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Original Article

The prognostic difference study on the individualized clopidogrel administration in Hmong and Dong patients based on the CYP2C19 gene polymorphism after percutaneous coronary intervention

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Abstract

This study explored the distribution characteristics of CYP2C19 gene polymorphism among Hmong and Dong patients in the Qiandongnan region of Guizhou province after percutaneous coronary intervention (PCI). The aim was to assess the clinical impact of individualized clopidogrel administration based on CYP2C19 genotypes. A total of 208 patients were classified into ultra-fast, fast, intermediate, and slow metabolic groups. They were randomly assigned to clopidogrel individualized administration (IA) or conventional treatment (CA) groups. Patients were followed for 6 months to evaluate major adverse cardiovascular events (MACE) and adverse reactions. The CYP2C19 genotype distribution was in Hardy-Weinberg equilibrium, showing consistency in the population. While no significant ethnic differences were found in genotype and metabolic distribution, allele distribution varied, with Hmong patients exhibiting a higher proportion of CYP2C19*1 alleles than Dong patients. Following individualized administration, the IA group demonstrated lower incidences of non-fatal myocardial infarction and emergency revascularization compared to the CA group. Bleeding events were higher in the IA group, but the total MACE incidence was lower. No statistical difference in MACE and adverse drug reactions (ADR) was observed in the CA group across metabolic types, but MACE incidence was higher in intermediate and slow metabolic groups. In the IA group, no significant difference in MACE was noted among metabolic types, but ADR incidence varied significantly, particularly in dyspnea. The study highlighted significant CYP2C19 allele distribution differences between Hmong and Dong patients post-PCI in Qiandongnan. Patients with slow metabolic profiles demonstrated higher MACE incidence with conventional clopidogrel dosage, whereas CYP2C19-guided therapy reduced MACE without increasing bleeding risk. These findings supported clinical individualized clopidogrel administration in post-PCI patients in the Qiandongnan region, contributing to rational clopidogrel use.

Keywords: CYP2C19, Hmong, Dong, Clopidogrel, Individualized administration.

1. Introduction

Located in the south-eastern part of Guizhou Province, the Hmong and Dong Autonomous Prefecture of Qiandongnan has a total of 3.06 million ethnic minorities, with the Hmong and Dong accounting for 73.7% of the total population. The unique living environment and dietary habits of the ethnic groups have led to the formation of different genetic backgrounds among the different ethnic groups.

In recent years, the prevalence of coronary atherosclerotic heart disease (CAD) in China has been increasing year by year, posing a serious threat to people's health [1]. Percutaneous coronary intervention (PCI) has become an important tool to improve the prognosis of patients with CAD [2]. After PCI, patients are routinely treated with dual antiplatelet therapy (DAPT) with aspirin and clopidogrel to reduce the rate of stent thrombosis and ischaemic adverse cardiovascular events at the lesion [3,4]. Nevertheless, adverse cardiovascular events still occur after PCI, which can have a serious impact on the prognosis and quality of life of patients [5].

Studies have shown that clopidogrel resistance (CR) is an important cause of cardiovascular adverse events [6,7]. Clopidogrel is a precursor drug that requires activation and metabolism of cytochrome P-450 (CYP) system to play its anti-platelet aggregation effect, while CYP2C19 is a key enzyme in the metabolic activation process of clopidogrel [8,9]. Since CYP2C19 enzyme activity is significantly different among individuals and races, CYP2C19 gene polymorphism is an important internal genetic factor affecting the clinical therapeutic effect and drug safety of clopidogrel.

The purpose of this study was to explore the distribution of CYP2C19 gene in Hmong and Dong patients after

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PCI in southeast Guizhou region and to study the value of CYP2C19 gene detection in guiding the antiplatelet therapy of patients after PCI, so as to provide reference for the individualized medication of clopidogrel in patients after PCI in this region.

2. Materials and methods

2.1. Research object

A total of 208 Hmong (n=105) and Dong (n=103) patients who were admitted to the Department of Cardiovascular Medicine of the Second Affiliated Hospital of Guizhou Medical University from May 2021 to May 2022 and underwent PCI were included. Basic information such as ethnicity, gender, age, body mass index (BMI) and co-morbidities were collected. Inclusion criteria: (1) ACS diagnostic criteria jointly issued by the American Heart Association (AHA) and the College of Cardiology (ACC) in 2014 [10]. (2) Patients who were prescribed aspirin combined with clopidogrel antiplatelet therapy for more than 6 months. (3) Not using drugs other than clopidogrel that affect the metabolic activity of the CYP2C19 enzyme. (4) Patients of Hmong and Dong ethnicity born and permanently residing in Qiandongnan, with no history of intermarriage with a different ethnic group within three generations. Exclusion criteria: (1) Age less than 18 years or more than 80 years. (2) Pregnant and lactating women. (3) Patients treated with warfarin and other anticoagulants. (4) Patients with bleeding constitution. (5) Patients with malignant tumors. (6) With other end-stage diseases, life expectancy is less than 1 year. (7) Patients who refused to participate in this study. This study protocol was reviewed and approved by the Medical Ethics Committee of the hospital (Ethics Review number: 2021-Ethics Approval -17), and all subjects signed informed consent.

2.2. Genotyping assay

2~3 ml of peripheral venous blood was drawn from the subject, placed in a blood collection tube containing EDTA anticoagulant, mixed well and then 10 μL was taken for the detection of the CYP2C19 gene SNP locus (CYP2C19*2 c.681 G>A, CYP2C19*3 c.636 G>A, CYP2C19*17 c.806 C>T) using the Sequencing Reaction Universal Kit SNP-U3. The reagent instructions were strictly followed and negative and positive controls were set for each experiment to ensure the quality of the assay. SNP-U3 kit and Fascan 48E multi-channel fluorescence quantitative analyzer were purchased from Xi'an Tianlong Technology Co., LTD. (Xi'an, China).

2.3. Comparison of patients' prognosis after individualized drug therapy

Randomized charts were used to divide the enrolled subjects into individualized administration (IA) group and conventional treatment (CA) group, with 104 cases in each group. All enrolled patients were treated with conventional secondary prevention drugs for coronary heart disease after admission, including oral loading dose of aspirin enteric-coated tablets [Specification: 100 mg, approval number: National Medicine Approval number H20065051, Shenyang Ogina Pharmaceutical Co., LTD.] 300 mg and Clopidogrel bisulfate tablets [Specification: 75 mg, approval number: Sinopol H20056410, Sanofi (Hangzhou) Pharmaceutical Co., LTD., Hangzhou, China] 300 mg before operation. The CA group was given conventional maintenance doses: aspirin (100 mg, qd) and clopidogrel (75 mg, qd) orally after surgery. In group IA, the dosage of aspirin enteric-coated tablets (100 mg, qd) was maintained after surgery, and individualized administration regimen was developed according to the results of gene metabolism. UM and EM: clopidogrel (75 mg, qd), IM: clopidogrel (75 mg, bid), PM: Ticagrelor (90 mg, bid). Ticagrelor tablets (Specification: 90 mg, document number: National Medicine approval number H20203436, Zhejiang Hisun Pharmaceutical Co., LTD., Taizhou, China).

2.4. Observational indicators

Patients were followed up for 6 months after PCI by readmission, outpatient follow-up and telephone for major adverse cardiovascular events (MACE) and other adverse events, including non-fatal myocardial infarction, in-stent thrombosis, stroke, emergency revascularisation, cardiovascular death, haemorrhage and respiratory depression.

2.5. Statistical analysis

Statistic Package for Social Science (SPSS) 27.0 statistical software (IBM, Armonk, NY, USA) was used for data analysis. The χ^2 test was used to analyze whether the frequencies of alleles and genotypes were consistent with Hardy-Weinberg law of genetic balance, and if $P > 0.05$, the sample was representative. Measurement data were represented, and independent sample t-test was used for comparison between the two groups. Count data were expressed as frequency and percentage, and comparison between groups was performed using the 2 test or Fisher's exact probability method. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Determination of genotyping results

Allele CYP2C19 *2 is a base mutation G→A in exon 5 at position 681. CYP2C19*3 is a base mutation G→A in exon 4 at position 636. CYP2C19* 17 is a mutation of base C→T at -806 in the flanking sequence of the 5' promoter region [11,12]. Among them, CYP2C19*2 and *3 diminish the enzyme activity and CYP2C19 * 17 enhances it [13]. Therefore, CYP2C19 genotypes are classified as: mutation-free wild type * 1 / * 1 (681G / G, 636G / G, -806C / C). Mutant heterozygotes * 1 / * 2 (681G / A, 636G /G, - 806C / C), * 1 / * 3 (681G /G, 636G/A, -806C / C), * 1 / * 17 (681G / G, 636G / G, -806C / T), * 2 / *3 (681 G / A, 636G/A, -806C/C), *2/*17 (681G / A, 636G / G, -806C / T), *3/*17 (681G / G, 636G / A, -806C / T). Mutant homozygous types *2/*2 (681A / A, 636G / G, -806C / C), *3/*3 (681G / G, 636A / A, -806C / C), * 17 / * 17 (681G / G, 636G / G, -806T / T). To clopidogrel metabolism ability can be divided into: ultrarapid metabolizers type (UM) / * 17 * 17, 17 * 1 / * and extensive metabolizer (EM) * 1 / * 1, intermediate metabolizer (IM) * 1 / * 2, 3 * 1 / * and * 2 / * 17, 3 / * * 17, slow poor metabolizer (PM) * 2 * 2 * 2/3 * 3 * 3, / *.

3.2. Comparison of baseline information

There was no statistical difference in the baseline information between the Hmong and Dong patients after PCI ($P > 0.05$), and there was no statistical difference between the IA and CA groups after PCI ($P > 0.05$), as detailed in Table 1.

Table 1. Comparison of baseline data for patients.

Groups	Hmong	Dong	*P*	IA group	CA group	*P*
	(*n*=105)	(*n*=103)		(*n*=104)	(*n*=104)	
Age (year, $\bar{x}$±s)	61.31±11.19	61.74±9.64	0.770	61.58±11.48	63.92±10.56	0.127
BMI[(kg/m^2, $\bar{x}$±s]	24.41±3.49	24.36±3.54	0.933	24.45±3.65	24.32 ±3.37	0.784
Male [case (%)]	79 (75.2)	70 (68.0)	0.283	79 (76.0)	79 (76.0)	1.000
History of hypertension [case (%)]	72 (68.6)	67 (65.0)	0.659	73 (70.2)	66 (63.5)	0.377
History of diabetes mellitus [case (%)]	35 (33.3)	28 (27.2)	0.367	31 (29.8)	32 (30.8)	1.000
History of hyperlipidaemia [case (%)]	34 (32.4)	29 (28.2)	0.548	32 (30.8)	31 (29.8)	1.000
History of smoking [case (%)]	47 (44.8)	40 (38.8)	0.402	45 (43.3)	42 (40.4)	0.779
History of alcohol consumption [case (%)]	39 (37.1)	39 (37.9)	1.000	38 (36.5)	40 (38.5)	0.886

3.3. Results of Hardy-Weinberg genetic balance test

A total of 208 patients were included in this study and were divided into 2 cases in the UM group (CYP2C19 * 1 / * 17), 81 cases in the EM group (CYP2C19 * 1 / * 1), 105 cases in the IM group (CYP2C19 * 1 / * 2, CYP2C19* 1/ * 3, CYP2C19 * 2 / * 17) and 20 cases in the PM group (CYP2C19 * 2 / * 2, CYP2C19 * 2 / * 3) according to their metabolic type. The genotypes of CYP2C19*17/*17, CYP2C19 * 3/* 17 and CYP2C19 * 3 / * 3 were not detected. The genotype frequencies of CYP2C19 * 2, * 3 and * 17 loci were all in Hardy-Weinberg equilibrium (P>0.05), indicating constancy and population representability.

3.4. Genotype, allele and metabolic distribution of Hmong and Dong patients

There was no statistical difference in the distribution of genotypes and metabolic phenotypes between Hmong and Dong patients after PCI ($P > 0.05$), but there was a statistical difference in the distribution of CYP2C19 alleles between the two ethnic groups ($P < 0.05$), with the proportion of CYP2C19 * 1 alleles being higher in Hmong than in Dong, 68.6% and 60.2% respectively, which was statistically different ($P < 0.05$), as shown in Table 2.

3.5. Occurrence of MACE and adverse reactions 6 months after PCI in CA group and IA group

3.5.1. Occurrence of MACE and adverse reactions in CA and IA groups

At 6-month follow-up, non-fatal myocardial infarction was higher in the CA group (9 cases, 8.6%) than in the IA group (2 cases, 1.9%), with a statistical difference ($P < 0.05$). Emergency revascularization was higher in the CA group (10 cases, 9.6%) than in the IA group (3 cases, 2.9%), with a statistical difference ($P < 0.05$). There was no significant difference between the CA group (5 cases, 4.8%) and the IA group (11 cases, 3.6%) in terms of bleeding (P>0.05), and all bleeding events were mild (gingival and skin mucosal bleeding). The total incidence of MACE was higher in the CA group (24 cases, 23.1%) than in the IA group (6 cases, 5.8%), with a highly significant statistical difference ($P < 0.001$). The total incidence of ADR was lower in the CA group (6 cases, 5.8%) than in the IA group (14 cases, 13.5%), with no significant difference ($P > 0.05$), as shown in Table 3.

3.5.2. MACE and adverse effects in CA and IA groups with different metabolic types

After 6 months of follow-up, there was no statistical difference in the incidence of MACE and adverse reactions under the routine dosage of clopidogrel in CA group among patients with different metabolic types (all $P > 0.05$). However, the incidence of MACE in IM (29.8%) and PM (27.3%) groups was higher than that in UM (0%) and EM (15.6%) groups. There were no statistical differences in the incidence of MACE among patients with different metabolic types in group IA after individualized administration (all $P > 0.05$), but there were statistical differences in the incidence of ADR among patients with different metabolic types ($P < 0.05$). The incidence of dyspnoea was statistically significantly different between metabolic patients ($P < 0.001$), as shown in Table 4.

4. Discussion

Located on the Yunnan-Guizhou Plateau, Qiandongnan Prefecture is rich in ethnic minority resources. The population living in this region still rarely interacts with the outside world and lives in relative isolation, which is a valuable genetic resource for studying genetic polymorphisms in ethnic minorities. Studies have shown that CYP2C19 gene polymorphisms related to drug metabolism are influenced by geographical environment, culture, dietary habits and genetic background, and vary among individuals, regions, races and ethnic groups [14,15]. There are abundant studies on CYP2C19 gene distribution in Han Chinese population in related reports [16,17], but there are few studies on CYP2C19 gene polymorphisms in Hmong and Dong ethnic groups in Qiandongnan, Guizhou Province, and no relevant reports involving Hmong and Dong patients after PCI in this region.

In this study, the frequencies of *1, *2, *3 and *17 alleles in patients with PCI in southeast Guizhou were 68.6%, 28.6%, 2.8% and 0% in the Hmong nationality and 60.2%, 31.5%, 6.8% and 1.5% in the Dong nationality, respectively. There were statistical differences in the distribution of CYP2C19 allele and CYP2C19 *1 allele between the two nationalities, but there was no statistical difference in the distribution of genotype and metabolic pattern. The CYP2C19*1 allele-carrying rate of Hmong and Dong people in this region is close to that of Asian people (except West Asia), but significantly lower than that of black African people and white European people [18]. The *1, *2, *3 allele-carrying rates of Hmong people are similar to the results of the Tibetan study by Guo Zhiqiang et al. [19], and the *1, *2, *3 allele-carrying rates of Dong people are similar to the objects and results of the Inner Mongolia study by Li Guimei et al. [20]. In this study, it is found that there is a difference in the proportion of CYP2C19 metabolites between the two nationalities. The

Table 2. Distribution of CYP2C19 genotypes, alleles and metabolic phenotypes in Hmong and Dong patients after PCI in Qiandongnan[case (%)].

Groups	n	Genotype							Allele				Metabolic			
		*1/*1	*1/*2	*1/*3	*1/*17	*2/*2	*2/*3	*2/*17	*1	*2	*3	*17	UM	EM	IM	PM
Hmong	105	48 (45.7)	43 (40.9)	5 (4.8)	0 (0)	8 (7.6)	1 (1.0)	0 (0)	144 (68.6)	60 (28.6)	6 (2.8)	0 (0)	0 (0)	48 (45.7)	48 (45.7)	9 (8.6)
Dong	103	33 (32.0)	45 (43.7)	11 (10.7)	2 (1.9)	8 (7.8)	3 (2.9)	1 (1.0)	124 (60.2) *	65 (31.5)	14 (6.8)	3 (1.5)	2 (2.0)	33 (32.0)	57 (55.3)	11 (10.7)
χ^2						9.055			7.855				5.731			
P						0.171			0.049				0.125			

Note: vs. Hmong, $^{*}P<0.05$.

Table 3. Comparison results of MACE and ADR incidence in CA and IA groups [case (%)].

Adverse events	CA group (*n*=104)	IA group (*n*=104)	χ^2	*P*
MACE	24(23.1)	6(5.8)	12.620	0.000
Non-fatal myocardial infarction	9 (8.6)	2 (1.9)	4.703	0.030
Intra-stent thrombosis	1 (1.0)	1 (1.0)	0.000	1.000
Stroke	3 (2.9)	0 (0)	3.044	0.081
Emergency revascularisation	10 (9.6)	3 (2.9)	4.021	0.045
Cardiovascular death	1 (1.0)	0 (0)	1.005	0.316
ADR	6(5.8)	14(13.5)	3.540	0.060
Hemorrhage	5 (4.8)	11 (10.6)	2.438	0.118
Respiratory depression	1 (1.0)	3 (2.9)	1.020	0.313

Table 4. Comparison results of MACE and ADR incidence of different metabolic types in the CA and IA groups [case (%)].

Adverse events	CA group (*n*=104)				χ^2	*P*	IA group (n=104)				χ^2	*P*
	UM (n=1)	EM (n=45)	IM (n=47)	PM (n=11)			UM (n=1)	EM (n=36)	IM (n=58)	PM (n=9)		
MACE	0 (0)	7(15.6)	14(29.8)	3(27.3)	3.035	0.386	0 (0)	1(2.8)	5(8.6)	0 (0)	2.072	0.558
Non-fatal myocardial infarction	0 (0)	3(6.7)	4(8.5)	2(18.2)	1.584	0.663	0 (0)	0 (0)	2(3.4)	0 (0)	1.617	0.655
Intra-stent thrombosis	0 (0)	0 (0)	1(2.1)	0 (0)	1.225	0.747	0 (0)	0 (0)	1(1.7)	0 (0)	0.801	0.849
Stroke	0 (0)	1(2.2)	2(4.3)	0 (0)	0.742	0.863	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Emergency revascularisation	0 (0)	3(6.7)	6(12.8)	1(9.1)	1.097	0.778	0 (0)	1(2.8)	2(3.4)	0 (0)	0.364	0.948
Cardiovascular death	0 (0)	0 (0)	1(2.1)	0 (0)	1.225	0.747	0 (0)	0 (0)	0 (0)	0 (0)	-	-
ADR	0 (0)	2(4.4)	3(6.4)	1(9.1)	0.485	0.922	0 (0)	1(2.8)	9(15.5)	4(44.4)	11.310	0.010
Hemorrhage	0 (0)	2(4.4)	2(4.3)	1(9.1)	0.536	0.911	0 (0)	1(2.8)	9(15.5)	1(11.1)	3.933	0.269
Breathing difficulties	0 (0)	0 (0)	1(2.1)	0 (0)	1.225	0.747	0 (0)	0 (0)	0 (0)	3(33.3)	32.607	0.000

percentages of UM, EM, IM and PM metabolites in the Hmong nationality are 0%, 45.7%, 45.7% and 8.6%. The proportion of Dong nationality was 2.0%, 32.0%, 55.3% and 10.7%, respectively. Among them, the proportion of EM metabolic type patients of Hmong nationality is significantly higher than that of Dong nationality, and the metabolic type of UM, IM and PM is significantly lower than that of Dong nationality. Compared with the Han nationality studied by Li He et al. [21], the EM metabolic type of Hmong nationality in this region is significantly higher than that of Han nationality, the PM metabolic type is lower than that of Han nationality, and the EM metabolic type of Dong nationality is significantly lower than that of Han nationality, and the PM metabolic type is higher than that of Han nationality. It is suggested that there may be differences between the distribution of metabolic type of PCI patients of Hmong and Dong nationality and Han nationality.

At present, the prevalence rate and mortality of coronary heart disease are continuously increasing due to the aging population and the continuous epidemic pressure of metabolic risk factors [1]. The P2Y12 inhibitor clopidogrel, as the cornerstone of antiplatelet therapy in patients with coronary heart disease after PCI, generates active metabolites that inhibit platelet aggregation mainly through the metabolism of CYP2C19, a key enzyme. The gene encoding CYP2C19 is located on chromosome 10 (10q24.1-24.3), and there are more than 25 known variant alleles for CYP2C19 [22]. Associated with clopidogrel metabolism are CYP2C19*1, the gene encoding normal enzyme activity, loss-of-function alleles CYP2C19*2 and CYP2C19*3, and the acquired function allele CYP2C19*17. Among them, CYP2C19*2 is the site with the highest mutation frequency in the Chinese population (about 57.3%) [23]. Therefore, the single nucleotide polymorphism of CYP2C19 is one of the important reasons for the insufficient anti-platelet effect of clopidogrel in conventional dose antiplatelet therapy, increasing the risk of adverse reactions and the occurrence of "clopidogrel resistance (CR)" [6]. Patients included in this study were treated with dual antiplatelet therapy (DAPT) with aspirin and clopidogrel, and then divided into two groups. Patients with IM and PM in the IA group had their clopidogrel dose adjusted or changed according to CYP2C19 gene test results, while the remaining patients were treated with regular doses of clopidogrel. At 6-month follow-up, the incidence of MACE was significantly higher in the CA group than in the IA group, and the incidence of total MACE, non-fatal myocardial infarction and emergency revascularization were statistically different between the two groups.

There was no statistically significant difference in the incidence of MACE between the different metabolic groups in the CA group, but the incidence of MACE was higher in the IM and PM groups than in the UM and EM groups, which may be related to their anti-platelet aggregation ability and needs to be further investigated by expanding the sample size and extending the follow-up period. In the IA group, the incidence of total ADR, bleeding and respiratory depression were all higher than those in the CA group, but the difference between the two groups was not statistically significant. However, the incidence of ADRs in the IA group differed between the metabolic groups, with all bleeding events in the IA group being mild (gingival and skin mucosal bleeding), presumably related to the high dose of clopidogrel in the IM group and not to the replacement of tigretol [24]. Respiratory depression in the IA group was a normal adverse reaction to tigretol in the PM group.

In conclusion, there were significant differences in CYP2C19 allele distribution and CYP2C19*1 allele carriage rates between Hmong and Dong patients after PCI in Qiandongnan. The incidence of MACE was high in patients with CYP2C19 slow metabolic phenotype when clopidogrel was applied at conventional doses. However, antiplatelet therapy based on CYP2C19 gene test results reduced the incidence of MACE and did not increase the risk of severe bleeding in patients. This study provides some data to support the clinical individualisation of clopidogrel in post-PCI patients in this region. However, the small sample size and short follow-up period of this study have some limitations, and we will continue to expand the sample and validate it through multi-centre clinical studies.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Medical Ethics Committee of The Second Affiliated Hospital of Guizhou Medical University (Ethics Review number: 2021-Ethics Approval -17).

Informed consent

All subjects signed informed consent.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions

Xiangyi Yuan and Minzhen Han designed the study and performed the experiments, Yang Liu and Teng Zhang collected the data, Jie Xia, Xue Lan and Qinxiang Pan analyzed the data, Xiangyi Yuan and Minzhen Han prepared the manuscript. All authors read and approved the final manuscript.

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