

# Platelet Aggregometry May Not Identify Clopidogrel-Treated Patients at High Risk of Peri-Operative Bleeding in Dialysis Access Surgery: A Pilot Study

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## Abstract

Patients treated with Clopidogrel are usually instructed to discontinue treatment for 7 days prior to surgery because of concern for excessive peri-operative blood loss. Limited data exist regarding blood loss resulting from continuing treatment with Clopidogrel. Our goal was to compare peri-operative blood loss in Clopidogrel (CC) treated patients with Non-Clopidogrel (NC) patients undergoing upper extremity dialysis access surgery.

**Methods:** Following informed consent, 23 patients, 18-90 years old were enrolled in a pilot, prospective study. Nine patients continued treatment with Clopidogrel, while 14 patients had no exposure to the drug. Vascular fistula or graft placement was accomplished under brachial plexus anesthesia and sedation. ADP (adenosine diphosphate) induced inhibition of platelets was assayed by Impedance-based Whole Blood Platelet Aggregation (IWBPA) on immediate preoperative blood sample obtained from all participants to determine baseline platelet aggregation status (Figure 1). Intra-operative blood loss (IBL) was estimated from suction canister output and sponge weights. Interventions such as blood or blood product transfusion were noted. Postoperative bruising or bleeding for up to 24 hours was recorded.

**Results:** Nine (39.2%) of study participants were in the Clopidogrel group and 14 (60.8%) in the Non-Clopidogrel group. There was no correlation between IWBPA levels and IBL. No study participants developed postoperative bruising or hematomas. No blood or blood products were administered.

**Conclusion:** Continued peri-operative treatment with Clopidogrel did not increase IBL or postoperative bruising compared to no Clopidogrel patients. IWBPA values did not correlate with IBL, and represented a poor predictor of peri-operative blood loss in Clopidogrel treated patients with end stage renal disease.

**Keywords:** Clopidogrel; Platelet aggregometry; End stage renal disease; Dialysis access surgery

## Introduction

The use of antiplatelet therapies (APT) has increased dramatically over the last several years, largely due to the increased use of percutaneous interventions for the treatment of atherosclerotic vascular disease in the aging population [1-3]. The mainstays of anti-platelet therapy are aspirin, thienopyridines (Ticlopidine and Clopidogrel), and glycoprotein IIb/IIIa inhibitors. Aspirin and clopidogrel are most commonly prescribed [1]. Both act by irreversibly inhibiting platelet activation, through two different mechanisms [4]. Aspirin irreversibly acetylates the serine 529 of cyclooxygenase-1 (COX-1) resulting in inhibition of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) which plays a pivotal role in the final phase of platelet aggregation while Clopidogrel acts by bonding to a cysteine residue of the adenosine diphosphate (ADP) receptor P2Y<sub>12</sub>, which attenuates platelet aggregation in response to ADP release from activated platelets [2-5]. When used in combination, these drugs provide an additive effect on platelet inhibition.

In patients scheduled to undergo surgery, the risk and benefits of continuing treatment versus temporary interruption of treatment must be carefully evaluated. Uninterrupted treatment can result in excessive peri-operative blood loss while even temporary interruption can result in acute vessel thrombosis or graft occlusion [4,6,7]. Recent studies suggest that discontinuation of APT in patients with intracoronary stents undergoing surgery lead to increased risk of acute coronary thrombosis, myocardial infarction and even death [8-10].

Current guidelines on APT therapy in patients with intracoronary stents recommend that APT should be continued for up to one year without interruption in patients with drug eluting stents and up to 6 weeks in patients with bare metal stents [1,4,6]. The guidelines further recommend that elective surgeries should be postponed until the completion of the initial uninterrupted treatment. For emergency surgery, bridging treatment with titrated heparin infusion is suggested while APT is interrupted. Available evidence suggests that the degree of platelet inhibition in patients treated with APT's is not uniform or predictable [5]. Consequently, bleeding risk and intra-operative blood loss (IBL) would be expected to differ among patients on the usual therapeutic dose of APT undergoing surgery [5].

This pilot, prospective study evaluates peri-operative blood loss in Clopidogrel treated patients compared to patients who were never treated with Clopidogrel undergoing upper extremity dialysis access

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surgery. Secondly, the relationship between impedance-based Whole Blood Platelet Aggregation (IWBPA), a measure of platelet activity inhibition, and perioperative blood loss is examined in both groups.

## Material and Methods

The study was approved by The University of Texas Southwestern Medical Center at Dallas Institutional Review Board. Following informed consent, 23 patients, between 18 and 90 years old undergoing upper extremity dialysis access surgery were enrolled in a pilot, prospective study. Nine patients continued treatment with Clopidogrel (CC group), while 14 patients had no exposure to the drug (NC group). Patients included in the study were on the standard dose of Clopidogrel, 75 mg daily, as prescribed by their primary physician. To ensure that such patients had reached a pharmacologic steady state, they must have been taking the medication for at least 3 months for inclusion. None of the patients were taking aspirin. All patients were processed through the vascular access and anesthesia preoperative clinics for routine evaluation. All surgeries were performed by the same surgeon for consistency in surgical technique. Anesthesia for all procedures consisted of ultrasound guided brachial plexus block and intravenous midazolam/fentanyl sedation. Prior to the establishment of anesthesia, but before infusion of intravenous fluids, approximately 5 cc of blood was obtained to determine baseline preoperative platelet aggregation status using impedance-based Whole Blood Platelet Aggregation (IWBPA) testing. Blood samples were collected in 3.8-mL tubes containing 0.38 mL (0.129 mol/L) buffered (pH 5.5) sodium citrate (Sarstedt, Nuernbrecht, Germany) and analyzed after a resting phase of 30 min. IWBPA was performed using the multiplate analyzer (Multiplate, Dyna byte Medical, Munich, Germany) which allows platelet aggregation to be determined by measuring the increase in impedance between a pair of metal electrodes immersed in diluted whole blood after the addition of commonly used agonists. The increase in impedance correlates with the quantity of platelet aggregates being deposited on the electrodes [11,12].

The intraoperative blood loss (IBL) was estimated using the suction canister volume and operative sponge weights. The operating surgeon also provided a subjective assessment of intra-operative hemostasis using a bleeding scale with 0-2. 0=expected level of difficulty, 1=higher than expected difficulty requiring change of surgical technique, and 2=diffuse oozing that is difficult to control even after modification of surgical technique. Requirement of interventions such as blood or blood products were recorded. A follow-up telephone call was made to inquire about postoperative bruising and bleeding.

Statistical analysis was performed with the SPSS/PC software package (version 16.0; SPSS, Inc, Chicago, IL, USA). A statistical significance level of 0.05 was considered significant. Continuous variables are expressed as median with interquartile range (IQR) given the lack of normal distribution of the data. Comparisons were done using Mann Whitney test. Spearman's correlation coefficient was used to determine the relationship between IWBPA values and intraoperative blood loss.

## Results

Twenty three patients were included in the study. Fourteen patients (60.8%) were Clopidogrel naive (NC group). Nine patients (39.2%) were on treatment with Clopidogrel (CC) group. 18 study participants were male (78.3%) and 5 (21.7%) were female. 57% were African-American, 33% Hispanic, 9% Caucasian and 1% were of other ethnic groups. The median age of study participants in the NC group was 52.5

years (IQR 48.75–59 years) compared to 54 years (IQR 50.5–66 years) in the CC group. The median BMI was 22.8 (IQR 20.2–28.3) in the NC group compared to 27.5 (IQR 24.7 – 30.5) in the CC group. The median duration of surgery was 64.5 minutes (IQR 57 – 84 min) in the NC group compared to 70 minutes (IQR 58–87 min) in the CC group. Median blood loss was 27cc (IQR 17–38 cc) in the NC group compared to 20 cc (IQR 11–59 cc) in the CC group. There was no statistical difference between the groups with respect to the age ( $p=0.25$ ), BMI ( $p=0.13$ ), duration of surgery ( $p=0.80$ ) and the IBL ( $p=0.45$ ).

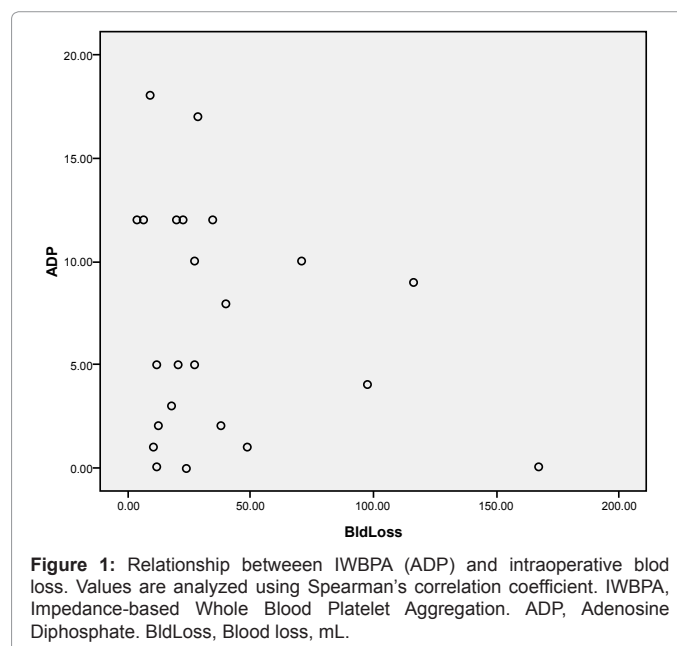
Of the 14 patients assigned to the NC group, 4 had AV grafts and 13 had AV fistula performed. In the CC group, 2 patients had AV graft while 7 patients had AV fistula performed. There was no significant difference in IBL between patients with AV graft compared to patients with AV fistula ( $p=0.3$ ).

Five of nine subjects in the CC group had IWBPA value of  $>4\Omega$  indicating inadequate inhibition of platelet aggregation at baseline while 5 of 14 of subjects in the NC group had IWBPA value of  $\leq 4\Omega$ , indicating platelet inhibition, although patients were Clopidogrel naive. IBL was not significantly different in subjects with IWBPA of  $\leq 4\Omega$  compared with those with IWBPA of  $>4\Omega$  ( $p=0.61$ ) irrespective of Clopidogrel status.

There was no correlation between IWBPA value (ADP status) and blood loss ( $r=-0.19$ ,  $p=0.37$ ) (Figure 1). Two of nine patients (22%) in the CC group and one of fourteen patients (0.07%) in the NC group were classified as having higher than expected difficulty with hemostasis requiring change of surgical technique (level 1 difficulty). No study participants developed postoperative bruising or bleeding or required blood or blood product transfusion.

## Discussion

Point of care testing to assess platelet inhibition is generally helpful when determining the degree of platelet inhibition and is therefore efficacious after APT therapy. In the peri-operative setting, these tests have the potential to help physicians with identification of patients at risk of increased perioperative blood loss as a result of their platelet aggregation status. Patients with IWBPA values greater



**Figure 1:** Relationship between IWBPA (ADP) and intraoperative blood loss. Values are analyzed using Spearman's correlation coefficient. IWBPA, Impedance-based Whole Blood Platelet Aggregation. ADP, Adenosine Diphosphate. BldLoss, Blood loss, mL.

than  $4\Omega$  indicating sub optimal platelet inhibition are thought to be at low risk for bleeding and can therefore safely undergo surgery. In this study, intra-operative blood loss (IBL) was not different in subjects with IWBPA values above or below  $4\Omega$  and hence, no correlation was found between IWBPA value and IBL. Additionally, no participants developed postoperative bruising or hematoma, and no blood or blood products were given.

Several studies have suggested that there may be differences in individual responsiveness to clopidogrel [13,14]. Impedance aggregometry has also been suggested as a useful tool in differentiating clopidogrel responders from non-responders and also as a guide for dose titration [5]. For this purpose, this optimal dose will be the dose that prevents thrombosis, and does not increase the risk of bleeding.

This study did not establish a relationship between the level of IWBPA values and peri-operative blood loss. A comparison of IWBPA status in subjects treated with and continuing treatment with clopidogrel and patients without prior exposure to clopidogrel showed no significant differences in IBL. Interestingly, 5 of 9 subjects in the CC group had IWBPA measurements consistent with inadequate inhibition of platelet aggregation at baseline while 5 of 14 of subjects with no history of treatment with clopidogrel had evidence of platelet inhibition by IWBPA. A review of the medication history on these subjects did not show evidence of co-administration of other medications such as aspirin or non steroidal anti-inflammatory drugs that could alter test results.

A confounding factor in this study is the influence of uremia on the coagulation status of our subjects with end stage renal disease (ESRD). Although, all subjects underwent hemodialysis on the day prior to surgery or on the morning of surgery, azotemia induced platelet dysfunction may have altered the IWBPA readings. Hemodialysis may partially correct, but not eliminate the intrinsic platelet abnormalities and impaired platelet-vessel wall interaction present in ESRD. The observed wide-spread individual variation in platelet inhibition irrespective of clopidogrel therapy likely reflects the baseline platelet inhibition influenced by ESRD.

Our choice of ESRD patients undergoing extremity surgery highlights the difficulty of implementing a protocol evaluating continuing treatment with anticoagulants and antiplatelet agents in patients undergoing surgery. To minimize risk in the event of excessive bleeding, surgery on an extremity was studied so as to facilitate early detection and treatment of potential excessive bleeding, including the ability to use simple pressure application. Given the increased prevalence of diseases requiring antiplatelet therapy in ESRD, these patients provide the majority of patients undergoing extremity surgery with easy access to the surgery site in the case of excessive bleeding.

Although this study did not find a relationship between IWBPA scores and clopidogrel use, several studies using point of care aggregometry have shown a therapeutic window for Clopidogrel [13,14]. These studies excluded patients with chronic renal disease and peri-operative patients. A limitation of our study is therefore the use of subjects with ESRD.

In summary, continued peri-operative treatment with clopidogrel did not result in significantly higher IBL or postoperative bruising compared to patients never treated with clopidogrel. This pilot study suggests that upper extremity access surgery could be performed

without the interruption of clopidogrel therapy. There was no correlation between IWBPA values and IBL. Based on these findings, IWBPA testing is a poor predictor of peri-operative blood loss in clopidogrel treated ESRD patients. Future studies are needed to assess platelet inhibition drug therapy in the ESRD population.

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