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Research Article

RESPONSIVENESS OF STATE AND RESPONSE ENTROPY AND ALGESIOMETRY DURING INTRAVENOUS FENTANYL ADMINISTRATION: A COMPARISON BETWEEN MALE AND FEMALE PATIENTS

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ABSTRACT

Objectives: The aim of the study was to assess the gender difference in response to fentanyl on the entropy and algesiometry and to compare hemodynamic difference in between the gender.

Methods: It was a prospective observational study carried out in a group of 100 patients, of which 50 were males and 50 females. In both the groups, baseline entropy (response entropy [RE] and state entropy [SE]) and algesiometry values were recorded, 2 mic/kg of fentanyl was administered, and entropy values were recorded for 5 min and another algesiometry reading was taken at the end of 5 min.

Results: Both the groups were found to be comparable age and weight ($p<0.05$). However, the mean height of male patients was found to be more as compared to females, and the difference was found to be statistically significant ($p=0.037$). There was no statistically significant difference in the American society of anesthesiologists grades of male and female patients ($p=1$). Comorbidities were analyzed using Pearson's Chi-square test and both the groups were comparable in terms of distribution of comorbidities. ($p=1.000$). All parameters such as heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen Saturation, RE, and SE at various time intervals were found to be comparable in male and female patients. There was no statistically significant difference in any of the parameters till 5 min after fentanyl administration ($p>0.05$). There was no significant difference in entropy values among males and females before and after fentanyl administration. Females had significantly ($p=0.033$) lower pain threshold and a statistically significant increase in pain threshold as compared to males after fentanyl administration ($p=0.012$).

Conclusion: We conclude that fentanyl administration has not influenced the entropy values based on gender and females had an initial low pain threshold and a greater increase in pain threshold after fentanyl administration.

Keywords: Gender difference, Response entropy, Fentanyl, Hemodynamics, Pain threshold.

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INTRODUCTION

Pain is often the most frequent complaint in clinical practice. Gender plays an important role in the perception of pain [1]. The effect of gender on the pharmacokinetic and pharmacodynamics variables has not been routinely investigated. It still is debatable whether gender affects analgesic and anesthetic requirements. Various randomized clinical trials have shown females to experience considerable intensity of pain and they are said to be less tolerant to pain compared to males [2]. The existing literature regarding the gender difference in response to opioids, is inconsistent. Few studies show that female patients experience greater analgesic efficacy as compared to males following administration of opioids; however, other studies have found that women require a higher drug dose as compared to males to achieve analgesia to the same extent. Further, there are also reports on gender difference in response to nonopioid analgesics [3]. Therefore, understanding gender differences in relation to pain, study of such factors which can influence response to drugs such as age, gender, genetic history, metabolic phenotype, body fat content, and general disease state which can alter drug metabolism and excretion can help in making appropriate adjustments in dose, monitoring and other aspects of drug administration which could improve patient's outcome [4].

Entropy is an electroencephalogram (EEG)-based monitoring method used to measure the depth of anesthesia. Entropy expresses the disorder and unpredictability in the system. When applied to EEG waveforms, entropy decreases at deeper planes of anesthesia [5]. The entropy module consists of two components state entropy (SE) and response entropy (RE). SE is calculated in a frequency band of 0.8 to 32 hz and reflects the hypnosis component. RE is calculated in a band of 0.8–37 hz and reflects both hypnosis and analgesia; the additional spectrum being dominated by EMG activity [6].

Quantification of sensation of pain is important for diagnostic and monitoring purposes. Most practical as well as theoretical methods of pain assessment relies upon behavioral methods and are subjective. Different pain modalities (thermal, electrical, chemical, and mechanical) are applied, of which measurement of mechanical pain sensitivity is the most widely used [7]. Objective assessment of pain sensitivity is performed by means of an electronic pressure algometer [8].

IN recent past gender influences on pain and analgesia has become an upcoming area for research. The components that form neurobiological basis for sex differences among opioid drugs include brain opioid receptor density (greater in males and under low estradiol condition) and dopaminergic function (greater in females and under high estradiol condition) [9]. In addition to these factors' progesterone and its metabolites, in particular have hypnotic effects that are thought to occur through direct action on GABA-A receptor complex. Thus, further studies are needed to determine differences in pain sensitivity and opioid requirement in males and females [10].

The study was undertaken to observe the change in entropy and algesiometry values on administration of mu-opioid agonist, Fentanyl, and the difference in values between male and female patients and thus determining the differences in opioid sensitivity and dosages.

METHODS

This was a prospective observational study conducted in the department of anesthesiology of a tertiary care center after obtaining approval from the institutional ethics committee and registered in Clinical Trial Registry of India. After obtaining written and informed consent, this study was carried out over a period of 6 months in 100 American society of anesthesiologists (ASA) I and ASA II patients aged 18–60 years on the basis of a predefined inclusion and exclusion criteria. Keeping power (1-Beta error) at 80% and confidence interval (1-alpha error) at 95%, the minimum sample size required, as calculated on the basis of pilot studies involving the assessment of pain threshold was found to be 80 patients; therefore, we included 100 (more than minimum required number of cases) specimens in this study. All patients were premedicated with tablet pantoprazole 40 mg on the morning of the day of surgery, thereby avoiding sedative/anxiolytic premedication. After wheeling the patient in to the operation theater, an intravenous access was secured with 18 G cannula, baseline hemodynamic values such as heart rate (HR), systolic and diastolic blood pressure (DBP), mean blood pressure, and oxygen Saturation (SPO_2) values were recorded.

A special composite electrode with three elements was applied to the forehead in accordance with the manufacturer's instruction and was connected to the entropy monitor (M- Entropy plug-in Module S/5Ô; Datex-Ohmeda Division, Instrumentarium Corporation, Helsinki, Finland). After an initial control for electrode impedance, the monitor calculates an index from the raw EEG signals using an unpublished algorithm based on entropy principles. Initial sampling time was 30 s with update time of 10 s. The indices RE and SE were read manually and recorded. The frontal electromyogram was included in the entropy analysis yielding RE, while only the cortical EEG was evaluated in the SE index.

FPIX 50 algesiometer of WAGNER Instruments was used in our study to identify pain threshold and pain tolerance. The standard protocol recommended by the manufacturer was followed for calibrating the algesiometer, the pressure algometer was applied to the nail of the middle finger without touching the nail fold. The algometer reading at which the subject complains of pain is called the pain detection threshold. The stimulus was intensified until the subject experienced unbearable pain. This is called pain tolerance threshold (PTT). We

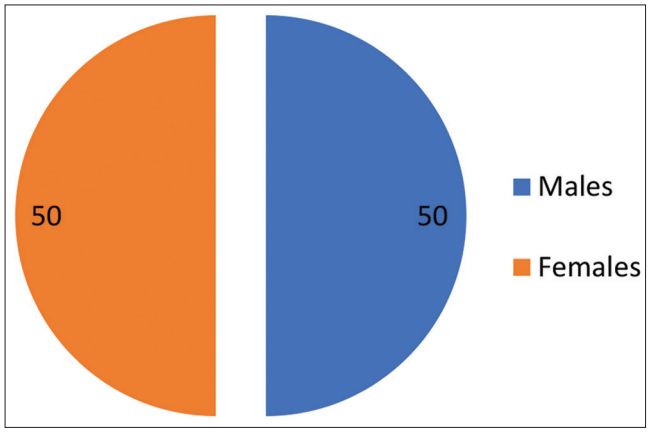

Fig. 1: Gender distribution of the studied cases

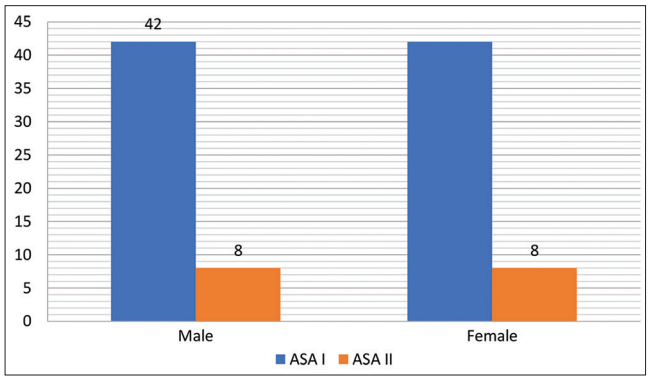

Fig. 2: ASA grades of male and female patients

Table 1: Comparison of age, weight, and height in male and female patients

Demographic details	Males-Mean±SD	Females-Mean±SD	p-value
Age (in years)	43.397±11.58	44.054±11.52	0.581 (Not significant)
Weight (in Kilograms)	63.64±11.93	60.86±9.21	0.195 (Not significant)
Height (In centimeters)	159.72±4.72	157.58±5.368	*0.037 (Significant)

Table 2: Comparison of comorbidities among groups

Co-morbidities	Number of males (%)	Number of females (%)	p-value
None	42 (84)	42 (84)	1.000
Diabetes mellitus	4 (8)	4 (8)	(Not significant)
Hypertension	4 (8)	3 (6)	
Hypothyroidism	0 (0)	1 (2)	

Table 3: HR, Systolic and diastolic blood pressure, men arterial pressure, SPO_2

Duration after Fentanyl Administration	Males	Females	p-value
HR			
Baseline	86.08±16.67	89.10±14.50	0.336
1 min	81.70±17.54	85.42±16.48	0.277
2 min	80.64±17.64	83.78±16.08	0.355
3 min	81.02±17.15	82.68±16.14	0.619
4 min	80.42±16.17	80.26±14.15	0.958
5 min	78.50±16.732	78.92±14.156	0.892
Systolic blood pressure			
Baseline	136.48±19.52	143.60±23.04	0.099
1 min	134.06±20.38	139.36±22.48	0.220
2 min	129.42±20.39	134.56±21.26	0.220
3 min	126.18±20.31	129.90±18.79	0.160
4 min	126.66±18.45	128.02±18.44	0.133
5 min	124.16±17.91	126.20±19.00	0.708
Diastolic blood pressure			
Baseline	84.58±12.52	83.94±12.06	0.795
1 min	82.10±11.32	81.64±11.04	0.837
2 min	80.22±12.16	79.12±12.25	0.653
3 min	79.26±14.06	76.92±12.73	0.385
4 min	77.84±12.46	77.26±13.45	0.824
5 min	76.90±11.97	76.12±13.45	0.744
Mean arterial pressure			
Baseline	101.88±13.96	103.83±14.53	0.495
1 Min	99.42±13.71	100.88±13.50	0.592
2 Min	96.61±14.32	97.60±13.94	0.727
3 Min	94.90±15.24	94.57±13.53	0.911
4 Min	94.11±13.65	94.18±13.39	0.980
5 Min	92.65±12.90	92.81±12.91	0.952
SPO_2			
Baseline	98.71±1.15	98±1.14	0.880
1 Min	98.51±1.41	98±1.39	0.712
2 Min	98.12±1.61	98±1.59	0.238
3 Min	97.69±1.87	97±2.02	0.775
4 Min	97.34±1.90	97±2.12	0.686
5 Min	97.26±2.16	97±2.32	0.858

SPO_2: Oxygen saturation, HR: Heart rate

measured these variables in Newtons in the algesiometer readings. We had recorded only the PTTs. Baseline entropy and algesiometry values were recorded, and fentanyl was administered in a dose of 2 microgram per kg body weight. The changes in entropy values were noted along with other vital parameters every minute for a period of 5 min. Another single reading of algesiometry was taken 5 min after fentanyl administration. Anesthesia was then further induced with standard anesthesia protocol. The patient was pre-oxygenated with 100% O^2 for 3 min and induced with thiopentone 5 mg/kg and sevoflurane 2%. The ability to ventilate confirmed after which atracurium was given for muscle relaxation in a dose of 0.5 mg/kg. Patient's trachea was intubated with appropriately sized oral cuffed endotracheal and was fixed after confirming equal bilateral air entry. The patient was maintained on isoflurane with a MAC of ≈ 0.7–1.3, tailored to the need, and was ventilated with tidal volume of 6 mL/kg with fiO_2 of 50%. At the end of the surgery, all the anesthetic agents were stopped, and the patient was extubated once the recovery criteria were met and after reversing the residual neuromuscular blockade with neostigmine 0.05 mg/kg and glycopyrrolate 10 mg/kg. The patient was shifted to post-anesthesia care unit for further care and monitoring. For statistical purposes, statistical package for the social sciences 22.0 software was used, and $p<0.05$ was considered statistically significant.

RESULTS

The analysis of cases on the basis of gender distribution showed that there were equal numbers of male and female patients (50 each) with a M: F ratio being 1:1. There was no statistically significant difference in gender distribution of the studied cases (Figure 1).

The mean age of the male patients was found to be 43.397±11.58, whereas the mean age of female patients was found to be 44.054±11.52. The mean age of male and female patients was found to be comparable (p=0.581). The mean weight of male and female patients was found to be 63.64±11.93 and 60.86±9.21. The mean weight of male and female patients was also found to be comparable with no statistically significant difference between males and females. However, the mean height of male patients (159.72±4.72) was found to be more as compared to females (157.58±5.368), and the difference was found to be statistically significant (p=0.037) (Table 1).

The analysis of patients on the basis of ASA grades showed that in male as well as female patients' equal number of cases belonged to ASA class I (42 males and 42 females) and ASA Class II (8 males and 8 females). There was no statistically significant difference in ASA grades of male and female patients (p=1) (Figure 2).

The analysis of comorbid conditions present in studied cases showed that in male as well as female patients, 4 (8%) patients were diagnosed cases of Type II diabetes mellitus, whereas 4 men were having essential hypertension. Among females, 3 (6%) patients had hypertension. 1 (2%) female patient was found to have hypothyroidism. Comorbidities were analyzed using Pearson's Chi-square test and both the groups were comparable in terms of distribution of comorbidities (p=1.000) (Table 2).

Male and female patients were compared for hemodynamic parameters such as HR, SBP and DBP, mean blood pressure, and SPO2. All parameters such as HR, systolic blood pressure (SBP), DBP, mean arterial pressure (MAP), SpO2, RE, and SE at various time intervals were found to be comparable in male and female patients. There was no statistically significant difference in any of the parameters till 5 min after fentanyl administration (p>0.05) (Table 3).

The analysis of SE as well as RE among male and female patients showed that baseline till 5 min post-fentanyl administration SE as well as RE was found to be comparable with no statistically significant difference between male and female patients (p>0.05) (Table 4).

The analysis of pain sensitivity between male and female patients as assessed by algesiometry showed that males have a higher pain threshold as compared to female patients at the time of baseline as well as 5 min after fentanyl administration. The difference was found to be statistically significant (p<0.05) (Table 5).

Table 4: State entropy and response entropy in male and female patients

Duration after fentanyl administration	Males	Females	p-value
State entropy			
Baseline	88.60±3.505	88.70±2.003	0.861
1 Min	87.58±2.778	88.08±1.338	0.254
2 Min	86.72±3.764	87.10±2.705	0.254
3 Min	83.60±10.513	85.70±4.630	0.199
4 Min	82.22±12.238	85.16±4.722	0.116
5 Min	81.90±10.744	84.94±5.991	+0.084
Response entropy			
Baseline	97.32±2.142	97.70±1.474	0.304
1 Min	96.72±2.110	96.82±1.521	0.786
2 Min	95.76±3.166	95.92±3.168	0.801
3 Min	93.16±8.709	94.74±4.247	0.252
4 Min	91.62±11.183	94.18±4.480	0.136
5 Min	91.22±8.879	92.46±6.312	0.423

Table 5: Comparison of algesiometry findings in male and female patients

Algesiometry value	Males-mean±SD	Females-mean±SD	p-value
Baseline	125.108±23.770	114.334±25.958	0.033 (Significant)
5 min post fentanyl	146.548±21.593	134.928±23.962	0.012 (Significant)

SD: Standard deviation

DISCUSSION

The results of this prospective observational study showed that there was no statistical difference in entropy values between males and females after fentanyl administration and also the hemodynamics. There was no significant difference in hemodynamics (HR, SBP, DBP, and MAP) and oxygen saturations between both the groups. This finding is in agreement with the study conducted by Larijani *et al*., where they found no significant differences between hemodynamics among genders in postoperative period who received intravenous morphine [11].

In our study, we did not find any statistically significant difference in RE and SE values between males and females during fentanyl administration. This finding was in compliance with the findings of a study done by Vassiliadis *et al*. where entropy values were compared between males and females in awake and anesthetized state before and after remifentanil bolus. They found that, remifentanil, given as a bolus, did not show any significant difference between male and female patients in awake state, but in anaesthetized patients, they found a significant reduction in SE and RE values among female patients [12]. In contrast, in an observational study was done by Nagasaka *et al*. to study the pattern of BIS changes in both the genders after fentanyl administration, the conclusion was that there was a higher fentanyl-induced BIS increases in females as compared to males, although the reason was not explained [13].

Another finding in our study results showed that there was no significant difference in hemodynamics (HR, SBP, DBP, and MAP) and oxygen saturations between both the groups. This finding is in agreement with the study conducted by Niesters *et al*. where they found no significant differences between hemodynamics among genders in post-operative period who received intravenous morphine [14].

Our study results showed that there was a significant difference in algesiometry reading before (p=0.033) and after (p=0.012) fentanyl administration between males and females. Males were found to be having a higher pain tolerance and pain threshold as compared to females. This is in compliance with the study conducted Buchanan and Midgley in their study which consisted of measuring pressure pain threshold using simple pressure algometer that significantly lower pain thresholds were observed females. Another interesting finding in their study was that pressure pain threshold was higher in dominant hand. However, in our study, we have not investigated the difference between the dominant and non-dominant hand pain thresholds [15].

The study conducted by Cepeda and Carr concluded that women had more intense postoperative pain than men which bears similarity with the findings of our study in terms of pain threshold. Further, on the grounds of opioid requirement, they found that women had larger weight-adjusted morphine requirements than men to achieve a similar degree of analgesia [16]. In a study conducted by Sarton *et al*., serial concentration of morphine and its metabolites in the plasma were measured, and it was found that concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide did not differ between men and women, so the difference in analgesic requirements might be having a pharmacodynamic basis [17]. Apart from pharmacokinetic and pharmacodynamic basis for lower pain threshold among women, as per a review by Barsky *et al*., a number of contributory factors have been implicated, supported by varying degrees of evidence [18]. These include innate differences in somatic and visceral perception, differences in symptom labeling, description, and reporting and sex differences in pain perception and a different socialization process for men and women that influence bodily experience and the willingness to communicate distress.

Several studies concluded that there was no sex difference in analgesic requirements between males and females. Among them are, a study done by Olofsen *et al*., who concluded that there was no sex difference detected after alfentanil infusion in experimental pain models [19].

Similarly, Fillingim *et al.* concluded that there was no sex difference in pentazocine analgesia across multiple experimental pain assays [20]. These findings are important because they suggest that sex differences in opioid analgesia may be specific to certain types of pain.

Limitations

Our study mainly focused on changes in entropy in awake state and we could not find a significant gender differences after fentanyl administration, but we did not evaluate the changes in the intraoperative period. We also did not assess the dose requirement among males and females to achieve the same amount of reduction in entropy. Further studies are required in this domain to establish the sensitivity of opioids among genders.

CONCLUSION

We conclude that fentanyl administration does not influence the entropy values based on gender. Females were found to have a low baseline pain threshold as well as at the end of 5 min after fentanyl administration. There was a greater increase in pain threshold in female patients after fentanyl administration as compared to male patients.

CONFLICT OF INTEREST

None.

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