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Review

Integrative Medicine on Optimizing Clopidogrel and Aspirin Therapy*

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ABSTRACT This article reviews the available published data on optimizing clopidogrel and aspirin therapy using translational and integrative medicine. Translational and evidence-based medical studies show that the *CYP2C19* gene mutation (*CYP2C19*2* and *CYP2C19*3*) could affect > 50% of the Chinese population, and that this mutation is closely associated with clopidogrel resistance and an increased risk of major adverse cardiovascular events, particularly stent thrombosis in patients following percutaneous coronary intervention (PCI). Adjusted-dose warfarin and aspirin reduce stroke in patients with atrial fibrillation (AF), and warfarin is substantially more efficacious than aspirin. However, a poor compliance is a big problem in warfarin use especially in China. The genetic variants of vitamin K expoxide reductase might account for the universally lower warfarin dosage used in Chinese population. The available evidence indicates that the integrating mainstream treatments (e.g., clopidogrel, CYP2C19 genotyping) and non-mainstream medicines [e.g., Chinese medicines, Naoxintong Capsule (脑心通胶囊, NXT)] to treat *CYP2C19* gene mutation patients following PCI can be effective. Aspirin combined NXT and the adjusted-dose warfarin was equally effective in elderly patients with non-valvular AF in prevention of ischemic stroke.

KEYWORDS integrative medicine, clopidogrel, aspirin, optimizing therapy, Chinese medicine

Platelet activation and aggregation are key components of the coagulation cascade that develop following percutaneous coronary intervention (PCI). Dual antiplatelet therapy (i.e., aspirin and clopidogrel) is an essential part of treatment. However, the available medical evidence shows that a significant proportion of patients remain at risk of death, myocardial infarction, stent thrombosis, and stroke because of insufficient clopidogrel-induced platelet inhibition.

The primary prevention of arterial thromboembolism and ischaemic stroke in patients with atrial fibrillation (AF) normally involves aspirin or warfarin therapy. It has been certified that warfarin is substantially more efficacious than aspirin. However, a poor compliance is a big problem in warfarin use especially in China.

This article reviews the available data on optimizing clopidogrel and aspirin therapy using translational and integrative medicine.

Effects of Translational Medicine on Clopidogrel Therapy

Translational medicine is an emerging field that uses preclinical studies to advance clinic practice. Translational medicine is considered the natural progression from evidence-based medicine and can help predict, prevent, diagnose, and treat diseases by using the findings of clinical studies to sharpen and improve preclinical efforts and drug discovery. Translational medicine also represents a paradigm shift in biomedical research. In short, it is the process of turning appropriate biological discoveries into drugs and medical devices that can be further used to treat patients.

Pharmacogenetics and pharmacogenomics play important roles in improving translational medicine. Pharmacogenetics is the study of the

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genetic causes of any individual variations in drug response, whereas pharmacogenomics studies the simultaneous impact of multiple mutations on patient drug responses (e.g., genetic modifiers of the clopidogrel response). Recently, a novel bedside genetic test was developed that can identify *CYP2C19*2* allele carriers and patients who should avoid clopidogrel treatment. This rapid technique was designed to shorten the turn-around time and further develop pharmacogenomic approaches for guiding antiplatelet treatments following PCI. A proof-of-concept study reported that point-of-care genetic testing after PCI can be effectively performed at the bedside, thereby advancing the feasibility of individualized antiplatelet therapies.[1]

Clopidogrel is an inactive prodrug that requires hepatic bioactivation via several cytochrome P450 enzymes, including *CYP2C19*. There are three major *CYP2C19* genetic polymorphisms: CYP2C19**1* corresponds to normal function and *CYP2C19*2* (c.681G>A; rs4244285) and *CYP2C19*3* (c.636G>A; rs4986893) is loss-of-function alleles that cause most of the reduced function associated with "poor metabolizers". Poor metabolizers demonstrate two loss-of-function alleles, whereas intermediate metabolizers have one copy of a loss-of-function allele and may also demonstrate.[2] In contrast, the *CYP2C19*17* allele (c.-806C>T; rs12248560) results in increased activity due to enhanced transcription. Individuals carrying this allele may be categorized as ultra-rapid metabolizers (e.g., **17*/**17*). Some studies indicate that this allele results in enhanced platelet inhibition and clopidogrel response, and carriers are possibly at higher risk of bleeding complications.[3,4] However, other studies have not identified the effects of *CYP2C19*17*,[5] and adequate evidence of the independent effects of this allele on clinical outcomes is lacking.

On March 12, 2010, the US Food and Drug Administration approved a new label for clopidogrel that includes a "boxed warning".[6] The boxed warning was issued primarily because of concerns that the antiplatelet effects of clopidogrel require activation by the CYP system. Patients with decreased *CYP2C19* function due to genetic polymorphisms poorly metabolize clopidogrel and demonstrate higher rates of cardiovascular events, including acute coronary syndrome and the need for PCI, than patients with normal *CYP2C19* function.[7,8] A meta-analysis reported that among patients treated with clopidogrel following PCI, carrying even one reduced-function *CYP2C19* allele appears to be associated with significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis.[9] The prevalence of the **2* and **3* alleles varies by ethnicity. In Asians, the proportion of patients who carry at least one copy of **2* is higher by about 50%[10-12] decreased active metabolite levels and reduced antiplatelet effects when treated with clopidogrel, while only 7% of Asians carry the **3* allele. Another meta-analysis reported a higher risk of adverse clinical events in Asians with loss-of-function *CYP2C19* variants in comparison with Western populations.[13] Therefore, alternative treatment strategies for patients identified as "poor *CYP2C19* metabolizers" should be considered.

Increasing the clopidogrel dose is one way to overcome clopidogrel-response deficits.[14] However, Mega's study reported that tripling the daily clopidogrel maintenance dose to 225 mg achieved levels of platelet reactivity in *CYP2C19*2* heterozygous patients that were similar to non-carriers who received the standard 75-mg dose; in contrast, daily doses as high as 300 mg did not demonstrate comparable levels of platelet inhibition in *CYP2C19*2* homozygous patient.[15] Price's study reported that administering 150-mg clopidogrel maintenance dosing to PCI patients with *CYP2C19* gene mutation could not improved prognosis in comparison to patients who received daily 75-mg clopidogre.[16] Another strategy is to administer newer, more potent platelet inhibitors (e.g., prasugrel, ticagrelor) instead of clopidogrel.[17] The Clinical Pharmacogenetics Implementation Consortium Guidelines for cytochrome *CYP2C19* and clopidogrel therapy recommend standard clopidogrel dosing, as recommended in the product insert, for patients with the *CYP2C19* extensive metabolizer or ultra-rapid metabolizer phenotype (e.g., **1*/**1*, **1*/**17*, **17*/**17*). The current literature supports the use of alternative agents (e.g., prasugrel, ticagrelor) if clinical genotyping identifies a patient as a poor *CYP2C19* metabolizer (e.g., **2*/**2*, **2*/**3*, **3*/**3*). The most challenging patients are those with *CYP2C19* intermediate phenotypes (e.g., **1*/**2*,**1*/**3*, **2*/**17*), and the data also support administering alternative antiplatelet agents.[18] Another approach is to add a third drug (e.g., cilostazol) to aspirin and clopidogrel in order to further enhance platelet inhibition.[19] However,

these strategies are often associated with higher risks of bleeding, possibly due to the inhibition of the thromboxane A_2 (TXA_2) and adenosine diphosphate (ADP) platelet activation pathways that are essential for normal hemostasis.[20,21] In accordance with unified therapy, adding clopidogrel dose or switching to prasugrel/ticagrelor may not only increase the economic burden, but also increase the risk of bleeding and other adverse reactions associated with these drugs. Further studies are needed to assess the effects of individualized clopidogrel treatments in patients with various *CYP2C19* genotypes.

Role of Integrative Medicine in Optimizing Clopidogrel Therapy

Integrative medicine is the combination of alternative and evidence-based medicine. In other words, integrative medicine combines conventional Western medicine with alternative or complementary treatments such as herbal medicine. The term "complementary" is used with mainstream medicine, not as a replacement or alternative.

Stent thrombosis after PCI is associated with platelet activation, inflammation, and endothelial injury. One study reports the association between inflammatory markers, dual antiplatelet therapy, platelet function, and outcomes in patients Post-PCI,[22] and sCD40L and diabetes mellitus might also influence clopidogrel resistance.[23] CD40L and its soluble counterpart, sCD40L, are members of the tumor necrosis factor superfamily and demonstrate dual prothrombotic and proinflammatory effects. These family members are expressed in a variety of tissues, such as the immune system, vasculature, and activated platelets. sCD40L is mainly derived from activated platelets and contributes to the pathophysiology of atherosclerosis and atherothrombosis. It has even been suggested that sCD40L may play a pathogenic role in triggering acute coronary syndrome.[24] One study reports that the CD40/CD40L signaling system enhances microvascular thrombosis in inflammatory models.[25] These results suggest that protecting against thrombosis could help rebuild the steady state via multiple regulatory routes.

Chinese medicine (CM) has a unique system for diagnosing and treating illness. Clinical diagnosis and treatment are mainly based on yin-yang and Five Elements theories.[26] These theories apply the laws of nature and associated phenomena to the study of physiological and pathological activities. According to CM, PCI is caused by qi deficiency and blood stasis. Our data show that severe blood stasis and *CYP2C19*2* mutation are not only associated with clopidogrel resistance in patients with coronary atherosclerotic heart disease, but also a higher risk of adverse cardiovascular events in patients following PCI.[10] Patients with the *CYP2C19*2* gene mutation, qi deficiency, and blood stasis following PCI often develop platelet activation and endothelial injury.[27]

The compounds used in CM contain multiple components and demonstrate multiple actions, levels, and targets. Buyang Huanwu Decoction (补阳还五汤, BYHWD) consists of 7 kinds of Chinese medicine—*Radix Astragali seu Hedysari*, *Radix Angelicae Sinensis*, *Radix Paeoniae Rubra*, *Rhizoma Ligustici Chuanxiong*, *Flos Carthami*, *Semen Persicae*, and *Pheretima*—all of which are recorded in the Chinese Pharmacopoeia (2005 edition). In China, BYHWD is typically administered to treat patients with coronary heart diseases, qi deficiency, blood stasis, and stroke-induced disability.[28,29] Research on rats with myocardial ischemia shows that the effects of BYHWD are not only related to its antioxidative actions and regulatory effects on lipid metabolism, but also the inhibition of inflammatory pathways due to decreased inducible nitric oxide synthase, CD40 and CD40L expression.[30] Naoxintong Capsule (脑心通胶囊, NXT, produced by Xianyang Buchang Pharmaceutical Co., Ltd., China) is a compound prepared by combining BYHWD, scorpio, and leech, etc. NXT, commercially available product, quality standards are disclosed in 2002 compiled by the State Drug Administration of "national medicine standard compilation-proprietary local standards rising national standard part" of the "medicine - brain system" volumes, standard number: ws-10001 (ZD-0001) -2002) by astragalus, red peony, salvia, angelica, Sichuan bend, safflower, peach, frankincense (system), myrrh (system), Millettla, Achyranthes, Cinnamomum cassia Presel, mulberry, earthworm, scorpion, and leech 16 flavor ingredients commonly used in clinical processed into CM, with qi and blood circulation, circulation network effect, for the deficiency of blood stagnation, stasis context stroke caused by the meridian and chest pain, chest tightness, heart palpitations, shortness of breath, cerebral infarction, angina pectoris treatment (patent CN103207255A). NXT is cheap, widely applied in

Chinese clinical practice, convenient to administer, and, thereby, demonstrates good patient compliance, uniform dosing, and standardization in clinical settings. Our study found that NXT in combination with dual antiplatelet therapy inhibits platelet aggregation, balances pro- and anti-inflammatory cytokines, serum endothelin-1, and endothelial nitric oxide synthase, and could be used to sequentially decrease coronary microembolization (CME) in rats. In addition, NXT also reduced the risk of intraoperative bleeding when administered as part of dual antiplatelet therapy to a rat model of CME.[31,32] NXT also increases the catalytic activities of drug-metabolizing *CYP2C19* enzymes *in vitro*.[33] According to *in vivo* studies, combination NXT and clopidogrel demonstrates enhanced antiplatelet effects and decreased sCD40L in volunteers with the *CYP2C19*2* mutation.[10] In small clinical trials, combination NXT and standard clopidogrel 75-mg maintenance dosing enhances antiplatelet effects and decreases subsequent major adverse cardiovascular events in patients with the *CYP2C19*2* gene mutation who are receiving PCI.[34]

Role of Integrative Medicine in Optimizing Aspirin Therapy

The maintenance, safety, and effectiveness of international normalized ratio (INR) within range can be influenced by the pharmacogenetics of vitamin K antagonists therapy, particularly the *CYP2C9* gene (*CYP2C9*, the primary enzyme responsible for inactivating warfarin) and the vitamin K epoxide reductase complex 1 gene (*VKORC1*, the pharmacological target for warfarin). Studies found that there were associations between *VKORC1-1639* G>A and *CYP2C9* 106l A>C transformation and decreased warfarin dose. The major genotype of *VKORC1-1639* (AA) might account for the universally lower warfarin dosage used in Chinese population. The *VKORC1-1639* G > A gene variant results in a 50% decreased transcription of the VKOR gene and increases a patient's sensitivity to warfarin. Compared with Chinese stroke patients with AF, patients in Western countries had more oral anticoagulation usage.[35,36] Our study showed that the number of patients using aspirin was larger than adjusted-dose warfarin in elderly patients with high-risk non-valvular AF. The main reasons of nonuse warfarin included elderly, associated with other diseases, complicated drugs, hepatic or renal dysfunction, lack of knowledge, and too much worry about bleeding complications.[37]

In CM, qi deficiency and blood stasis syndrome are the most common syndromes in patients with cerebral infarction[38] or coronary heart disease. It means to treat the patient as a whole, not just focusing on single disease. Treating heart and brain simultaneously is also based on this theory. NXT is an approved CM for stroke,[39] which is widely used, and is well tolerated. Furthermore, it can also achieve the goal of treating coronary heart disease and stroke at the same time.[39] Studies showed NXT treatment for stroke with qi-deficiency and blood-stasis syndrome (cerebral infarction) was safe and effective and can protect cortical neurons from hypoxia-induced apoptosis in cultured cortical neurons.[40] Chen's study showed NXT combined with aspirin could enhance the antiplatelet effect in patients with cardio-cerebrovascular diseases.[47] Our study showed that aspirin combined NXT and the adjusted-dose warfarin were equally effective in elderly patients with non-valvular AF in prevention of ischemic stroke. The combination therapy could reduce the risk of the antithrombotic drug therapy without the associated bleeding.[42]

Conclusion

Translational and evidence-based medical studies indicate that the *CYP2C19* gene mutation could affect > 50% of the Chinese population, and that this mutation is closely associated with clopidogrel resistance. The *VKORC1-1639* G > A gene variant increases a patient's sensitivity to warfarin. NXT could significantly improve clopidogrel resistance and increase effects of aspirin in patients with qi deficiency, blood stasis. Integrating mainstream treatments (e.g., clopidogrel, *CYP2C19* genotyping), non-mainstream medicines, and NXT to treat *CYP2C19* gene mutation patients following PCI requires further large-scale, multicenter, prospective clinical trials. Such research may provide new integrated medical models and findings that could be applied to multi-target therapies.

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