Original Article

Correlation of pain perception and fentanyl consumption after major abdominal surgery with CGRP 4218T/C polymorphism: A prospective interventional study

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ABSTRACT

Background and Aims: Genetic polymorphisms contribute to patients' variability in pain perception and response to opioid treatment. The present study evaluated the association of calcitonin gene-related peptide (CGRP) 4218T/C polymorphisms with fentanyl consumption over 24 h postoperatively in patients after major abdominal surgery. **Methods**: Eighty-five patients undergoing major abdominal surgery under general anaesthesia were recruited. For postoperative analgesia, epidural fentanyl and intravenous paracetamol were provided. The CGRP 4218T/C genotype was analysed, and the association between the genotype of the patient and the total consumption of fentanyl in the first 24 h after surgery was assessed. The association between different genotypes, the severity of postoperative pain and the side effects of opioids were also studied. **Results**: Our study population distribution included 52.9% of the T/T genotype (wild homozygote), 35.3% of the T/C genotype (heterozygote) and 11.8% of the C/C genotype (mutant homozygote). Mean (standard deviation) total fentanyl consumption in the first 24 h was found to be highest in the C/C group (212.0 [7.5] μg), followed by the T/T group (182.8 [9.9] μg) and was the least in the T/C group (159.6 [7.5] μg). The C/C group reported higher pain scores in all the study periods. There was no significant difference in the side effects of opioids, such as nausea, vomiting, sedation among different genotypes of CGRP 4218T/C. **Conclusion:** The polymorphism of CGRP 4218T/C affects postoperative pain perception and analgesic consumption. Patients with the C/C genotype had higher postoperative fentanyl consumption and pain scores.

Key words: Analgesia, calcitonin gene-related peptide, CGRP 4218T/C, epidural analgesia, pharmacogenetics, postoperative analgesia, single-nucleotide polymorphisms

INTRODUCTION

One of the important challenges in delivering satisfactory postoperative analgesia is interindividual variability in postoperative pain intensity.[1] This variability has been attributed to complex genetic, environmental and social factors.[2] Growing evidence shows that genetic factors are critical in pain sensitivity and susceptibility to developing chronic pain after surgery.[3] The genetic variations in catechol-*O*-methyltransferase (*COMT*) and mu-opioid receptor gene (*OPRM1*), brain-derived neurotrophic factor (*BDNF*) genes have previously been reported for interindividual differences in postoperative pain

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perception. Calcitonin gene-related peptide (CGRP) is a neuropeptide involved in the nociceptive pathway, and it is widely distributed in the central and peripheral nervous systems. It plays a crucial role in pain perception and modulation.[4] The genetic polymorphism in the CGRP gene 4218T/C significantly influences postoperative fentanyl consumption.[5,6] Patients with the C/C genotype have been reported to have reduced sensitivity to fentanyl and increased pain perception. However, the influence of CGRP polymorphism on postoperative pain has not been evaluated in other ethnic populations.

The present study was designed to assess the role of different genotypes of CGRP on postoperative pain after major abdominal surgery. The primary objective was to evaluate the association of CGRP 4218T/C polymorphisms with fentanyl consumption over 24 h postoperatively following surgery. The secondary objectives were to assess the association of CGRP 4218T/C polymorphisms with the severity of postoperative pain, the incidence of nausea and vomiting, pruritus, sedation and respiratory depression over 24 h postoperatively. We hypothesise that there would be no difference in postoperative pain perception and analgesic consumption in patients with different CGRP genotypes.

METHODS

This prospective interventional study was conducted on 85 patients from January 2019 to January 2020. The study was started after obtaining approval from the Institutional Ethical Committee (vide approval number 17/IEC/MAMC/2018/11, dated 26 October 2018) and was registered under the Clinical Trial Registry-India (vide registration number CTRI/2019/01/016986, https://ctri.nic.in/). Adult patients aged between 20 and 65 years belonging to the American Society of Anesthesiologists (ASA) physical status I/II, who were scheduled to undergo elective major abdominal surgeries under general anaesthesia, who could comprehend and describe verbal or visual pain scale and who were without any history of drug dependence or recreational drug use were recruited in our study. Patients with a history of allergy to opioids or any other drugs to be given intraoperatively or with any contraindication to epidural block and pregnant patients were excluded from our study. Written informed consent was obtained from patients to participate in the study and use patient data for research and educational purposes. The study procedures followed the guidelines in the World Medical Association (WMA) Declaration of Helsinki-ethical Principles (2013) for medical research involving human subjects. Pre-anaesthetic checkup as per the institutional protocol was carried out in all patients. Standard anaesthetic monitors were applied in the operating room, including continuous electrocardiogram (ECG), noninvasive blood pressure and pulse oximeter, and baseline readings were noted. An intravenous (IV) access was secured, and a 3 ml venous blood sample was collected in an ethylenediaminetetraacetic acid (EDTA) vial; after proper labelling, the CGRP genetic analysis was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using HiPurA™ blood genomic DNA miniprep purification kit (Himedia, Mumbai, India). Under all aseptic precautions, and after local infiltration with 2 ml of 2% lignocaine, an 18G Tuohy epidural needle was inserted in the desired space and an epidural catheter was threaded in up to 3–5 cm depth inside the epidural space. After proper fixation of the epidural catheter, the patients were premedicated with IV fentanyl 1.5 μg/kg lean body weight (LBW). Anaesthesia induction was done with IV thiopentone sodium 3–5 mg/kg titrated dose. After establishing the ability to ventilate via bag and mask, IV vecuronium 0.1 mg/kg was administered to facilitate tracheal intubation. Anaesthesia was maintained using a gaseous mixture of oxygen and nitrous oxide (50:50) in isoflurane. After 3 min of vecuronium administration, tracheal intubation was performed under direct laryngoscopy with an appropriately sized endotracheal tube. After successful tracheal intubation, controlled ventilation was established to target end-tidal carbon dioxide ($EtCO_2$) between 32 and 36 mmHg. Fentanyl IV infusion was started at 1 μg/kg/h 15 min after induction of anaesthesia. IV paracetamol 1 g was administered to all patients. Intraoperative titration of anaesthetic was left to the discretion of the attending anaesthesiologist. About 20–30 min before the anticipated conclusion of the surgery, fentanyl infusion was stopped, and IV ondansetron 4 mg was administered as prophylaxis for postoperative nausea and vomiting (PONV). At the end of the surgery, the neuromuscular blockade was antagonised with an appropriate dose IV neostigmine and glycopyrrolate. The patients were monitored at 0, 6, 12 and 24 h in the postoperative period. The severity of postoperative pain and side effects of opioids, such as nausea, vomiting, pruritus and respiratory depression, were assessed. Patients received IV paracetamol 1 g eight

hourly for postoperative analgesia and epidural fentanyl infusion. For epidural analgesia, a background infusion of fentanyl at the rate of 5 μg/h was started as soon as the patients reached the postoperative care unit. The severity of postoperative pain was assessed using the visual analogue scale (VAS) with a rating of 0–10, where a score of 0 indicated no perceptible pain and a score of 10 indicated severe pain. If the patient complained of VAS more than 3, a rescue dose of IV fentanyl 5 μg was administered. The patient was re-evaluated 5–10 min after the rescue dose; if the patient still complained of VAS more than 3, the rescue dose was repeated. The rescue doses were repeated till VAS was less than 3. The total amount of fentanyl consumed over 24 h postoperatively was recorded. The side effects of opioids, such as PONV, pruritus, sedation and respiratory depression, were recorded at the study intervals. Vomiting was assessed by using a PONV impact scale. A PONV impact scale score of ≥5 defines clinically important PONV. Sedation was assessed using the Ramsay sedation scale, where a score of 1 meant anxious and agitated and 6 meant the patient exhibited no response. Respiratory depression was defined as a respiratory rate of fewer than 8 breaths per minute (bpm) or shallow breathing or oxygen saturation (SpO_2) value of less than 94%. The number of patients who had pruritus in the postoperative period was also recorded, and the severity was classified as mild, moderate and severe. The venous blood sample taken from the patients was analysed for CGRP 4218T/C polymorphisms. Based on the CGRP 4218T/C genotypes, we predict the influence of pain perception and analgesic consumption for developing effective postoperative pain management strategies. A study participant's specific type of genotype was known only after performing the above-mentioned genotyping method. Based on this genotyping procedure, patients were categorised into respective genotypes, that is, C/C, C/T or T/T genotype. The investigator administering the anaesthesia and recording the parameter was blinded to the genotypes of the patients revealed at the time of data analysis.

For sample size calculation, a moderate correlation between CGRP 4218T/C polymorphisms with the total amount of fentanyl consumption over 24 h postoperatively was considered meaningful. To detect a moderate correlation ($r = 0.30$), a sample of 85 subjects provides 80% power to discover that the correlation is significantly different from there being no correlation (i.e. the correlation is zero) at the 0.05 level. Statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS) program for Windows, version 25.0 (IBM Corp., Armonk, NY). Continuous variables are presented as mean ± standard deviation (SD), and median (interquartile range [IQR]), and categorical variables are presented as absolute numbers and percentages. The genotype distribution was checked by Hardy–Weinberg Equilibrium (HWE) with the χ^2 test. Data were checked for normality before statistical analysis using the Shapiro–Wilk test. The Kruskal–Wallis test was used for those variables that were not normally distributed, and further comparisons were made using the Mann–Whitney U test. Categorical variables were analysed using the χ^2 test. A $P < 0.05$ was taken for all statistical tests to indicate a significant difference. For measurement of the effect size of the difference between the genotypes, Cohen's d was calculated.

RESULTS

After the genetic analysis for CGRP 4218T/C polymorphisms, three different types of genotypes of CGRP4218T/C polymorphism was identified in the Indian population, C/C genotype, T/C genotype and T/T genotype, and the frequency of distribution of genotypes was 11.8% (10), 35.3% (30) and 52.9% (45), respectively. The patients' demographic profiles were comparable among the three genotypes [Table 1], and the mean amount of fentanyl consumed in the first 24 h of the postoperative period, its effect size and precision were comparable [Table 2]. The mean total fentanyl consumption in the first 24 h was found to be highest in the C/C group, followed by the T/T group and was the least in the T/C group. In the paired comparison of C/C versus T/C and C/C versus T/T, the C/C group had a significantly higher requirement

Table 1: Demographic profile of the patients

Parameters	Genotypes of CGRP 4218T/C		
	C/C (*n*=10)	T/C (*n*=30)	T/T (*n*=45)
Age (years)	34.70 (9.15)	39.00 (11.86)	41.22 (9.05)
Gender (Female:Male)	7:3	20:10	24:21
Height (cm)	165.00 (7.06)	162.03 (7.29)	163.76 (6.48)
Weight (kg)	61.90 (8.35)	58.13 (7.79)	60.44 (6.57)
LBW (kg)	46.20 (6.27)	43.15 (6.29)	46.41 (5.84)
ASA PS (I:II)	9:1	22:8	31:14
Duration of surgery (min)	173.50 (26.57)	157.67 (31.26)	167.33 (32.34)

Values are represented as mean (standard deviation) or numbers. C/C=Wild homozygote, T/C=Heterozygote, C/C=Mutant homozygote, CGRP=Calcitonin gene-related peptide, ASA PS=American Society of Anesthesiologists Physical Status, LBW=Lean body weight

of mean total postoperative fentanyl in the first 24 h than T/T ($P < 0.001$) and T/C ($P < 0.001$). In a paired comparison of T/C versus T/T, the T/T group had a significantly higher requirement of mean total postoperative fentanyl in 24 h than T/C ($P < 0.001$), with comparable effect size and precision [Table 2]. The mean VAS scores among genotypes and paired comparison showed that in the C/C genotype, the mean VAS score was highest in all periods. In the T/C genotype, the mean VAS score was least in all periods, and in the T/T genotype, the mean VAS scores were between the VAS of C/C and T/C in all periods. In the paired comparison of C/C versus T/C and C/C versus T/T, the C/C group had highly significant VAS or pain perception than T/C ($P < 0.001$) and T/T ($P < 0.001$) in all periods [Table 3]. The respiratory rate among genotypes and paired comparison showed that, in the paired comparison of respiratory rate in C/C versus T/C, statistically significant results were seen at the sixth hour (14.5 [1.3] vs. 12.5 [2.1] bpm) and the 12th-hour (13.3 [1.9] vs. 11.4 [2.2] bpm) assessment, with C/C having more respiratory rate compared to the T/T group. However, this data has no clinical relevance as the respiratory rate was more than 8 in all periods among genotypes. No significant results were observed with sedation scores, PONV scores and O_2 saturation. A negligible number of patients had complaints of pruritus (mild) at 0 h and 6-h assessment in all three genotypes. At 12-h (C/C [30%] and T/T [15.6%]) and 24-h (C/C [50%] and T/T [33.3%]) assessment, a significant number complained of pruritus. The frequency of pruritus in the T/C group was statistically insignificant at all periods.

DISCUSSION

The present study demonstrated that in the Indian population, CGRP4218T/C polymorphism was associated with variable fentanyl consumption in the postoperative period following major abdominal surgeries. The mean fentanyl consumption in the C/C group was significantly higher than in the T/T and T/C genotypes 24 h after surgery.

Yi *et al*.,[6] in a study involving ethnic Han Chinese patients undergoing open abdominal and lumbar surgeries, reported that the mean fentanyl consumption at 24 h after surgeries in T/T, T/C and C/C groups was 14.8 ± 6.1, 19.6 ± 6.4 and 23.4 ± 6.8 μg/kg, respectively. This is in contrast to our study and may be attributed to the difference in the postoperative analgesic protocol and the nature of the surgery included in their research. Yi *et al*. employed fentanyl with flurbiprofen axetil or fentanyl with propacetamol for patient-controlled analgesia (PCA), whereas in the present study, we used an epidural infusion of fentanyl and paracetamol IV. Another study by Xie *et al*.[5] also supported the findings of our research. They reported that in parturients who underwent caesarean section, the C/C genotype was significantly linked to high consumption of patient-controlled epidural fentanyl.

CGRP is expressed ubiquitously in the body and has a well-documented role as a pronociceptive and proinflammatory neurotransmitter. It is released from the dorsal horn of the spinal cord in response to noxious stimuli. It amplifies the release of several

Table 2: Comparison of the amount of IV fentanyl consumed postoperatively among genotypes and paired comparison of genotypes

Amount of IV fentanyl consumed (μg)	Type of genotype			*P*	Effect size (95% CI) C/C versus T/C	Effect size (95% CI) C/C versus T/T	Effect size (95% CI) T/C versus T/T
	C/C (*n*=10)	T/C (*n*=30)	T/T (*n*=45)				
0–6 h	32.0 (8.8)	13.0 (3.8)	27.9 (4.5)	<0.001	3.46 (2.78–4.25)	0.75 (0.04–1.44)	3.52 (2.78–4.25)
6–12 h	28.0 (6.3)	11.8 (4.8)	20.8 (3.9)	<0.001	3.09 (2.09–4.08)	1.61 (0.85–2.36)	2.06 (1.48–2.62)
12–24 h	27.5 (7.2)	15.0 (4.9)	14.1 (4.0)	<0.001	2.26 (1.37–3.12)	2.84 (1.96–3.70)	0.20 (0.66–3.81)
The total amount in the first 24 h	212.0 (7.5)	159.6 (7.5)	182.9 (9.9)	<0.001	6.94 (5.22–8.65)	3.04 (2.14–3.93)	2.56 (1.94–3.18)

Values are represented as mean (standard deviation) or effect size (95% CI). C/C=Wild homozygote, T/C=Heterozygote, C/C=Mutant homozygote., CI=Confidence Interval, IV=Intravenous

Table 3: Mean pain scores among genotypes and paired comparison

VAS score	Type of genotype			*P*	Effect size (95% CI) C/C versus T/C	Effect size (95% CI) C/C versus T/T	Effect size (95% CI) T/C versus T/T
	C/C	T/C	T/T				
0 h	5.9 (0.5)	3.8 (0.8)	5.3 (0.7)	<0.001	2.65 (1.71–3.57)	1.03 (0.31–1.74)	1.87 (1.32–2.42)
6 h	5.3 (0.5)	3.2 (0.9)	4.4 (0.6)	<0.001	2.49 (1.57–3.39)	1.52 (0.77–2.25)	1.50 (0.97–2.02)
12 h	4.8 (0.9)	2.7 (1.1)	3.9 (0.8)	<0.001	2.07 (1.21–2.91)	1.18 (0.46–1.90)	1.79 (1.19–2.37)
24 h	4.5 (0.8)	2.6 (0.8)	3.4 (1.0)	<0.001	2.19 (1.31–3.05)	1.19 (0.46–1.91)	0.74 (0.26–1.21)

Values are represented as mean (standard deviation) or effect size (95% CI). C/C=Wild homozygote, T/C=Heterozygote, C/C=Mutant homozygote, CI=Confidence interval, VAS=Bisual analogue scale

other transmitters, such as substance P. Opioid medications act on the presynaptic terminals of afferent nociceptors and inhibit the release of these neurotransmitters.[7,8] It seems plausible that polymorphism in CGRP 4218 T/C leads to variable expression of these nociceptor transmitters in the pain signalling pathway, influencing the severity of pain.[9] The present study noted that C/C genotype patients reported higher VAS scores during all study periods.

In agreement with previous studies, we found no association between the CGRP 4218T/C polymorphism and the side effects of opioids like pruritus, PONV, respiratory depression and sedation.[5] The strength of the present study is that it is the first study done in the Indian population, as the previous studies were conducted in the Chinese Han ethnic group. There is limited data from our country regarding the effects of genetic variation on postoperative pain and the requirement for analgesics. A recent study by Kumar *et al*.[10] on 257 South Indian women undergoing major breast surgery found that single nucleotide polymorphism (SNP) opioid receptor mu-1 (*OPRM1*) (rs1799971) was associated with higher postoperative fentanyl requirement.

Our study adds another important evidence on the association of genetic polymorphisms with postoperative fentanyl consumption in patients undergoing surgery. In the future, incorporating genetics and epigenetic analysis into clinical practice will allow anaesthesiologists to tailor the analgesic dosage to maximise drug efficacy and minimise unnecessary adverse reactions. Our study has certain limitations; it was a single-centre study having a small sample size. In our research, intraoperatively, we used an infusion of IV fentanyl to provide analgesia. The epidural catheter was not activated, which would have confounded the analgesic assessment. Infusion of fentanyl without monitoring the depth of anaesthesia may raise concern for overdosing. However, it has been reported that bispectral index monitoring, commonly used to assess the depth of anaesthesia, fails to show the hypnotic-enhancing effect of fentanyl.[11] We included patients of either gender with various major abdominal surgeries, which could have affected the patient-reported pain perception and not standardised the surgical procedure. The analgesics protocol used in the present study consisted of only fentanyl given through epidural and IV routes. As the combination of local anaesthetics and opioids is commonly used for postoperative analgesia, the study results need to be considered carefully. Future studies with larger sample sizes are required to support the current study's findings.

CONCLUSION

Our study concludes that the CGRP 4218T/C polymorphism is associated with variability in postoperative pain perception and fentanyl requirement. Patients with the C/C genotype experience more significant pain and have an increased demand for analgesics compared to those with T/C and T/T genotypes. However, there is no association between the polymorphism of CGRP4218T/C and the adverse effects of opioid analgesic medication.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest

There are no conflicts of interest.

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