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The pharmacodynamics of low and standard doses of ticagrelor in patients with end stage renal disease on hemodialysis

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ABSTRACT

Background: Patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD) respond poorly to clopidogrel. We assessed the utility of low-dose ticagrelor in ESRD patients on maintenance HD.
Methods: In this single-center, prospective, randomized pharmacodynamic study, 52 ESRD patients on HD were prescribed clopidogrel (300 mg loading dose [LD], then 75 mg daily), standard-dose ticagrelor (180 mg LD, then 90 mg twice daily), or low-dose ticagrelor (90 mg LD, then 90 mg daily) for 14 days. Platelet function was evaluated before and after therapy via light transmittance aggregometry and the VerifyNow™ $P2Y_{12}$ assay.
Results: The adenosine diphosphate (ADP)-induced maximal extent of platelet aggregation differed significantly between the low-dose ticagrelor and clopidogrel groups (ANCOVA, $p = 0.04$ after stimulation with 5 μmol/L ADP; $p < 0.01$ after stimulation with 20 μmol/L ADP). Inhibition of platelet aggregation increased significantly in the order of clopidogrel, low-dose ticagrelor, and standard-dose ticagrelor, as revealed by adjusted intergroup comparison analysis (ANCOVA, $p = 0.04$ after stimulation with 5 μmol/L ADP; $p = 0.005$ after stimulation with 20 μmol/L ADP). The rates of onset of the antiplatelet effect curves from 0 to 5 h after administration of the LDs were greater in the standard- and low-dose ticagrelor groups than in the clopidogrel group. Significant sequential reductions in $P2Y_{12}$ reaction units were noted, in the following order: clopidogrel, low-dose ticagrelor, and standard-dose ticagrelor (ANCOVA, $p < 0.001$). No bleeding occurred in the low-dose ticagrelor group.
Conclusions: Low-dose ticagrelor afforded greater platelet inhibition than did clopidogrel in ESRD patients on HD.

1. Introduction

Chronic kidney disease (CKD) is a growing worldwide public health problem associated with a high risk of progression to end-stage renal disease (ESRD), triggering a need for kidney replacement [1,2]. Although it is very clear that ESRD is a strong risk factor for the development of cardiovascular morbidity and mortality, increasing the need for coronary revascularization therapies [3–6], there is no consensus on treatment with aspirin and platelet adenosine diphosphate $P2Y_{12}$ receptor antagonists such as clopidogrel, prasugrel and ticagrelor. As the hemostatic features of ESRD patients are complex, these patients have often been excluded from clinical trials, leading to a lack of evidence regarding treatment options. Thus, drug efficacies in ESRD patients remain unclear. More detailed pharmacokinetic studies of antiplatelet agents are needed in such patients, particularly those on maintenance hemodialysis (HD).

Recently, we described the fast onset/offset effects of ticagrelor, which is associated with a significant reduction in platelet reactivity, in ESRD patients on maintenance HD [7]. However, the patient dropout rate was problematic and adverse reactions were apparent in the previous study. In a study on patients with normal kidney function, a low loading dose (LD) (90 mg) and a low maintenance dose (MD) (90 mg daily) of ticagrelor afforded more potent platelet inhibition than did clopidogrel (300 mg LD; 75 mg MD daily) [8]. A recent clinical

Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; Agg_{max}, maximal extent of aggregation; AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; CKD, chronic kidney disease; ESRD, end stage renal disease; HD, hemodialysis; HPR, high on-treatment platelet reactivity to adenosine diphosphate; IPA, inhibition of platelet aggregation; LD, loading dose; LPR, low on-treatment platelet reactivity to adenosine diphosphate; LTA, light transmittance aggregometry; MD, maintenance dose; MI, myocardial infarction; OPR, on-treatment platelet reactivity; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction units.

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trial compared two doses of ticagrelor (60 or 90 mg twice daily); both doses significantly reduced the risks of cardiovascular death, myocardial infarction (MI), and stroke [9]. Thus, we questioned whether the currently recommended ticagrelor dose (90 mg twice daily) was appropriate, especially for ESRD patients on maintenance HD.

In the current study, we investigated the pharmacodynamic efficacy and safety of clopidogrel (300 mg LD, 75 mg once daily MD), low-dose ticagrelor (90 mg LD, 90 mg once daily MD), and standard-dose ticagrelor (180 mg LD, 90 mg twice daily MD), in ESRD patients on maintenance HD.

2. Methods

2.1. Study design and subjects

This was a prospective, randomized, single-center pharmacodynamic study performed on ESRD patients on regular (≥6 months) maintenance HD. Patients were screened in terms of platelet reactivity if they took low-dose aspirin (100 mg/day) and clopidogrel (75 mg once daily MD) for at least 14 days as part of their standard treatment regimens. A total of 52 ESRD patients on regular HD were enrolled. The exclusion criteria were a known allergy to aspirin, clopidogrel, or ticagrelor; concomitant use of other antithrombotic drugs (oral anticoagulants, dypiridamole); liver disease (serum bilirubin level > 2 mg/dL); symptomatic severe pulmonary disease; active bleeding or bleeding diathesis; gastrointestinal bleeding within the last 6 months; hemodynamic instability; an acute coronary or cerebrovascular event within the last 3 months; pregnancy; any malignancy; concomitant use of a cytochrome P450 inhibitor or a nonsteroidal anti-inflammatory drug; and/or recent treatment (within 30 days) with a glycoprotein IIb/IIIa antagonist. All study procedures complied with the Declaration of Helsinki and were approved by the Institutional Review Board of the Kyung Hee University College of Medicine (KMC IRB no. 1425-02). Written consent was obtained from all patients. The study was registered at www.clinicaltrials.gov (identifier: NCT02406911).

As shown in Fig. 1, an independent investigator randomized the patients in a 1:1:1 ratio to one of three treatment groups. The investigator employed a computerized random number generation method. The groups were 1) clopidogrel (300 mg LD, 75 mg once a day MD for 14 days), 2) low-dose ticagrelor (90 mg LD, 90 mg once daily MD for 14 days, and 3) standard-dose ticagrelor (180 mg LD, 90 mg twice daily MD for 14 days). All patients were prescribed aspirin (100 mg once daily). Pharmacodynamic assessments were performed at five time points using the two assays described below. Compliance was assessed by noting the amounts of medication returned at each visit. Bleeding was classified using the Bleeding Academic Research Consortium (BARC) definition [10]. Heart and respiratory rates and the extent of arterial oxygen saturation were measured at each visit. All adverse events, including bleeding, bradyarrhythmia, and dyspnea, were recorded. No HD feature changed during the study period.

2.2. Blood sampling and pharmacodynamic assays

Blood samples were collected at five time points: predosing (before administration of the LD; 0 h), and at 1, 5, and 48 h and 14 days after the first dose. Each blood sample was collected from an antecubital vein using a loose tourniquet and a 21-gauge needle just before the HD sessions, with the exception of the 5 h sample, which was drawn after the HD sessions. Samples were processed within 1 h by operators blinded to the drug treatment.

At each time point, two platelet function assays (pharmacodynamic assessments) were performed. The first was light transmittance aggregometry (LTA) and the second was the VerifyNow™ $P2Y_{12}$ assay [7,11,12]. In brief, the LTA of platelet-rich plasma was assessed by a turbidimetric method using a two-channel aggregometer (Chrono-Log Model 490; Chrono-Log Corp., Havertown, PA, USA) after stimulation with 5 and 20 μmol/L adenosine diphosphate (ADP); aggregation percentages were recorded 7 min later. To estimate the maximal extent of aggregation (Agg_{max}), inhibition of platelet aggregation (IPA) was defined as the percentage decrease in the aggregation values after treatment compared with baseline, as follows: IPA (%) = [(intensity of aggregation at baseline) − (intensity of aggregation after treatment)] / (intensity of aggregation at baseline). The VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA) estimates platelet-induced aggregation by recording increases in light transmittance; data are reported as both PRUs and percentage inhibition. We defined platelet activity ≤85 PRU as a low on-treatment platelet reactivity to adenosine diphosphate (LPR) and 275 < PRU as a high on-treatment platelet reactivity to adenosine diphosphate (HPR), according to data from studies based on East Asian populations [13–15].

2.3. End points and sample size calculation

The primary end point was the difference in Agg_{max} values after stimulation with 5 μmol/L ADP, on day 14, in each group. We previously found that 14 days of ticagrelor therapy afforded a 43% reduction in Agg_{max}, compared with clopidogrel, in ESRD patients on HD [7]. Assuming that a 20% reduction in Agg_{max} would result from low-dose ticagrelor therapy, with a standard deviation of 9%, each group had to contain at least 12 patients to afford a statistical power of 95% and a two-sided α-level of 0.05. The secondary end points included other

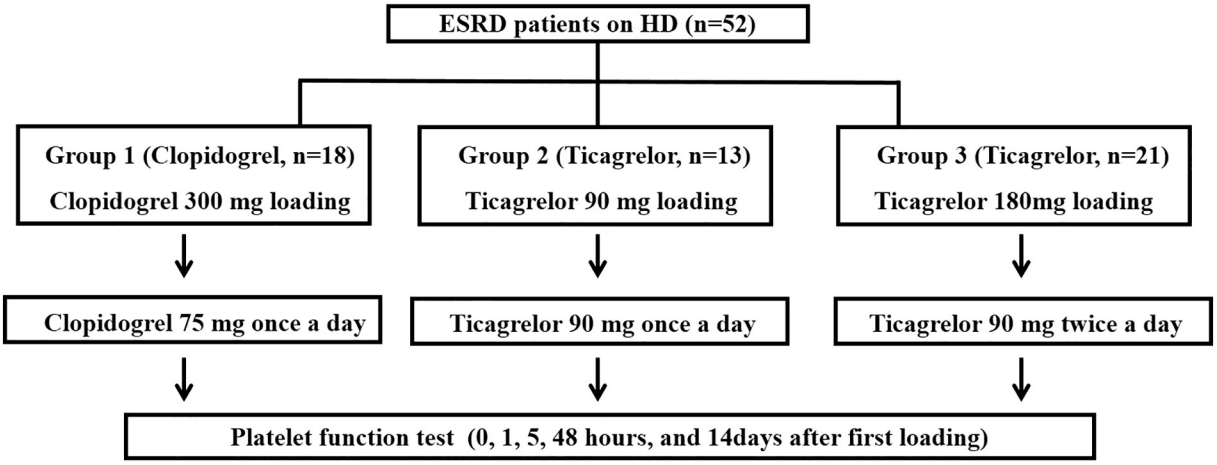

Fig. 1. Flow diagram of the study. ESRD, end-stage renal disease; HD, hemodialysis; PRU, $P2Y_{12}$ reaction unit.

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