ORIGINAL ARTICLE

Impact of CYP3A4 single nucleotide polymorphism to lidocaine therapy in Pakistani population

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Abstract

Objective: To evaluate the role of the Cytochrome P450 3A4*22 mutation on the postoperative analgesic effects of lidocaine.

Method: The study was conducted at the Pakistan Ordinance Factories Hospital, Wah Cantt, Pakistan, from March 2021 to December 2022, and comprised adult patients undergoing elective laparoscopic cholecystectomy. The patients were randomised into intervention group A and control group B. Patients in group A were given a bolus dose of lidocaine 2mg/kg in addition to the standard anaesthesia protocol, while the patients in group B received the standard anaesthesia protocol. Visual analog scale was used at 6 hours and 12 hours post-surgery. Blood samples for genetic analysis were taken after the start of surgery. Data was analysed using SPSS 26.

Results: Of the 300 patients, 215(71.7%) were females and 85(28.3%) were males. The overall mean age was 48.49±11.34 years and mean body mass index was 23.40±7.0546kg/m2. However, owing to unsuccessful genotyping, 42(14%) patients could not be evaluated. Patients with a GA allele sequence with GG in the Cytochrome P450 3A4*22 (rs35599367) had a higher postoperative pain threshold than those with GG and AA alleles alone ($p<0.01$).

Conclusion: Patients with a GA allele succession with GG in the Cytochrome P450 3A4*22 (rs35599367) had a higher postoperative aggravation edge than those with GG and AA alleles alone.

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Introduction

Multimodal analgesia and opioid-sparing concepts have been the mainstays of postoperative pain management. Lidocaine is an amide-type local anaesthetic, and it works by blocking voltage-gated sodium channels in nerve cell membranes.[1] This action inhibits the generation and conduction of nerve impulses, leading to a local anaesthetic effect. Lidocaine is commonly used in various medical and dental procedures to induce local anaesthesia. It is particularly useful for numbing specific areas of the body, making it a valuable tool for minor surgical procedures, dental work, and certain medical interventions. The safety profile of lidocaine has contributed to its widespread use in the clinical setting. However, like any medication, it should be used with caution, and healthcare professionals should consider various factors, such as patient health, potential drug interactions, and dosage, when administering lidocaine to ensure its safe and effective use. Intravenous (IV) administration of lidocaine has analgesic effects when used as an anaesthetic adjuvant.[2,3] The liver extensively metabolises in the liver. In patients with serious liver disease, the average removal half-life of lidocaine increases to >6 h compared to 1.6 hours in normal patients. Many medicines used during anaesthesia are metabolized by P450 isozymes, and their concurrent administration can slow the hepatic metabolism of anaesthetic agents.[4]

Cytochrome P450 (CYP) enzymes are categorized into families and subfamilies, with CYP1, CYP2, and CYP3 being the major families involved in drug metabolism in humans. These enzymes are responsible for metabolizing a large proportion of drugs, contributing significantly to their clearance from the body.[5]

The CYP superfamily is of particular interest when considering phase I reactions. CYP3A4 is involved in the metabolism of drugs, such as local anaesthetics. The liver, specifically the smooth endoplasmic reticulum within hepatocytes, is the primary site for the expression of these enzymes.[4,5]

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The expression and functionality of CYP enzymes can be influenced by various factors including age, sex, disease, and epigenetic factors. Genetic polymorphisms, including mutations such as frameshift mutations, deletions, and splicing defects, can affect the structure and function of CYP enzyme genes. This genetic variability can lead to inter-individual differences in drug metabolism, influencing an individual's response to medications, including anaesthetics.[6]

Understanding the genetic and environmental factors that affect CYP enzyme activity is crucial in personalized medicine as it allows healthcare providers to tailor drug therapies to individual patients, taking into account their unique metabolic profiles. This field of study, known as pharmacogenetics, aims to optimize drug efficacy and minimize adverse effects based on an individual's genetic makeup.[7]

The existence of numerous allelic variants of CYP3A4 highlights the genetic diversity within the human population. Genetic variations can alter drug responses and should be considered during lidocaine therapy. The functional consequences of these variations can be significant, affecting the ability of the enzyme to metabolize drugs and leading to variations in drug responses among individuals. Understanding the genetic polymorphisms of CYP3A4 is essential for personalized medicine and optimized drug therapies. It can help predict an individual's likelihood of experiencing adverse effects or therapeutic failure and guide healthcare providers in adjusting drug doses or choosing alternative medications based on the patient's genetic profile.[8]

The rs35599367*22 polymorphism in CYP3A4 is a specific variant of CYP3A4. Centuries of intricate sociocultural traditions, such as ethnic variety, consanguinity, and endogamy, have resulted in diverse populations with distinctive genetic architectures. Studying certain single nucleotide polymorphisms (SNPs), such as those in CYP3A4, a crucial enzyme implicated in drug metabolism, is made possible by genetic variability. Understanding CYP3A4 polymorphisms in the Pakistani population is essential for developing safe and efficient treatment plans, because these variations can have a substantial impact on the pharmacokinetics and pharmacodynamics of medications such as lidocaine.

The current study aimed to evaluate the role of CYP3A4*22 mutation in the postoperative analgesic effects of lidocaine.

Materials and Methods

This double-blind randomized control trial (RCT) [IRCT20220830059302N1] was conducted at the Pakistan Ordinance Factories Hospital, Wah Cantt, Pakistan, from March 2021 to December 2022. After approval from the institutional ethics review committee, patients aged ≥18 years who underwent elective laparoscopic cholecystectomy with normal renal and hepatic function tests were included, and written informed consent was obtained. Patients with an American Society of Anesthesiologists (ASA) scale of III and above, abnormal liver and renal function tests, known epilepsy, and use of opioids were excluded. A Genetic Association Study (GAS) power calculator was used to estimate the required sample size, ensuring adequate statistical power to detect meaningful associations. The minor allele frequency (MAF) was set at 0.30, reflecting the average of the 4MAFs observed in the Pakistani population. To achieve robust and reliable results, the power of the study was set at 90%, minimizing the likelihood of Type II error. Additionally, the significance level was set at 0.05%, ensuring stringent control of the Type I errors. This careful consideration of parameters aimed at optimising the study design and enhancing the validity of the findings.[9]

The patients were randomized using computerized generated numbers into intervention group A and control group B. Patients in group A were administered a bolus loading dose of lidocaine 2 mg/kg and then continuously infusion at 1.5 mg/kg body weight at a rate of 8 drops/minute (total dose 50 mg) until the closure of the incision.[10] The patients in group B received the standard anaesthesia protocol. In all cases, anaesthesia was induced with propofol, lidocaine, and rocuronium, after which it was maintained with sevoflurane inhalation supplemented with rocuronium, and no nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids were administered during the operation. Anaesthesiologists performed the randomisation process on the day of the surgery, and did not participate in the patient assessment process at any point.[11]

No premedication was given, including hypnotic drugs for insomnia or anxiety. Routine intraoperative monitoring included noninvasive blood pressure, electrocardiogram (ECG), pulse oxygen saturation, end-tidal concentrations of carbon dioxide (CO2) and inhaled anaesthetics, and body temperature. Invasive arterial pressure was monitored when necessary. After surgery, nalbuphine was given to patients who demanded analgesia, and that, too, was given once only.[12]

In the post-anaesthesia care unit (PACU), primary care nurses and in-charge surgeons were blinded to the dosage assignment of the patients. The patients were evaluated after they regained consciousness in PACU,

marked as time zero, and each patient was visited at 2 hours, 4 hours, 6 hours and 8 hours postoperatively. Additionally, the patients were blinded to their assigned dosage and remained unaware of these assignments while recording their self-reported Visual Analogue Scale (VAS) scores at 6 hours and 12 hours post-surgery.[13]

Immediately after the initiation of surgery, blood samples were taken in vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) for deoxyribonucleic acid (DNA) extraction and further genotyping of CYP3A4*22. Patients demographic data was noted before the start of surgery. VAS, ranging from 0 = no pain to 10 = very severe pain, and Using the Numerical Pain Rating Scale (NPRS), the mean pain score for all aetiologies was used to measure pain intensity.[12]

For genotyping analysis, conventional proteinase K/phenol extraction technique was used to extract genomic DNA from EDTA-anticoagulated tubes. The sequence variant rs35599367*22 in the sixth intron were detected by polymerase chain reaction (PCR) amplification of DNA and PCR-restriction fragment length polymorphism (PCR/RFLP) were used for genotyping by using the following primers:

Forward: 5'- 5´-TGCTAGTGATCACATCCATGC-3'.

Reverse: 5'- CAAGATGGGTAAGCACTGTGC-3'.

RFLP CGCTGGGT by enzyme Dra III (restriction enzymes)

A total of 12µL of 12.5 mM PCR Master Mix, 2µL of extracted DNA, 1µL each of forward and reverse primer (30nmol), and 9µL of nuclease-free PCR water comprised the PCR reaction mixture, which had a final volume of 25µL. In a GeneAmp PCR system (Thermal Cycler Bio RAD T100 USA), PCR was carried out under the following conditions: 35 cycles of denaturation at 94°C for 1 minute, primer annealing at 55°C for 1 minute, extension at 72°C for 1 minute, and final extension for 5 minutes at 72°C. The results of the PCR reaction were examined using gel electrophoresis on a 2% agarose gel. After being kept overnight at 37°C using the restriction enzyme, the PCR products were electrophoresed on a 3% agarose gel containing ethidium bromide, and examined under an ultraviolet (UV) lamp.[14]

Data was analysed using SPSS 26. Data was expressed as mean ± standard deviation or as frequencies and percentages, as appropriate. Hardy-Weinberg equilibrium (HWE) was used to evaluate the genotype-wise differences. Chi-square test was used to compare data for categorical variables. P<0.05 was taken as statistically significant. Logistic regression was used to assess the impact of CYP3A4 genotypes on clinical efficacy, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.[15]

Results

Of the 350 patients assessed, 300(85.7%) were enrolled; 215(71.7%) females and 85(28.3%) males. The overall mean age was 48.49±11.34 years and mean body mass index (BMI) was 23.40±7.0546kg/m^2. However, owing to unsuccessful genotyping, 42(14%) patients could not be evaluated. The patients were subgrouped according to GG (Figure 1), GA (Figure 2) and AA (Figure 3) alleles (Table 1). . No significant correlation was observed

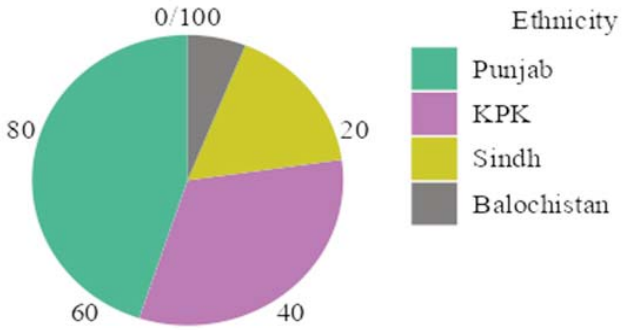

Figure-1: Distribution of GG allele.

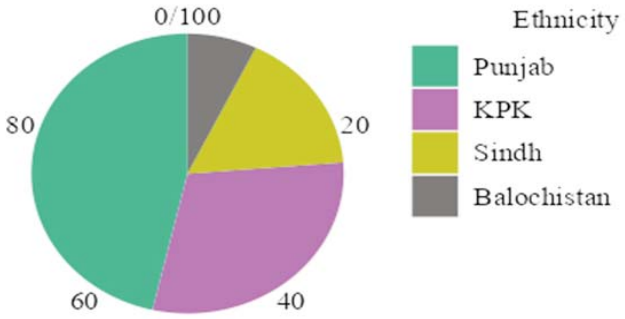

Figure-2: Distribution of GA allele.

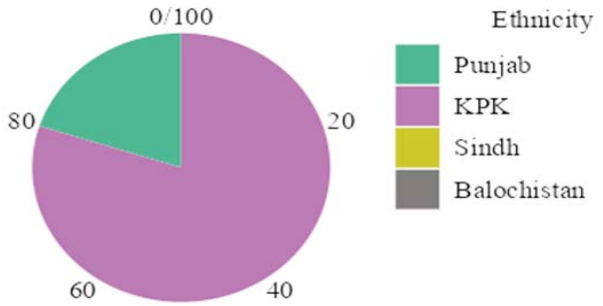

Figure-3: Distribution of AA allele.

Table-1: Association and distribution of CYP3A4 genotype with analgesic effects of lidocaine in Pakistani population.

Variables	GG (n=198)	GA (n=97)	AA (n=5)	Pearson chi-square	P-Value
Gender					
Male	57	25	3	1.5	0.002
Female	153	60	2		
Age (Mean±SD	48.49±11.66	46.04±10.22	47.49±11.01	-	0.07
BMI (Mean±SD	23.4±7.056	22.4±4.05	23.1±2.01	-	0.05
VAS		-			
0	-	-	-		
1	-	-	-		
2	61	39	0		
3	30	17	0		
4	35	14	0	7.24	0.01
6	34	16	0		
7	28	16	0		
9	1	4	5		
10	-	-	-		
NPRS(Mean±SD)	1.69 ± 0.80	4.4 ± 0.78	-	-	0.001
Ambulation after surgery					
2hrs					
4 hrs	65	35	0		
6 hrs	42	20	0		
8 hrs	31	15	0	7.17	0.03
10 hrs	50	20	0		
12hrs	12	5	0		
	0	0	5		
Ethnicity					
Punjab	89(135)	45(135)	1(135)		
KP	64(97)	29(97)	4(97)	6.309	
0.0004*					
Sindh	33(49)	16(49)	0(49)		
Balochistan	12(19)	7(19)	0(19)		

BMI: Body mass index , NPRS: Numerical pain rating scale, KP: Khyber Pakhtoonkhwa

between the various rs35599367*22 genotypes (Table 2).

The amplified fragment length of CYP3A4 rs35599367*22 was 322 base pairs (bp). It was cleaved into segments of 163bp and 159bp by the Pst1 restriction enzyme, and the resulting PCR products of GG, GA and AA were separated. Three fragments of 322bp, 163bp and 159bp were seen in heterozygous GA, but only a 322bp fragment was seen in wild-type GG. Two fragments of 163bp and 159bp were seen in minor homozygous AA.

The genotype frequencies for CYP3A4 rs35599367*22 were 198(66%), 97(32.33%), and 5(1.66%) for major homozygous GG, heterozygous GA, and minor homozygous AA, respectively. The G and A alleles of rs35599367*22 had MAFs 0.2755 and 0.7254, respectively.

The heterozygous GA genotype was present in 295(98.33%) patients who responded to lidocaine, and the patients who exhibited hypaeralgesia were more

Table-2: Correlation of VSA and ambulation in rs35599367 polymorphism with lidocaine infusion.

			rs35599367	VSA	Ambulation
GG	Kendall's tau_b	VSA	Correlation Coefficient	1.00	.194**
			Sig. (2-tailed)	.	.05
			N	213	213
		Ambulation	Correlation Coefficient	.19**	1.00
			Sig. (2-tailed)	.000	.
			N	213	213
	Spearman's rho	VSA	Correlation Coefficient	1.00	.24**
			Sig. (2-tailed)	.	.00
			N	213	21
		Ambulation	Correlation Coefficient	.24**	1.00
			Sig. (2-tailed)	.00	.
			N	213	213
GA	Kendall's tau_b	VSA	Correlation Coefficient	1.00	.117
			Sig. (2-tailed)	.	.17
			N	87	87
		Ambulation	Correlation Coefficient	.11	1.00
			Sig. (2-tailed)	.17	.
			N	87	87
	Spearman's rho	VSA	Correlation Coefficient	1.00	.13
			Sig. (2-tailed)	.	.21
			N	87	87
		Ambulation	Correlation Coefficient	.13	1.00
			Sig. (2-tailed)	.21	.
			N	87	87

**. Correlation is significant at the 0.01 level (2-tailed).

likely to have an allele of rs35599367*22 (p≤0.001). Of those who responded to lidocaine, 198(67%) were full responders. The majority genotype (66%) in complete responders was GG, while the most common genotype

(32%) was GA in partial responders. Among partial responders, GG versus GA group showed a significant intergroup difference (p=0.03). Using the Numerical Pain Rating Scale (NPRS), the mean pain score for all aetiologies decreased to 1.69±0.80 for GG alleles and 4.4±0.78 for GA alleles.

Discussion

Interindividual differences in the effectiveness and tolerance of medications may be linked to erratic clinical results, which calls for pharmacogenetic research on potential gene candidates. Finding the genetic variant responsible for the metabolism of lidocaine can improve postoperative analgesia and early mobilisation, which will lessen the load on patients and hospitals. The current study improved robustness by controlling for confounding variables in a number of ways. The randomised, double-blind design reduced bias and made sure that factors like gender and age were distributed evenly. Normal renal and hepatic functions were among the inclusion criteria that accounted for physiological variables affecting the metabolism of lidocaine. The emphasis on elective laparoscopic cholecystectomy decreased procedural variability. Consistency in drug administration and response evaluation was guaranteed by standardised dose and monitoring. Furthermore, when used, statistical corrections for variables enhanced the findings' dependability. Together, these controls made sure that CYP3A4 polymorphisms were responsible for the effects that were seen.

Overall, 234 million operations are expected annually. It is predictable. that seven million people suffer detrimental effects, and one million die worldwide every year after surgery. Moreover, up to 50% of these harmful effects are predicted to be avoided. Surgical mortality has decreased in recent decades, mainly because of anaesthesia-related factors development and safety.[15]

The current study looked at the relationship between the clinical effectiveness and tolerability of lidocaine and CYP3A4 rs35599367*22 polymorphisms.

In individuals receiving lidocaine as an anaesthetic adjuvant, a strong correlation was seen between the CYP3A4 SNP rs35599367*22 and treatment responses. To our knowledge, the current study is the first to present the genotype frequency of CYP3A4 and its correlation with lidocaine tolerance and therapeutic response in a South Asian population.[16]

In line with earlier research, which found that more women than men complained of cholecystitis, the current study had more female participants. A larger ratio of females to males may result from biological differences in pain regulation, neural architecture, sex hormones, and neuroimmune systems that are specific to gender that may put females at a higher risk for chronic pain.[17,18]

A randomised, placebo-controlled study in China has shown that using IV lidocaine can substantially reduce postoperative pain and opioid use following laproscopic cholecystectomy. In addition, higher inflammatory mediators were found in major abdominal surgery. Efficient analgesia postoperatively ensures rapid healing and fewer complications. Lidocaine's analgesic and anti-hyperalgesic properties are obtained by blocking the sodium channel and inhibiting pro-inflammatory cytokines releases. Continuous IV lidocaine administration increased patient rehabilitation and shortened hospital stays during abdominal surgery. Less pain and lower anaesthetic requirements as well as early bowel return and a shorter stay in the hospital were recorded in patients who received lidocaine infusions. Nausea and vomiting are prominent side-effects linked to the systemic use of opioids. Paralytic ileus also develops after general surgery as a complication of general anaesthesia, triggering unintended long-term hospital stays that could delay recovery.[18] The lower risk of adverse effects related to ileus and opioids demonstrates the effectiveness and protection provided by IV lidocaine in the treatment of pain following abdominal cholecystectomy. The current results are in line with these findings, especially in patients carrying the GG and GA alleles.[19,20]

A study concluded that plasma concentrations of lignocaine between 2.3µg/ml and 3µg/ml is required to suppress the cough reflex under general anaesthesia, resulting in a decrease in the intraabdominal pressure and enhancing early recovery of bowel function and mobilisation. he findings supported the current study.[21]

CYP3A4 genetic variation can significantly affect the rate at which lidocaine is eliminated,, which may lead to unfavourable consequences or treatment failures. Individuals who have reduced enzymatic activity are more likely to have toxicity and a delayed recovery from anaesthesia, among other unfavourable side-effects.[22] Functionally characterising the enzymatic activity of CYP3A4 variations in the metabolism of lidocaine is, therefore, extremely important.[4,5]

The principal action site of local anaesthetics is the sodium channel, like ropivacaine, bupivacaine and lidocaine. Therefore, genetic mutations in the sodium channel gene are likely to be associated not only with the diverse binding abilities and behaviours, but also with the

metabolism of local anaesthetics. CYP3A4 metabolises lidocaine.[23] A mutation in CYP3A4*22 (rs35599367 G>A) variant leads to altered metabolism of lidocaine, causing hyperalgesia. These findings were in line with those of the current study.[24]

The frequencies of CYP3A4*22 (rs35599367 GG, GA and AA) in the current study were 66%, 37.96%, and 1.62%, respectively. Over the course of 12 hours, individuals with major homozygous GG genotype showed a significant and clinically relevant improvement in pain levels compared to baseline. The study revealed that heterozygous GA variant genotype was associated with varying therapeutic efficacy. In literature, hyperalgesic group was reported to have higher frequencies of the A alleles (p=0.001).[25] Numerous studies have shown certain side-effects linked to lidocaine that the current sample did not experience. This study found a strong correlation between CYP3A4*22 polymorphism (rs35599367) and several side-effects. Patients with the GA genotype experienced the highest level of adverse events (AEs), including hyperalgesia. These results are consistent with earlier research showing a higher frequency of dose-related AEs associated with lidocaine.[26] However, no study has examined the relationship between a particular genotype and the safety and clinical outcomes of lidocaine.

By emphasising the necessity of genetic testing for CYP3A4 polymorphisms in individuals, especially those with atypical drug reactions, the current findings may help direct individualised lidocaine therapy. This could improve safety and efficacy in clinical practice by minimising side-effects and optimising dosage techniques. Individualised patient treatment may also be improved by integrating genetic profiling into preoperative assessments.

However, the current study has limitations, including the exclusion of people with comorbidities or changed organ function, and a small sample size that may not have detected rare polymorphisms. Additionally, the results may not be generalisable to larger populations due to low-scale representation of Pakistan's numerous ethnic communities, and the focus on patients undergoing laparoscopic cholecystectomy only. Further research is required to examine the pharmacokinetic effects of CYP3A4 polymorphisms.

Conclusion

The CYP3A4*22 (rs35599367) polymorphism significantly affected therapeutic response to lidocaine, and the rs35599367 GA genotype was associated with negative effects.

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AUTHOR'S CONTRIBUTION:
AA: Agreement to be accountable for all aspects of the work.
UN: Revision.
AS & SR: Drafting.
AWS: Concept and design.