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Research article

The influence of CYP2C19 polymorphisms on clinical efficacy of clopidogrel in Sudanese patients undergoing percutaneous coronary intervention

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Keywords: Clopidogrel , Percutaneous coronary intervention, *CYP2C19* polymorphism, Adverse cardiac events.

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Abstract

Clopidogrel is commonly used anti-platelet drugs in treatment of patients undergoing percutaneous coronary intervention (PCI). It was documented that CYP2C19 loss of function variants may affect clopidogrel efficacy and exposed patients to risk of adverse cardiac events. This study aimed to appraise the link between CYP2C19 polymorphisms and adverse clinical outcomes in Sudanese patients undergoing PCI. This prospective observational cohort study recruited 197 PCI patients from Wad Medani Heart Diseases and Surgery Center from 2017 to 2021. The patients were distributed into three groups according to their genotype results as follow: Extensive metabolizers (EMs) 136, Intermediate metabolizers (IMs) 56, and Poor metabolizers (PMs) 5. All study cohort received aspirin and clopidogrel. Clinical ends points were evaluated after 12 months from PCI indexing by rechecking patients' records.
The metabolizing capacity among the groups did not show significant relations to demographics and clinical characteristics (P>0.05), except that PMs showed a significantly higher mean body weight than IMs (P=0.010). Ischemic heart disease was significantly higher among PMs in comparison to IMs and EMs (60.0% versus 5.5% and 11.0% respectively, P=0.006). Previous angiography was also significantly more common among PMs in comparison to IMs and NMs (60.0% versus 8.9% and 9.6% respectively, P=0.013). The frequency of adverse cardiac events (ACEs) was higher among PMs in comparison to IMs and EMs (40% vs 16.1%, 10.3%), however no significant association found between ACEs and the metabolizer capacity (P=0.078). On the other hand, revascularization was significantly related to the metabolizer capacity, where 40.0% of PMs developed revascularization compared to 7.1% in IMs and 4.4% in EMs (P=0.029). The risk of revascularization was 14.44 (2.019-103.317) in PMs and 1.67 (0.452-6.149) in IMs**.** In conclusion ACEs was more prevalent among PMs in comparison to IMs and EMs. Moreover, revascularization was significantly higher among PMs in comparison to IMs and EMs.

Introduction

Clopidogrel with aspirin remain the most widely adopted anti-platelet drugs used in acute coronary syndromes (ACS) patients undergoing percutaneous coronary intervention (PCI) to decrease the risk of cardiac events after PCI [1,2]. Nevertheless, adverse cardiovascular events arise on patients taking standard clopidogrel doses [3, 4].
CYP2C19 polymorphism represent a major contributor to differences in clopidogrel response, beside other factors but to lesser extent such as age, weight, diabetes, renal failure, and concomitant medications [5-7]. Many studies and meta-analysis proposed that individuals who harbor CYP2C19

lack of function alleles (LOFA) are vulnerable to ACEs due to diminished clopidogrel efficacy [8, 9]. Poor and intermediate phenotypes of CYP2C19 have reduce capability to activate clopidogrel. LOFA carriers showed about 32% decrease in the concentrations of clopidogrel active metabolite [10]. Therefore impede enzyme activity and /or expression resulting in reduction of clopidogrel bioactivation [11, 12].

In Sudan, no previous studies reflect the relation of CYP2C19 lack of function alleles and adverse clinical outcomes, hence this study conducted to address this issue among Sudanese Patient with acute coronary syndrome underwent PCI.

Aim of the study

To appraise the link between CYP2C19 polymorphisms and adverse clinical outcomes.

Methods

This prospective observational cohort study involved 197 Sudanese patients with ACS underwent PCI. The participants were recruited from catheterization unit at Wad Medani Heart Diseases and Surgery Center from 2017 to 2021. The eligibility criteria involve both sex of age ≥18 years old, perform percutaneous coronary intervention with drug eluting stent implantation and being managed with clopidogrel. Patients were excluded if they have severe cardiac or renal abnormalities, hepatic failure and serious infection. All study participants received clopidogrel loading dose (300mg or 600mg) within 12 hours from hospitalization, and discharged on clopidogrel maintenance dose 75mg twice daily for at least 12 months and aspirin 100mg/day. The blood samples were collected from patients and genotyped for CYP2C19 polymorphisms by Allele Specific Primer PCR (ASP-PCR) and Polymerase chain reaction with confronting two-pair primers technique (PCR-CTPP) for CYP2C19*2 and CYP2C19*3 respectively. According to genotype results, the participants were categorized into three groups according to CYP2C19 phenotypes as follow: 69% EMs (*1/*1), 28.4% IMs (*1/*2 or *1/*3), and 2.5% PMs (*2/*2). The demographic and clinical characteristics of participants were retrieved from the patients' medical records and recorded in a predesigned data collection form. After 12 months post PCI, patients record were rechecked for adverse cardiac events (myocardial infarction, recurrent ischemia, stent restenosis/ thrombosis, revascularization, cardiac death).The study protocol was approved by Ministry of Health ethics committee and University of Gezira Research Ethics Committee. Patients were informed about the study, and the reason for blood sampling, and that the participation is voluntarily.

Statistical analysis

Statistical analysis and presentation of data were conducted using SPSS (Statistical Package for the Social Sciences) version 22 computer program. Categorical data were presented as numbers and percentages to show their frequency. Chi-Square or Fisher's Exact tests as appropriate were applied to investigate the association between the categorical risk variables and the clinical outcomes. Significant results of the previous tests were followed by post hoc analysis to show the pairwise comparison between the studied phenotype metabolizers groups. This was followed by univariate logistic regression analysis for demonstrating the odds ratio and 95% confidence interval. The statistical significance was considered at $P < 0.05$.

Results

Baseline characteristics of study participants

Table 1 shows that the metabolizing capacity among the CYP2C19 metabolizer groups did not show significant relations to gender, age, hypertension, diabetes, smoking, previous PCI, and family history of CAD ($P>0.05$). Alternatively, PMs showed a significantly higher mean body weight than IMs (*P=0.014*). The incidence of ischemic heart disease (IHD) was significantly higher among PMs in comparison to the IMs and the EMs (60.0% versus 5.5% and 11.0% respectively). Previous angiography was also significantly more common among PMs in comparison to IMs and the EMs (60.0% versus 8.9% and 9.6% respectively).

Duration between stent instillation and adverse cardiac events

Out of the total number of participants, 25 (12.7%) patients exhibited adverse cardiac event as follow: 14 EMs (*1/*1), 9 IMs (*1/*2, *1/*3), and 2 PMs (*2/*2). All poor metabolizers, 44.4% of intermediate metabolizers, and 64.3% of extensive metabolizers developed adverse cardiac events within the first 3 months from PCI indexing table 2.

Distribution of cardiovascular events among metabolizer phenotypes

Generally, the frequency of adverse cardiac events was higher among poor metabolizers (40%), followed by intermediate metabolizers (16.1%), and the least among extensive metabolizers (10.3%). However, no significant relationship between the recurrence of events and the metabolizer capacity (P=0.078). The risk of recurrence of cardiac event was 5.81 (0.89-37.79) in PMs and 1.67 (0.68-4.11) in IMs as demonstrated in table 3.

Clinical end points after 12 months follow up

After 1 year follow up, 12.7% of the studied patients developed adverse cardiac events of which revascularization

was the most common (6.1%), followed by myocardial infarction (2.0%),

ischemia, stent thrombosis, and restenosis were less frequent. Only one patient developed cardiac death (0.5%). Regarding the distribution of types of cardiovascular events among CYP2C19 metabolizers, one cardiac death and four myocardial infarction occurred among extensive metabolizers , stent restenosis was detected in one normal metabolizer and one intermediate metabolizer, while stent thrombosis and ischemia were detected in one normal metabolizer and two intermediate metabolizers, with no significant associations (P>0.05). Nevertheless, revascularization was significantly related to the metabolizing capacity, where 40.0% of PMs developed revascularization compared to 7.1% in IMs and 4.4% in EMs (P=0.029). The risk of revascularization was 14.44 (2.019-103.317) in PMs and 1.67 (0.452-6.149) in IMs as shown in Table 4.

Table 1. Association of demographics, and clinical risk factors with CYP2C19 metabolizer phenotypes.

Characteristics	CYP2C19 phenotypes			*P-value*	Pairwise comparison (Post hoc test)
	EMs (N=136)	IMs (N=56)	PMs (N=5)		
Gender					
Male	93 (68.4)	37 (66.1)	4 (80.0)	0.954	NA
Female	43 (31.6)	19 (33.9)	1(20.0)		
Age (years) Mean ± SD	59.1 ±11.4	60.1 ±11.8	56.6 ±10.4	0.753	NA
Weight (Kg) Mean ± SD	71.6 ±13.5	64.6 ±14.3	82.0 ±5.2	0.014*	P1=0.010 * P2=0.089 P3=0.184
Hypertension	61(44.9)	20 (35.7)	4 (80.0)	0.139	NA
Diabetes Mellitus	69 (50.7)	26 (46.4)	2 (40.0)	0.770	NA
Previous IHD	15 (11.0)	3 (5.5)	3 (60.0)	0.006*	P1>0.96** P1>0.96** P3>0.96
Smoking	35 (25.7)	18 (32.1)	1 (20.0)	0.643	NA
Previous PCI	4 (3.0)	3 (5.6)	1 (20.0)	0.124	NA
Family History of CAD	18 (13.2)	8 (14.3)	1 (20)	0.691	NA
Previous angiography	13 (9.6)	5 (8.9)	3 (60)	0.013*	P1>0.96** P1>0.96** P3<0.96

*N: Number; SD: Standard deviation; CAD: Coronary Artery Disease; HI: Ischemic Heart Disease; PCI: Percutaneous coronary intervention; EMs:Extensive Metabolizer; IMs:Intermediate Metabolizer; PMs: Poor Metabolizer ;*Significant at p<0.05 ; **Significant at p >0.96 (post hoc analysis after Chi-Square test) P1: PMs versus IMs , P2: PMs versus EMs, P3= IMs versus EMs; NA: Not applicable.*

Table 2. The duration between PCI indexing and recurrent adverse events.

Duration/Months	CYP2C19 metabolizers			*P*-value
	EMs (N=14)	IMs (N=9)	PMs (N=2)	
1-3	9 (64.3)	4 (44.4)	2 (100)	0.736
4-6	3 (21.5)	1 (11.1)	0 (0.0)	
7-9	1 (7.1)	1 (11.1)	0 (0.0)	
10-12	1 (7.1)	3 (33.3)	0 (0.0)	

*N: Number of patients; EMs:Extensive Metabolizer; IMs:Intermediate Metabolizer; PMs:Poor Metabolizer, P>*0.05.

Table 3. Association between metabolizer phenotypes and cardiovascular events.

Cardiovascular Events	CYP2C19 metabolizers			P-value	OR (odds ratio) (95%CI)
	EMs (N=136)	IMs (N=56)	PMs (N=5)		
Yes	14 (10.3)	9 (16.1)	2 (40.0)	0.078	PMs: 5.81 (0.89-37.79) IMs: 1.67 (0.68-4.11)
No	122 (89.7)	47 (83.9)	3 (60.0)		

N: Number of patients; EMs:Extensive Metabolizer; IMs:Intermediate Metabolizer; PMs:Poor Metabolizer, P>0.05.

Table 4. Distribution of clinical outcomes among CYP2C19 metabolizer phenotypes after one year follow up.

Types of adverse cardiovascular events	CYP2C19 metabolizers			*P*-value	Pairwise comparison	OR (odds ratio) (95%CI)
	EMs (N=136)	IMs (N=56)	PMs (N=5)			
Cardiac death	1 (0.7)	0 (0.0)	0 (0.0)	>0.999	NA	PMs: 0.00 IMs: 0.00
Stent restenosis	1 (0.7)	1 (1.8)	0 (0.0)	0.525	NA	PMs: 0.00 IMs: 4.45 (0.15-39.94)
Stent thrombosis	1 (0.7)	2 (3.6)	0 (0.0)	0.264	NA	PMs: 0.00 IMs: 5.0 (0.44-56.29)
Myocardial infarction	4 (2.9)	0 (0.0)	0 (0.0)	0.390	NA	PMs: 0.00 IMs: 0.00
Ischemia	1 (0.7)	2 (3.6)	0 (0.0)	0.264	NA	PMs: 0.00 IMs: 5.0 (0.44-56.29)
Revascularization	6 (4.4)	4 (7.1)	2 (40.0)	0.029*	P1>0.96** P2>0.96** P3>0.96	PMs: 14.44 (2.019-103.317) IMs: 1.67 (0.452-6.149)

**Significant at P<0.05, ** Significant at P>0.96 (post hoc analysis after Chi-Square test) as follows P1:PMs versus IMs , P2: PMs versus EMs, P3= IMs versus Ems.*

Discussion

The variability of pharmacodynamics efficacy of clopidogrel is altered by genetic variations in CYP450 genes, mainly the genetic variation in the CYP2C19 because of its contribution in the two successive stages of clopidogrel activation [13, 14]. Pharmacokinetic and pharmacodynamics studies attributed this variability to plasma variation of clopidogrel active metabolite [15, 16]. Therefore, genetic polymorphism of CYP2C19 represent the most prominent contributor to interindividual variation to clopidogrel response [17, 18, 19].
The results of the present study revealed that the frequency distribution of adverse cardiac events was higher among poor metabolizers (40%), followed by intermediate metabolizers (16.1%), and the least among extensive metabolizers (10.3%) with no significant relationship between the recurrence of adverse cardiac events and the metabolizer capacity (P=0.078).
Our results were in line with a study conducted by Paré *et al* who reported that metabolizer phenotype didn't affect clopidogrel efficacy, as the response was similar among carriers of LOFA and non-carriers [20]. The non-significant result between adverse clinical outcomes among different CYP2C19 metabolizer groups in our study cohort could be explained by that all patients received clopidogrel loading dose (300 or 600) prior PCI, in addition to clopidogrel maintenance dose 75mg twice daily and aspirin 100mg/day. A meta-analysis conducted by Siller and his coworkers observed that clopidogrel loading dose 600mg resulted in 24% relative risk reduction in adverse cardiac events without increasing risk of major bleeding [21]. In this study all the participants discharge on clopidogrel 75mg twice daily and aspirin 100mg daily which have its impact in protecting from adverse clinical outcomes. Ernest and his colleagues reported that taking 150mg clopidogrel as maintenance dose increase bioavailability of clopidogrel, and compensate the reduction in clopidogrel response seen with CYP2C19 loss of function patients [22].
The CURRENT-OASIS 7 trial documented that doubling clopidogrel standard dose decreased stent thrombosis and adverse cardiac events among PCI patients compared to standard dose [23]. Furthermore, a large meta-analysis (comprising randomized controlled trial and observational studies) conducted to appraise evidence about the effect of daily maintenance dose of clopidogrel (75mg vs 150mg) on clinical outcomes of PCI patients showed a significant decrease in adverse clinical outcomes by using 150mg clopidogrel as maintenance dose [24].
All our patients received aspirin 100mg/ day with clopidogrel because of its synergistic effect in addition to its role in induction of CYP2C19 [25]. Chen et al stated that in vivo activity of CYP2C19 in healthy volunteers was induced by taking 50 mg of aspirin daily for 7 and 14 days [26]. Co administration of aspirin with clopidogrel affect clopidogrel pharmacokinetic and pharmacodynamics. After pretreatment with aspirin, the area under the curve of clopidogrel decreased by 14%, with no change in area under the curve of the active metabolite. Moreover, 15% increase in platelet inhibition was observed [27]. Another benefit of aspirin was through induction of Paraoxonase-1 (PON1) gene expression in the liver which represent a major determinant of clopidogrel activation and efficacy [28, 29].
After 1 year follow up, 12.7% of our participants developed adverse cardiac events of which revascularization was the most common (6.1%), followed by myocardial infarction (2.0%), ischemia, stent thrombosis, and restenosis were less frequent. Only one patient developed cardiac death (0.5%). Regarding the distribution of types of cardiovascular events among CYP2C19 metabolizers, no significant associations between groups (P>0.05). Nevertheless, revascularization was significantly related to the metabolizing capacity, where 40.0% of poor metabolizers developed revascularization compared to 7.1% in intermediate metabolizers and 4.4% in extensive metabolizers (P=0.029).
Several studies related the interindividual variability to clopidogrel response to the reduction of clopidogrel active

metabolite which consequently affects platelet inhibition [13, 16, 30-32]. Nevertheless, Shuldiner *et al* stated that the contribution of CYP2C19 polymorphisms in this variability is limited [33]. Our results were in agreement with systematic review and meta-analysis conducted by Holmes group who evaluate the relation between CYP2C19 genotype and clinical efficacy of clopidogrel. They observed that no significant influence of CYP2C19 metabolizer phenotype on ACEs, except for stent thrombosis [34].

Our result demonstrated that adverse clinical outcomes were more prevalent among PMs (CYP2C19*2/*2) when compared to IMs (*1/2; *1/*3) with no statistical significance. Previous studies reported that no significant correlation found between IMs and clopidogrel efficacy [12, 35]. Additionally, Bhatt and his colleagues didn't find correlation between ischemic events and IMs, except few bleeding outcomes [36].

Conclusion

Adverse cardiac events was more prevalent among PMs in comparison to IMs and EMs. Moreover, revascularization was significantly higher among PMs in comparison to IMs and EMs. However, despite the evidence that CYP2C19 variants influence clopidogrel efficacy, and clinical end points, extensive work is needed to adequately address the individual variation to clopidogrel response.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Author's contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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