Platelet reactivity with a third generation thienopyridine drug versus with a second-generation thienopyridine drug

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ABSTRACT

Prasugrel is a third generation thienopyridine drug and Clopidogrel is a second-generation thienopyridine drug. Both drugs used for reducing platelet aggregation in patients with coronary artery diseases. The aim of this study is to investigate the antiplatelet efficacy and safety of Prasugrel 5mg daily as compared to Clopidogrel 75 mg daily for period along to 12 days treatment. Fifty patients, (10 females, 40 males), their ages ranging from (50-60) years with stable angina were recruited from IbnAlbitar Center for Cardiac Surgery and enrolled in this case study. Of whom 25 patients (group A) received a dose of 75 mg daily of Clopidogrel and other 25 patients (group B) were on a dose of 5 mg daily of Prasugrel for a period of 12 days. Clinical laboratory data of lipid profile, renal function, and prothrombine time obtained at baseline (before treatment). While Platelet aggregation percent measured at the baseline and after 12 days of treatment. The maximal platelet aggregation percent for group A was fell from 78% to 43.5% (after 12 days treatment). While patients of group B showed dropping in the maximal platelet aggregation percent from 76% to 27.3% (after 12 days treatment). Analysis of adverse events showed three patients with minor bleeding occurred during Prasugrel treatment, and no bleeding occurred during Clopidogrel treatment. Compared with Clopidogrel 75mg treatment, Prasugrel 5mg treatment for 12 days averted platelets accumulation more quickly and steadily.

INTRODUCTION

Clopidogrel and Prasugrel drugs inhibit platelet activation and aggregation by irreversibly bound to platelet P2Y12- adenosine diphosphate (ADP) receptor. These drugs need metabolic and enzymatic conversion inside the body into their pharmacologically active metabolites (Hasan et al., 2014). Whereas Ticagrelor, another class of antiplatelet drugs, inhibits platelets accumulation by mutably connected to the P2Y12 receptor of platelet (Rada, 2018). Clopidogrel is a second-generation thienopyridine agent, while Prasugrel is a third generation thienopyridine agent. The chemical modification that exerted on Prasugrel structure made its metabolic conversion more rapidly and effectively occurred without needed for dependency on specific cytochrome P-450 enzymes. Thereafter produced earlier onset of action and more inhibition of platelet aggregation would occur as compared to Clopidogrel (Brandt et al., 2007; Jakubowski et al., 2007b). Moreover, the ability of Clopidogrel to inhibit
platelet collection is still sustained with co intake of Atorvastatin (Hasan et al., 2014) but it may provoke liver cholestasis (Rada et al., 2015) and not dependent on the existence of diabetes mellitus (Rada, 2016).

The aim of this study is to investigate the antiplatelet efficacy and safety of Prasugrel 5mg daily as compared with Clopidogrel 75 mg daily for treatment period along to 12 days.

**MATERIALS AND METHODS**

**Study design**

Of 80 patients (53 males, 27 females) their ages ranging (50-60) years with stable angina recruited from IbnAlbitar Center for Cardiac Surgery, only 50 patients (40 males, 10 females), their ages ranging (50-60) years completed the intended period of this case-study at which they divided into two groups ;group A and group B. Many causes precipitated in the losses of some participants like follow up interruption, patients with counteractive behavior.

**Patients’ selection**

Diagnoses made depending on clinical symptoms, clinical analytical tests like cardiac troponin I and tests like Electrocardiogram (ECG), Echocardiogram stress test. Patients with impaired liver function (diabetes Mellitus), renal function, heart function, and bleeding disorder are excluded. The institutional ethics committee of each study site approved patients’ selection and study protocol. Written informed assent procured from every patient.

**Data collection and laboratory measurements**

Starting therapy with a dose of Clopidogrel 75mg daily (Plavix, France) for group A and a dose of Prasugrel 5mg daily (Effient, Spain) for group B for a period of 12 days.

Blood samples are aspirated at baseline (before treatment) to measure maximal platelet aggregation percent (MPA %), prothrombin time and other clinical data. After 12 days of treatment another blood samples are aspirated to measure maximal platelet aggregation percent (MPA %).

The assay of MPA% done by measuring the inhibition of ADP (20µmol/L) -induced platelet aggregation of platelet-rich plasma (PRP) and quantitated by using light transmission aggregometry (Bio/Data, USA). Whereas the prothrombine time was measured by using (BIO LABO) reagents and international normalization ratio (INR) was calculated by using this formula: (INR= Patients Prothrombine time / Mean normal Prothrombine time).

The percentage of Inhibition of Platelet Aggregation (IPA %) computed by using this formula,

\[
IPA\% = \left( \frac{\text{Baseline MPA\% with treatment MPA\%}}{\text{Baseline MPA\%}} \right) \times 100%
\]

**Statistical analyses**

Results are shown as mean ± SD with 95% confidence interval (CI), and P values of (0 < 0.05) were regarded as statistically significant. All statistical analyses performed using SPSS version 18.0 for windows and Microsoft Excel.

**RESULTS AND DISCUSSION**

Baseline clinical characteristics of the studied participants, group A and group B, are displayed in Table 1. There were no significant differences noted between group A and group B in mean levels of the baseline clinical data that involved age, number, white B-cell (WBC) count, Platelet count, serum creatinine level, serum uric acid level, serum low density lipoprotein level (LDL), serum high density lipoprotein level (HDL) and international normalization ratio (INR).

The platelet responsiveness to ADP stimulation, MPA %, at baseline (before treatment) and after 12 days of treatments denoted high significant differences between patients on Clopidogrel therapy and patients on Prasugrel therapy. As well, high significant decrease was clarified in MPA% after 12 days treatment versus baseline for patients on Clopidogrel therapy and for patients on Prasugrel therapy (Table 2 and Figure 1).

Analysis of adverse events showed three patients on Prasugrel treatment have inferior hemorrhage and no hemorrhage presented in patients with Clopidogrel treatment.

The Bar graph that outlined in Figure 2 clarified the percentage of inhibition of platelet aggregation (IPA%) which was higher in patients with Prasugrel treatment as compared to patients with clopidogrel treatment after 12 days period.

The use of antiplatelet drugs that irreversibly bound to ADP receptors (P2Y12) became the preferable line for the treatment of the patients on coronary artery disease with or without stenting (Wallentin et al., 2009). Adenosine diphosphate (ADP), an extracellular nucleotide, has two types of receptors; P2X and P2Y. P2X receptor is a type of ligand-gated ion channels, while P2Y receptor is a type of G-protein coupled receptors. The platelets have two types of P2Y receptors; P2Y1 receptor and P2Y12 receptor (Gachet, 2008).
Table 1: Baseline clinical data and demographic characteristics of the participant’s patients

| Variables                  | Group A       | Group B       |
|----------------------------|---------------|---------------|
| Number (n)                 | 25            | 25            |
| Age (years)                | 50±8          | 55±5          |
| Gender (Males, Females )   | (19,6)        | (21,4)        |
| WBC count (x1000/mm)       | 6.3±1.3       | 6.6±1.5       |
| Platelet count (x1000/mm)  | 218±53        | 222±48        |
| S.Creatinine (μmol/L)      | 90.27±19.47   | 84.08±28.32   |
| S.Uric acid (μmol/L)       | 330±81        | 360±79.8      |
| S.LDL (mmol/L)             | 3.03±0.34     | 2.98±0.47     |
| S.HDL (mmol/L)             | 1.09±0.21     | 1.14±0.17     |
| INR                        | 1.3           | 1.3           |

Data are presented as mean ±SD (standard deviation) for continuous variables, μmol/L: micromole per liter, mmol/L: millimole per liter, x1000/mm: multiply by thousand cell permillimeter, WBC: white B-cell, Number (n): sample size of patients for each group, S.LDL-C: serum low density lipoprotein cholesterol, S.HDL-C: serum high-density lipoprotein cholesterol, (INR): international normalization ratio.

Table 2: Maximal platelet aggregation percent (MPA %) before and after 12 days treatment for the studied groups

| Group          | Mean Maximal Platelet aggregation percent (MPA %) |
|----------------|-----------------------------------------------|
| n=25           |                                               |
|                | Baseline (prior treatment)         | After 12 days treatment              |
| Group A (Clopidogrel 75mg daily) | 78% ± 6.3                                   | 43.5% ± 5.8 ***                      |
| Group B (Prasugrel 5 mg daily)     | 76% ± 7.4                                   | 27.3% ± 5.7 ***†††                   |

(n): sample size of patients for each group, *** high significant decrease (P<0.0002) as compared to baseline, ††† high significant decrease (P<0.0002) as compared to group A treatment after 12 days.

Figure 1: Line chart demonstrates the maximal platelet aggregation percent before and after 12 days treatments.
The binding of ADP to the platelet- P2Y1 receptor, which coupled to both Gq/11 and Gs, activate the platelets by different pathways and initiate platelets aggregation (Wihlborg et al., 2004). In contrast, the binding of ADP to the platelet- P2Y12 receptor, which coupled to Gi, stimulate the inhibitory pathway inside the platelet and thereafter inhibit activation and aggregation of platelets. Therefore, the binding of metabolically active form of Clopidogrel drug or Prasugrel drug to the platelet- P2Y12 receptor inhibit platelets activating and clustering (Gachet, 2008).

The results of this study that consistent with other study (Biondi-Zoccai et al., 2011), indicated that inhibition of platelet assembling through daily single dose were considerably higher with Prasugrel 5mg compared with Clopidogrel 75mg. Conspicuously, the consistently-state prohibition of platelets assembling by Prasugrel 5mg was verified more quickly than with Clopidogrel 75mg. As well, the usage of Prasugrel 5mg daily for 12 days was innocuous and well endured and accepted.

As reported in many clinical studies, Prasugrel was approximately 10-times more potent than Clopidogrel (Wilson et al., 2009; Bonello et al., 2010). Other stated that the usage of Prasugrel 10 mg or 20 mg daily to inhibit the platelets aggregation attained consistently-state level at 2–4 days and maintained its activity throughout the treatment period (Matsushima et al., 2006; Niitsu et al., 2005). While Clopidogrel 75 mg daily dosing attained its steady-state level at 5-6 days (Jakubowski et al., 2007a). Moreover, Prasugrel has independent reactivity against CYP2C19 genotype enzyme, while CYP2C19 genotype enzyme can change the reactivity of Clopidogrel (Kelly et al., 2012).

The employment of IPA% to demonstrate the magnitude of platelet prohibition of many antiplatelet drugs was presented in various studied (Valgimigli et al., 2012; Ernest et al., 2008). Interestingly, the high efficacy of platelet prohibition of prasugrel 5mg with its low tendency to yield high on treatment platelet reactivity (HPR), platelet resistance to the drug, that demonstrated in many studies encourage the cardiologist to use prasugrel 5mg instead of clopidogrel 150 mg to treat the old patient with HPR on clopidogrel (Capranzano et al., 2011; Alexopoulos et al., 2013).

CONCLUSIONS

The clinical properties of Prasugrel indicate that it has more potent antiplatelet activity, more rapid onset of action, and more efficacious in preventing ischemic events, but it may implicate high chance of bleeding. More studies needed to confirm the safety of Prasugrel for long period treatment.

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Conflict of Interest

None.

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