardinal role of psychological factors such as fear, stress, and anxiety in the preoperative environment, not only as mediators of pain but also as potential targets for intervention.

The results of our study can argue for broader perisurgical interventions, including cognitive-behavioral therapy addressed to patients with a high risk of altered pain perception in the perioperative period. It is important for clinicians to understand the role of psychological factors in contributing to the high variability in patients' pain sensitivity. This could enable a-priori organization of adequate analgesic therapeutic measures as well the creation of a perioperative environment conducive to allaying anxiety and stress.

Our study has some limitations. Though the sample size was adequate to elicit a significant difference in baseline and presurgical pain scalars, a larger sample size may provide a better correlation of pain scalars with other factors. The majority of our patients had a lower education status; this may have resulted in less comprehension of the APAIS scale, resulting in lower scores. We did not study the postoperative patient outcomes. However, a recent study by Luedi *et al.*[26] has shown that the preoperative pressure pain threshold is predictive of acute postoperative pain in patients undergoing anorectal surgery. Similar findings have also been demonstrated after joint replacement, abdominal surgery, and dental procedures.[27-29]

Conclusions

Stress of the impending surgery lowers pain threshold and pain tolerance in the immediate preoperative period. Such an increased pain perception is more in the female gender and in the presence of contextual psycho-social factors such as higher APAIS anxiety score and experience of a prior severe painful experience. Contextual modulation of pain is an evolving concept that could influence postoperative patient outcomes and warrants further research.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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