British Journal of Anaesthesia **102 (4):** 492–8 (2009)
doi:10.1093/bja/aep039

BJA

CLINICAL PRACTICE

Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by Thrombelastography® Platelet Mapping™

T. C. Collyer[1]*, D. J. Gray[2], R. Sandhu[2], J. Berridge[3] and G. Lyons[2]

[1]Academic Unit of Anaesthesia, Royal Perth Hospital, Perth, Australia. [2]Department of Anaesthesia, St James's University Hospital, Leeds, UK. [3]Department of Anaesthesia, Leeds General Infirmary, Leeds, UK

**Corresponding author. E-mail: tomcollyer@doctors.org.uk*

Background. Increasing numbers of patients prescribed clopidogrel and aspirin are presenting for non-elective surgery. No consensus on the timing of surgery exists after withdrawal of antiplatelet and tests of platelet function are not routinely available. The Thrombelastography® Platelet Mapping™ (TEG-PM) assay is designed to assess platelet inhibition secondary to antiplatelet therapy. We assessed its ability to detect platelet inhibition in preoperative acute surgical patients.

Methods. We conducted a prospective observational study in three groups of preoperative patients: those taking clopidogrel or aspirin up to admission, and a control group. TEG-PM was performed on the day of admission and alternate days until surgery.

Results. Mean (SD) platelet thromboxane A_2 receptor inhibition in the control group was 17.5% (23.8) (n=20), 52.6% (32.3) (n=18) in the aspirin group, and 31.9% (27.6) (n=21) in the clopidogrel group ($P<0.01$). Mean (SD) platelet adenosine diphosphate (ADP) receptor inhibition in the control group was 47.8% (18.9) (n=20), 52.6% (19.7) (n=18) in the aspirin group, and 71.5% (18.4) (n=21) in the clopidogrel group ($P<0.01$). Among the clopidogrel group awaiting surgery, mean platelet ADP channel inhibition decreased on day 3 to 67.1% (24.7) (n=11), 48.8% (24.4) (n=4) on day 5, and 36.1% (15.9) (n=2) on day 7 (P=0.57).

Conclusions. TEG-PM can identify statistically significant platelet inhibition after antiplatelet therapy; however, the overlap in platelet receptor inhibition between the three groups is likely to limit the clinical usefulness of this test.

Br J Anaesth 2009; **102**: 492–8

Keywords: blood, anticoagulation, aspirin; blood, coagulation; blood, platelets; measurement techniques, Thrombelastograph™

Accepted for publication: February 3, 2009

The thienopyridine, clopidogrel, is an antiplatelet drug known to work by non-competitive inhibition of the platelet adenosine diphosphate (ADP) ($P2Y_{12}$) receptor resulting in reduced platelet aggregation.[1] Acetylsalicylic acid (aspirin) is a non-competitive, irreversible antagonist of the enzyme cyclooxygenase 1 (COX 1) that inhibits the synthesis of prostaglandins and thromboxane A_2 (TxA_2) from arachidonic acid (AA). Reduced concentrations of TxA_2 lead to inhibition of platelet aggregation and adhesiveness. The proven clinical efficacy of both clopidogrel and aspirin in the prevention of cardiovascular and cerebrovascular events,[2–6] has led to increasing numbers of patients presenting for urgent surgery while prescribed these antiplatelet agents. This gives rise to a dilemma; continuation of antiplatelet therapy could lead to a higher chance of surgical haemorrhage[7–9] and limits, or prevents, regional anaesthetic techniques for fear of epidural or spinal haematoma.[10 11] However, cessation of antiplatelet agents before surgery can lead to an increased risk and severity of acute coronary syndrome.[12 13]

Traditional platelet assessment has included the platelet count, which gives a quantitative not qualitative result, and the bleeding time. The bleeding time has been shown to be inconsistent, insensitive, and operator-dependent.[14] Laboratory-based methods used to assess the degree, and variability, of platelet ADP inhibition rely upon specialist

techniques and are not routinely available in clinical practice.[15] As a result, point-of-care monitors of platelet function have recently been developed and include the Thrombelastography® Platelet Mapping™ assay (TEG-PM) (Haemoscope Corporation, Niles, IL, USA), a novel modification designed to look specifically at functional platelet inhibition secondary to clopidogrel and aspirin therapy. It has been shown to correlate with optical platelet aggregation which was the main *ex vivo* assay of platelet function used in the clinical studies of clopidogrel.[15 16]

We aimed to assess the ability of the TEG-PM to detect platelet inhibition secondary to clopidogrel and aspirin therapy in acute patients awaiting surgery.

Methods

After approval from local ethics committee for a prospective observational study and informed written consent, patients presenting for orthopaedic trauma surgery and acute general surgery were recruited in the Leeds Teaching Hospitals, between February 2006 and December 2006. Three groups were included in the study: a control group, an aspirin group, and a clopidogrel group. The control group consisted of patients who, before admission, had taken no antiplatelet agents. The aspirin and clopidogrel groups were comprised of patients who, before admission, had taken regular aspirin or clopidogrel that was discontinued by the admitting clinician. Patients in the aspirin and clopidogrel group were not on dual-antiplatelet therapy. Patients prescribed warfarin, i.v. heparin, treatment doses of low-molecular weight heparins (LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and any other antiplatelet agents were excluded. Patients with a known coagulopathy were excluded, as were patients with a full blood count, activated partial thromboplastin time (APTT), prothrombin time, and blood urea outside the laboratory reference range. Patients administered prophylactic doses of LMWH, enoxaparin, were not excluded as the utilization of heparinase TEG® cups for the citrated blood sample (channel 4) circumvented their effect. The heparinase TEG® cup contains 2.0 IU of lyophilized Heparinase I, which inactivates LMWH, including enoxaparin. All patients receiving LMWH in the study received enoxaparin according to hospital guidelines. Patients on statins were not excluded. The patients' age, sex, and weight were recorded. Patients were followed-up to the day of surgery and left the study upon completion of surgery.

The study was observational in nature and did not influence the timing of surgery. Blood samples for the TEG-PM were obtained by unblinded investigators starting on the day of admission and then on alternate days up to the day of surgery. Each blood sample required collection of 10 ml of blood from a single clean puncture of a forearm vein. A previously uncannulated vein was selected and a loose fitting tourniquet was used. The blood was collected into a 3.5 ml test tube containing sodium citrate 0.109 M (Vacuette™) and a 4.0 ml test tube containing lithium heparin 14.5 U ml^{-1} (Vacuette™). The blood samples were rested for 30 min and then reconstituted with appropriate reagents according to the manufacturer's protocol (Haemosope Corporation, TEG™ Guide to Platelet Mapping, monitor antiplatelet therapy). This process is summarized in Table 1. Two TEG® 5000 coagulation monitors with plain TEG® cups and pins were used, with the exception of heparinase cups in patients who had received a prophylactic dose of LMWH as discussed. Utilization of two thrombelastographs enabled all four channels to run in parallel.

Table 1 Constituents of the TEG® Platelet Mapping™ assay Channels. Channel 1 creates a fibrin mesh with no activated platelets. Channels 2 and 3 create a fibrin mesh with platelets stimulated only by the ADP and TxA_2 receptors, respectively. Channel 4 is a standard TEG® with maximally stimulated platelets. *Activator F™, reptilase and Factor XIII; †ADP, final concentration in TEG cup=2 μM; ‡AA, final concentration in TEG cup=1 mM

	Channel 1 Fibrin	Channel 2 ADP	Channel 3 TxA_2	Channel 4 Standard
Heparinized blood (μl)	360	360	360	0
Kaolin-activated citrated blood (μl)	0	0	0	360
Activator F™ (μl)*	10	10	10	0
ADP (μl)†	0	10	0	0
AA (μl)‡	0	0	10	0
$CaCl_2$ (0.1%) (μl)	0	0	0	20

TEG® gives both numerical and graphical information concerning the rate and strength of clot formation. Maximal clot strength is represented by the maximum amplitude (MA) and is determined by the binding of activated platelets to a fibrin mesh. In order to demonstrate the individual contribution of the fibrin meshwork to clot strength (MA_{Fibrin}), 360 μl of heparinized blood is added to 10 μl of Activator F (Reptilase and Factor XIIIa) in channel 1. The contribution of platelets, as activated by ADP or AA, to clot strength are assessed in channels 2 (MA_{ADP}) and 3 (MA_{AA}), respectively. This is performed by the addition of 360 μl of heparinized blood to 10 μl of Activator F and either 10 μl of ADP (final concentration 2 μM) in channel 2 or 10 μl of AA (final concentration 1 mM) in channel 3. Channel 4 represents maximal clot strength with maximally stimulated platelets. Kaolin-activated citrated blood 360 μl is added to calcium chloride 0.2 M, 20 μl ($MA_{Thrombin}$).[17]

Percentage platelet inhibition is defined by the extent of non-response of the platelet ADP or TXA_2 receptor to the exogenous ADP and AA as measured by TEG MA. The percentage platelet aggregation to agonist can be calculated by: $[(MA_{ADP/AA} - MA_{Fibrin})/(MA_{Thrombin} - MA_{Fibrin}) \times 100]$. Percentage platelet inhibition is thus 100% − %platelet aggregation. This calculation is performed by the TEG-PM software. Similarly, the percentage inhibition

resulting from the antiplatelets clopidogrel and aspirin can be calculated.[17] Percentage platelet inhibition was recorded as our primary endpoint. Two examples of TEG-PM traces, one showing 90% platelet ADP receptor inhibition and the second showing 0% platelet ADP receptor inhibition, are shown in Figures 1 and 2, respectively.

The use of regional anaesthetic techniques and any associated complications were recorded. Requirement for blood transfusion and the number of units transfused were recorded.

In order to assess a difference between the platelet receptor inhibition in the separate groups, using the platelet mapping assay, and achieve an α error of 0.05 and a β error of 0.8, it was calculated that 20 patients per group would be required (EpiCalc 2000, www.brixtonhealth.com). This was calculated from the test data using platelet ADP receptor inhibition from subjects not exposed to antiplatelet agents compared with subjects exposed to clopidogrel.[18] Raw MA data from the TEG-PM and overall percentage platelet inhibition data from the TEG-PM were assessed for normality using the Kolmogorov–Smirnov test. This proved the data to be parametric. Subsequent assessment used one-way ANOVA with Bonferonni's multiple comparison test. Patient characteristics were presumed to be parametric and were assessed using one-way ANOVA. Comparison of platelet ADP receptor inhibition in the clopidogrel group, on alternate days, was performed using the unpaired *t*-test. Statistical analysis was performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

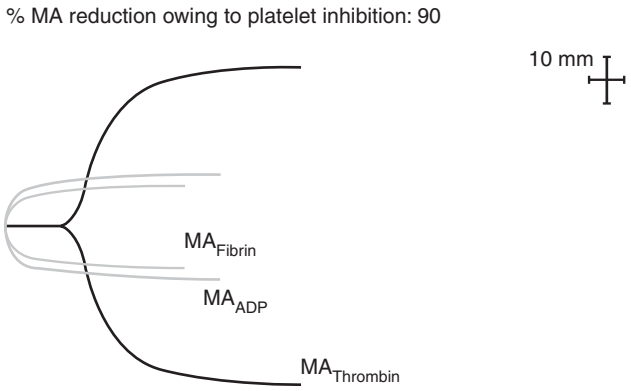

Fig 1 TEG® Platelet Mapping™ result. The trace represents a patient who has recently ceased clopidogrel and has a respective 90% platelet ADP receptor inhibition. The *x*-axis represents time and the *y*-axis millimetres. $MA_{Thrombin}$, maximal amplitude with thrombin-stimulated platelets and fibrin meshwork; MA_{ADP}, maximal amplitude with ADP-stimulated platelets and fibrin meshwork; MA_{Fibrin}, maximal amplitude with fibrin meshwork.

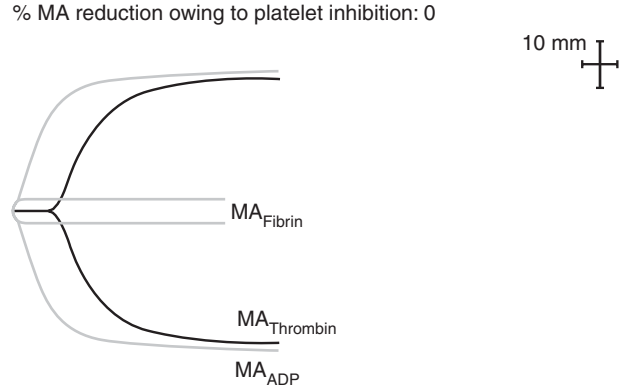

Fig 2 TEG® Platelet Mapping™ result. The trace represents a patient who before surgery did not take any antiplatelet agent. The tracings show 0% platelet ADP inhibition. The *x*-axis represents time and the *y*-axis millimetres. $MA_{Thrombin}$, maximal amplitude with thrombin-stimulated platelets and fibrin meshwork; MA_{ADP}, maximal amplitude with ADP-stimulated platelets and fibrin meshwork; MA_{Fibrin}, maximal amplitude with fibrin meshwork.

Results

Fifty-nine patients were recruited; 20 in the control group, 18 in the aspirin group, and 21 in the clopidogrel group. Patient characteristics with their haematological and coagulation variables are presented in Table 2. No significant differences between the three groups were observed. Mean time from admission to surgery was 1.3 days, 2.1 days, and 4.5 days for the control, aspirin, and clopidogrel groups, respectively. Table 3 summarizes operative procedures in the three groups. Prophylactic doses of enoxaparin, 40 mg, were administered to seven patients in both the control and aspirin group and two patients in the

Table 2 Patient characteristics and summary of their haematological and coagulation variables, median (range) for age, mean (SD) and count as appropriate. INR, international normalized ratio

	Control group (n=20)	Aspirin group (n=18)	Clopidogrel group (n=21)
Age (yr)	75 (40–92)	80.5 (52–91)	74 (41–90)
Sex (F:M)	13:7	12:6	13:8
Weight (kg)	70.6 (9.4)	69.8 (12.8)	68 (11.6)
Haemoglobin (g dl^{-1})	13.3 (1.5)	12.4 (1.9)	12.3 (1.5)
Platelets ($\times 10^9$ litre^{-1})	266.4 (151.3)	251 (77.7)	267.3 (76.1)
INR	1.1 (0.2)	1.2 (0.1)	1.1 (0.1)
APTT (s)	32.7 (5.8)	31.8 (4.6)	31.3 (4.0)
Fibrinogen (g litre^{-1})	>4.5	>4.5	>4.5

Table 3 Surgical procedures performed in patient groups

	Control group (n=20)	Aspirin group (n=18)	Clopidogrel group (n=21)
Surgical repair of fractured neck of femur	10	12	11
Open reduction and internal fixation of lower limb including pelvis	4	2	1
Open reduction and internal fixation of upper limb	4	2	5
Acute general surgery	2	2	4

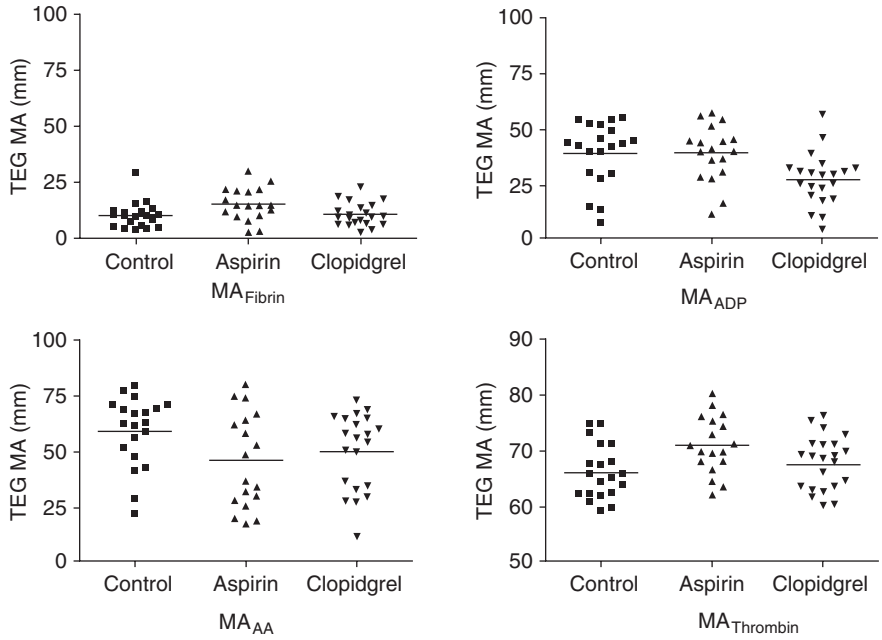

Fig 3 Scatter plot of raw thrombelastography maximal amplitude (TEG MA) data of the MA_{Fibrin}, MA_{ADP}, MA_{AA}, and $MA_{Thrombin}$ channels from Thrombelastography® Platelet Mapping™. The thick horizontal line represents the mean with all the individual data points shown.

clopidogrel group. Two patients in the control group were prescribed a statin compared with 14 in the aspirin group and 18 in the clopidogrel group. The constituent channel data for MA_{Fibrin}, MA_{ADP}, MA_{AA}, and $MA_{Thrombin}$ are shown in Figure 3.

On day 1, mean (SD) percentage platelet TxA_2 receptor inhibition in the control group was 17.5% (23.8) (n=20) compared with 52.6% (32.3) (n=18) in the aspirin group and 31.9% (27.6) (n=21) in the clopidogrel group ($P<0.01$; Fig. 4). Further evaluation with Bonferonni's multiple comparison test shows that there is a significant difference between the control and aspirin groups ($P<0.01$) but not between the control and clopidogrel groups ($P>0.05$) or the aspirin and clopidogrel groups ($P>0.05$).

On day 1, mean (SD) percentage platelet ADP receptor inhibition in the control group was 47.8% (18.9) (n=20) compared with 52.6% (19.7) (n=18) in the aspirin group, and 71.5% (18.4) (n=21) in the clopidogrel group ($P<0.01$; Fig. 5). Further analysis with Bonferonni's multiple comparison test shows that there are significant differences between the control and clopidogrel groups ($P<0.01$) and the clopidogrel and aspirin groups ($P<0.01$), but not between the control and aspirin groups ($P>0.05$).

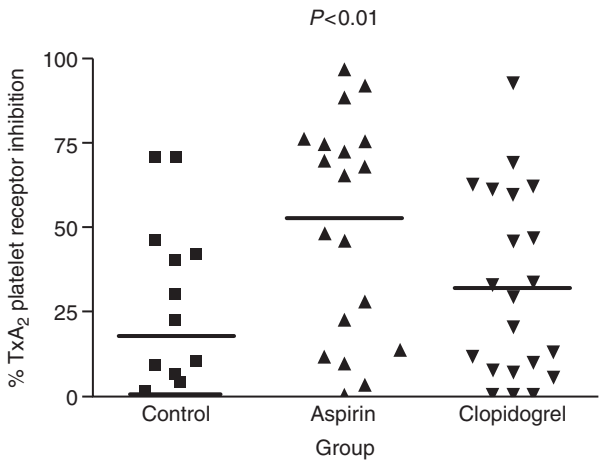

Fig 4 Scatter plot of thromboxane A_2 (TxA_2) receptor inhibition in all groups, day 1 after antiplatelet cessation. The horizontal lines represent the mean with all individual data points shown. P-value was calculated by one-way ANOVA.

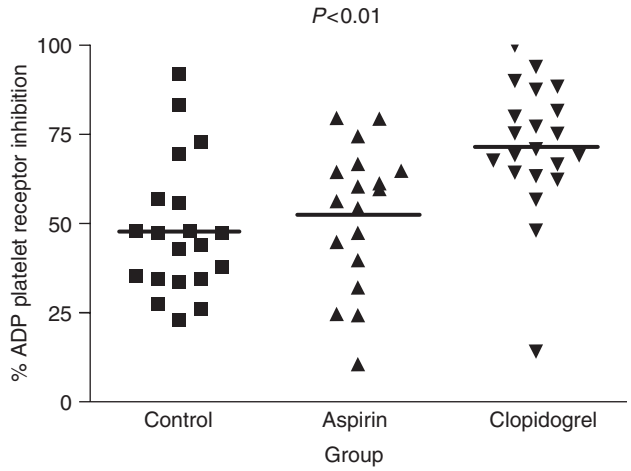

Fig 5 Scatter plot of platelet adenosine diphosphate (ADP) receptor inhibition in all groups, day 1 after antiplatelet cessation. The horizontal lines represent the mean with all individual data points shown. P-value was calculated by one-way ANOVA.

In the clopidogrel patients awaiting surgery, mean (SD) platelet ADP receptor inhibition fell from 71.5 (18.4) on day 1 to 67.1% (24.7) (n=11) on day 3, 48.8% (24.4) (n=4) on day 5 and 36.1% (15.9) (n=2) on day 7. There was no statistical difference between day 1 and day 3 platelet ADP receptor inhibition (P=0.57). No further analysis of ADP receptor recovery was performed because of the small sample sizes and preliminary nature of these data.

Two patients in the control and clopidogrel groups received femoral nerve blocks. Nine patients in the aspirin group received regional anaesthetic techniques: five spinal anaesthetics, two lumbar plexus blocks, and two interscalene nerve blocks. Two patients in the clopidogrel group received femoral nerve blocks. There were no reported complications.

One patient in each group suffered a perioperative cardiovascular event. One patient in the control group had a pulmonary embolus during their operation with ADP and TxA_2 receptor inhibition of 91.8% and 45.7%, respectively. The computed tomography scan was consistent with a thrombo-embolic event rather than fat or cement emboli. One patient in the aspirin group had a myocardial infarction 2 h after their operation, with ADP and TxA_2 receptor inhibition of 32.2% and 45.9%, respectively. One patient in the clopidogrel group had a myocardial infarction during their operation, with ADP and TxA_2 receptor inhibition of 14.1% and 0%, respectively.

Only one patient, in the aspirin group, required a blood transfusion during operation (two units of pack red cells).

Discussion

TEG-PM has evolved because of the limitations of standard TEG® to assess platelet function in patients who are prescribed clopidogrel and aspirin therapy. Normally activation of either the platelet ADP or TxA_2 receptor results in activation of the platelet GP IIb/IIIa receptor, with resulting platelet activation. However, standard TEG® MA is largely dependent on direct thrombin activation of the GP IIb/IIIa receptor. This bypasses the less-potent platelet activators ADP and TxA_2, making assessment of their contribution to platelet activation impossible.[17] The TEG-PM is designed specifically to overcome this problem and enables assessment of platelet inhibition secondary to inhibition of the platelet ADP and TxA_2 receptors. The potential role of this novel technology in the care of acute surgical patients is, as yet, unexplored.

The results of this prospective observational study in acute surgical patients show that the TEG-PM is able to identify statistically significant inhibition of the platelet ADP receptor after clopidogrel therapy and statistically significant inhibition of the platelet TxA_2 receptor after aspirin therapy.

Although statistically unproven, a trend towards recovering platelet function in acute surgical patients withdrawing from clopidogrel therapy was observed using the TEG-PM. These results should be treated with due caution. The study was not powered to test the ability of the TEG-PM to assess the time course of recovery of platelet function. The small sample size renders the results preliminary and of no clinical consequence. Future studies looking at larger populations withdrawing from antiplatelet agents may add further value to this observation.

Our results have demonstrated a spread of platelet ADP and TxA_2 receptor inhibition in the clopidogrel and aspirin groups, respectively. This was predictable given both the sample sizes and the knowledge that platelet inhibition is not uniform among patients prescribed either antiplatelet therapy.[16] In addition, both clopidogrel and aspirin resistance are well-reported.[19–22] However, an unexpected degree of platelet ADP and TxA_2 receptor inhibition was seen in all the groups. The cause for this is unknown. One might hypothesize that despite a targeted effect upon one receptor, the action of clopidogrel and aspirin has an indirect effect upon the other receptor, such that platelet receptor activation is interdependent. This does not, however, explain the finding of ADP and TxA_2 receptor inhibition in the control group. Variability of ADP and TxA_2 receptor inhibition in patients not otherwise taking antiplatelet medication has previously been reported.[23] Bochsen and colleagues performed TEG-PM in 43 healthy blood donors and found that platelet ADP receptor inhibition ranged from 0% to 58% and TxA_2 receptor inhibition ranged from 0% to 10%. The precise cause for this range of inhibition is not known but there is evidence that a number of factors unrelated to antiplatelet medication can affect platelet function. Examples include alcohol consumption and food types, such as garlic.[24 25] It is also possible that the concentration of the platelet receptor agonists used in the TEG-PM, ADP (2 μM), and AA (1 mM), results in sub-maximal stimulation of the platelet receptors. Higher concentrations have been shown to result in increased platelet activation in previous studies.[15] Sub-maximal stimulation would result in false-positive platelet receptor inhibition.

The ranges in the control group are greater than those reported above, at 23–92% and 0–70%, for the ADP and TxA_2 receptors, respectively. Whether the process of trauma and acute pathophysiological stress also has an effect on platelet ADP and TxA_2 receptor function is unknown. However, activation of the sympatho-adrenal axis and catecholamine release is implicated in the enhancement of platelet aggregability,[26 27] although conversely, *in vitro* platelet aggregometry studies have also shown reduced platelet ADP function in stressed patients.[28] We plan to investigate this in a further study, by comparing the concentrations of ADP and TxA_2 inhibition in our current no antiplatelet therapy group to a

matched elective group of surgical patients. Whatever the cause for the range of platelet receptor inhibition seen, such variability might ultimately limit the clinical usefulness of the test in this patient population.

In this study, TEG-PM has been used as the sole method of assessment of platelet function and has not been used in combination with a standard laboratory test of platelet function such as optical platelet aggregometry. This was because of a lack of availability at the study site. Such a comparison would have enabled an assessment of the correlation between the two tests in this particular patient population. However, this modification of TEG has previously been shown to be comparable with optical platelet aggregometry,[15 16] and superior to the PFA-100 in the assessment of platelet ADP receptor function.[16] In order to assess the assays precision, calculation of the specificity, sensitivity, and predictive values would be of benefit. However, it is currently unknown as to what level of *ex vivo* platelet receptor inhibition signifies normal or abnormal platelet function and how clinical endpoints, such as bleeding, correlate to *ex vivo* platelet receptor inhibition. Consequently, we have not calculated these measures of precision.

In conclusion, we have shown that the TEG® Platelet Mapping™ assay can demonstrate statistically significant platelet inhibition resulting from clopidogrel and aspirin therapy in acute surgical patients. Preliminary data point to a trend towards recovery of platelet function in patients withdrawing from clopidogrel therapy. The finding that patients not exposed to antiplatelet agents have a range of platelet ADP and TxA_2 receptor inhibition requires further investigation but might limit the clinical usefulness of this test. Whether the TEG® Platelet Mapping™ assay is able to provide valuable information to the anaesthetist when planning the conduct of anaesthesia and the timing of surgery currently remains uncertain.

Acknowledgement

Medicell International Ltd provided the TEG® Platelet Mapping™ assay reagents.

Funding

Leeds Teaching Hospital Trust and St James's Obstetric Anaesthetic Trust.

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