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Value of a single preoperative PFA-100® measurement in assessing the risk of bleeding in patients taking cyclooxygenase inhibitors and undergoing total knee replacement†

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Background. The usefulness of the PFA-100® in assessing the risk of bleeding in non-cardiac surgery is not clear. This study aims to examine this by correlating preoperative PFA-100® measurement with perioperative bleeding in patients receiving cyclooxygenase (COX) inhibitors.

Methods. PFA-100® with adenosine-5'-diphosphate (ADPCT) and epinephrine (EPICT) cartridges were measured before operation in consecutive patients undergoing elective total knee replacement and taking different COX inhibitors. Surgery and anaesthesia were performed by the same team using standardized techniques. Intraoperative blood loss and postoperative drain output were recorded by anaesthetists and nurses blinded to the PFA-100® measurements. Surgeons, similarly blinded, were asked to rate the quality of haemostasis. Correlation was sought between these data and PFA-100® measurements.

Results. Thirty patients were studied, involving 51 knees. Preoperative PFA-100® EPICT was correlated with drain output (r=0.30, P=0.03). The correlation becomes stronger when a 20% *in vitro* haemodiluted sample was used for measurement (r=0.42, P=0.01). Receiver-operating characteristic curve analysis using the diluted measurements [area under curve (AUC) 0.74 (95% CI 0.54–0.94)] suggested using a cut-off value of 188 s for EPICT, which will predict excessive drain output with 89% sensitivity, 54% specificity, and a likelihood ratio of 1.93. Diluted EPICT was also correlated with surgeon rating of haemostasis (r=0.36, P=0.04) although none of the measurements correlated with intraoperative blood loss.

Conclusions. Preoperative PFA-100® prolongation is correlated with increased postoperative drain output. It can be a potentially useful preoperative measurement in patients taking COX inhibitors.

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PFA-100® platelet function analyzer is a point-of-care platelet function monitor introduced in the late-1990s.[1 2] It has been used extensively to monitor the effect of aspirin[1 3] and other cyclooxygenase (COX) inhibitors[4] on platelets. It can also detect changes in platelet function related to normal and pre-eclamptic pregnancies,[5 6] hypothermia,[7] and changes caused by haemodilution with different colloids;[8] it

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is therefore highly relevant to the perioperative period. The PFA-100® has also been used successfully to monitor patients with congenital disorders of platelets or primary haemostasis, such as von Willebrand's disease.[9]

Impairment of platelet function or primary haemostasis would show up as prolonged 'closure times (CT)' on the PFA-100®. The principle of measurement of the PFA-100® has been reviewed in detail.[1 2] However, the significance of prolonged CT of the PFA-100® in terms of bleeding has not been adequately studied. Intuitively, a prolonged PFA-100® CT signifies impaired primary haemostasis and should be associated with increased risk of bleeding during general surgery. However, except for some studies in patients undergoing open heart surgery with conflicting results,[10–13] this remains largely unknown for general non-cardiac surgery.

We believe the best way to evaluate the significance of prolonged PFA-100® measurements is to observe whether normal and prolonged PFA-100® measurement results predict differently perioperative bleeding under otherwise identical conditions. These conditions should include the type of surgery performed and the surgical and anaesthetic techniques involved. The antiplatelet effect of COX inhibitors, including aspirin, is heterogeneous. Those whose platelets remain relatively unaffected are sometimes referred to as 'non-responders' to aspirin, and these patients seem to have increased risk of adverse cardiovascular events.[14] We have also observed this heterogeneity in preoperative patients receiving diclofenac.[15] We therefore performed this study to establish whether PFA-100® measurements in patients taking COX inhibitors are correlated with perioperative bleeding.

Methods

Subjects

With Institutional Review Board approval and written informed consent, patients scheduled for elective total knee replacement and receiving different COX inhibitors regularly for analgesia were recruited. We recruited patients taking COX inhibitors with different COX-1 and COX-2 selectivity,[16] which we expected to provide us with a wider range of preoperative PFA-100® measurements, and therefore well-suited for establishing correlation between these measurements and bleeding. Non-Chinese patients, patients undergoing revision surgery, patients receiving other antiplatelet drugs, dietary supplements or herbal preparations, and patients who had other known disorders of haemostatic function were excluded. Patients received no unfractionated or low molecular heparin perioperatively, which is our routine local practice. Patients were allowed to take all regular medications, including the COX inhibitor, on the morning of surgery. The dose and last intake time was verified with the patient and against the drug administration chart in the ward before blood sampling.

Preoperative measurements

Upon arrival in the operation theatre and before anaesthesia was started, 15 ml of whole blood was collected from an antecubital vein without stasis and subjected to the following tests:

(1) Complete blood count, prothrombin time (PT), and activated partial thromboplastin time (aPTT)
(2) Fibrinogen concentration (FIB)
(3) Platelet function analyzer (PFA-100®; Dade Behring, Inc., Deerfield, IL, USA).

Platelet function analyzer

Because considerable blood loss usually occurs during total knee replacement, patients will receive i.v. fluids to maintain circulating volume and will invariably be haemodiluted to different extents. In this study we considered it necessary to correlate not only the patients' preoperative PFA-100® measurement under physiological conditions, but also the PFA-100® measurement during haemodilution, to reflect clinical practice more closely. Therefore, PFA-100® was performed both with and without *in vitro* haemodilution to simulate the invariable haemodilution that develops *in vivo* after surgery. We did not actually collect another sample at the end of surgery because the aim of this study was to evaluate the usefulness of tests that could be performed before operation, and which might be useful in guiding preoperative management or risk stratification.

Whole blood samples were collected into 3.8% (0.129 M) buffered sodium citrate tubes (Vacutainer®, Becton Dickinson, Franklin Lakes, NJ, USA). This was then divided into two equal aliquots. One aliquot was measured without dilution and the other aliquot was arbitrarily haemodiluted by 20% with saline *in vitro*. Citrated whole blood of 800 μl from both aliquots were then measured in the PFA-100® with both collagen/epinephrine (COL/EPI) and collagen/ADP (COL/ADP) cartridges, which contain a membrane coated with 2 μg of equine Type I collagen and 10 μg epinephrine bitartrate or 2 μg of equine Type I collagen and 50 μg adenosine-5'-diphosphate (ADP), respectively. For all PFA-100® measurements, non-closure (i.e. failure of the aperture in the cartridge to close after 300 s) was designated a maximum value of 300 s. All measurements were performed by a single technician (S.F.T.) who was blinded to the blood loss data.

Other haematology tests

Complete blood counts were performed on an automated cell counter (Gen-S®, Beckman-Coulter, USA). PT and aPTT were performed immediately after collection of blood samples and centrifugation at 3000 rpm for 10 min

on an automated coagulometer (MDA-180®, Organon-Technika, USA). Fibrinogen concentration was assayed by Clauss method using a semi-automated coagulometer (Cobas Fibro®, Roche, Switzerland).

Surgery and anaesthetic management

All the patients underwent total knee replacement under a standardized combined general (GA)+regional anaesthesia (RA) with O_2/N_2O and isoflurane supplemented with femoral nerve block and i.v. morphine. Standard fluid replacement and transfusion protocols were followed and normothermia was maintained throughout surgery. Induced hypotension was not used. The operation was also performed in a standardized manner using the Insall approach for arthrotomy. After appropriate dissection, tibial cut, anterior and posterior distal femoral cut, and patella cut, a tourniquet was applied briefly to cover the cementation period and the knee prostheses were inserted with bone cement. The wound was then closed with drain. Both the anaesthesia and the surgery were performed by the same anaesthetists (K.F.J.N. and J.C.L.) and the same surgeons (W.M.T. and K.Y.C.).

Blood loss assessment

Intraoperative blood loss was recorded carefully by the anaesthetists (K.F.J.N. and J.C.L.) weighing sponges and measuring suction bottles. At the end of surgery, the surgeons (W.M.T. and K.Y.C.) would provide an assessment of the ease of haemostasis during operation on a scale 1–10, with 1 being the easiest haemostasis, and 10 for extreme difficulty in achieving surgical haemostasis. For patients undergoing bilateral knee replacements, these data were collected separately for each knee. After operation, the volume collected in each wound drain was measured every hour for 24 h by nurses. All anaesthetists, surgeons, and nurses involved in the estimation of blood loss were blinded to the PFA-100® measurement results.

Statistics

Correlations were sought between intraoperative blood loss, surgeon assessment of ease of haemostasis, and postoperative drain output in the first 24 h as dependent variables, and the preoperative PFA-100® measurements with or without haemodilution as the independent variables. To seek correlations, scattergraphs were drawn and visually inspected before subjecting the data to analysis by computer software. In addition, receiver-operating characteristic (ROC) curves were drawn for different cut-off values of PFA-100® CTs to evaluate the performance of PFA-100® as a predictor of excessive bleeding.

To detect a moderate correlation (correlation coefficient of 0.4) between PFA-100® measurements and blood loss, at an α-error level of 0.05 and a β-error level of 0.2, 46 knees are required.

Table 1 Patient characteristics. All values are mean (range), mean (SD) or count (%). Hb, haemoglobin concentration; PT, prothrombin time; aPTT, activated partial thromboplastin time; FIB, fibrinogen concentration

Patient characteristics ($n=30$)	
Age (yr)	66.3 (45–79)
Female	23 (77)
Body weight (kg)	65.2 (13.0)
Height (m)	1.55 (0.07)
BMI (kg m^{-2})	27.4 (5.3)
Hb (g dl^{-1})	12.6 (1.3)
PT (s)	11.5 (0.7)
aPTT (s)	28.0 (2.7)
Platelet count ($\times 10^9$ litre^{-1})	278 (77)
FIB (mg dl^{-1})	263 (104)
Bilateral knee replacement	21 (70)

Table 2 Details of surgery. All values are mean (SD) or count (per cent). *Surgeon rating was classified as difficult for scores >5, and as easy for scores ≤5. †For bilateral replacements, the total number of units transfused was divided by two to give the per knee requirement. ‡Median (range)

Details of surgery ($n=51$ knees)	
Total intraoperative blood loss (ml)	407 (221)
Operative time (min)	136 (44)
Surgeon rated easy haemostasis*	32 (63)
Drain output in first 24 h after operation (ml)	261 (105)
Intraoperative crystalloid infused (ml)	1311 (378)
Intraoperative colloid infused (ml)	353 (295)
Intraoperative red cell transfusion (unit)†,‡	0.5 (0–3.5)

ROC analysis was performed using GraphPad Prism 4.0 (GraphPad Software, Inc., San Diego, CA, USA) and sample size calculation using MedCalc 10.1 (MedCalc Software, Belgium). All other statistics were performed using Statistica 4.5 for Windows (Statsoft Inc., USA). $P<0.05$ was considered statistically significant.

Results

Thirty patients were studied. Twenty-one patients underwent bilateral knee replacements, therefore there were data from a total of 51 knees for analysis. Most (21) patients were taking diclofenac, five were taking piroxicam, two were taking naproxen, and one each was taking indomethacin and ibuprofen, respectively. Patient characteristics and perioperative blood loss are summarized in Tables 1 and 2.

Similar to our previous findings in patients taking diclofenac,[15] the patients exhibit a wide range of before operation CTs using the COL/ADP cartridge (ADPCT) and the COL/EPI cartridge (EPICT) on the PFA-100®. The mean ADPCT is 122 s (95% CI 105–139); and that of EPICT is 195 s (95% CI 173–217). *In vitro* haemodilution for PFA-100® was successfully carried out in 37 samples for ADPCT and 35 samples for EPICT. Failure to measure in the rest was usually because of inaccuracies in the dilution process, or technical difficulty with the measurement

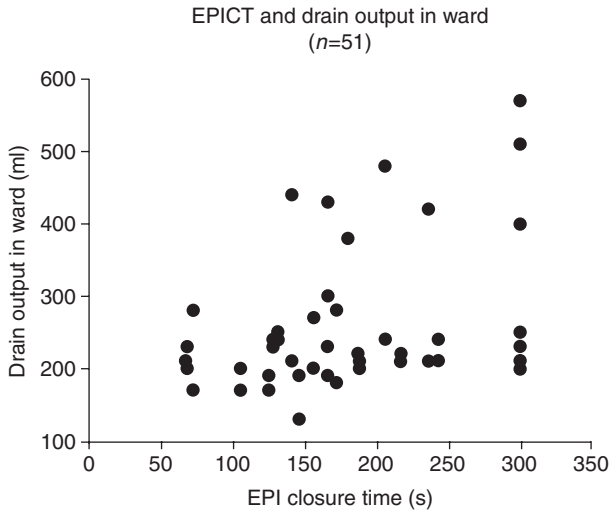

Fig 1 Correlation of preoperative EPICT measured by the PFA-100®, with drain output in the first 24 h after operation (n=51, r=0.30, P=0.03). EPICT refers to PFA-100® closure times measured with epinephrine cartridge.

process, such as flow obstruction or insufficient sample volume to carry out dilution.

There was no correlation with or without haemodilution, between the preoperative PFA-100® measurements and intraoperative blood loss. However, wound drain output in the first 24 h was significantly correlated with preoperative EPICT (Fig. 1). Upon *in vitro* haemodilution, the correlation was stronger, and drain output also correlated with ADPCT (Fig. 2). In addition to correlating with postoperative drain output in the first 24 h, preoperative haemodiluted EPICT also correlated with the surgeons' subjective and blinded rating of haemostasis as easy or difficult (r=0.36, P=0.04). There was no correlation between intraoperative blood loss and postoperative drain output (r=0.13, P=0.38).

Using the top 25 percentile of drain output in our study (270 ml) to define excessive blood loss from the drain in the first 24 h after operation, ROC analysis confirmed that the best prediction can be achieved using the preoperative EPICT with 20% haemodilution (Fig. 3 and Table 3). For this measurement, the best cut-off value is 188 s, which can give a sensitivity of 89%, specificity of 54%, and positive likelihood ratio of 1.93 in predicting excessive postoperative drain output. The diagnostic performance of using the cut-off of 188 s, compared with that of the conventional upper normal limit of 165 s and the maximal prolongation of 300 s is summarized in Table 4.

Except preoperative PT that correlated with intraoperative blood loss only, no other preoperative blood tests, such as platelet count, aPTT, and fibrinogen concentration, nor intraoperative mean arterial pressure and body temperature show any correlation with either intraoperative or postoperative blood loss.

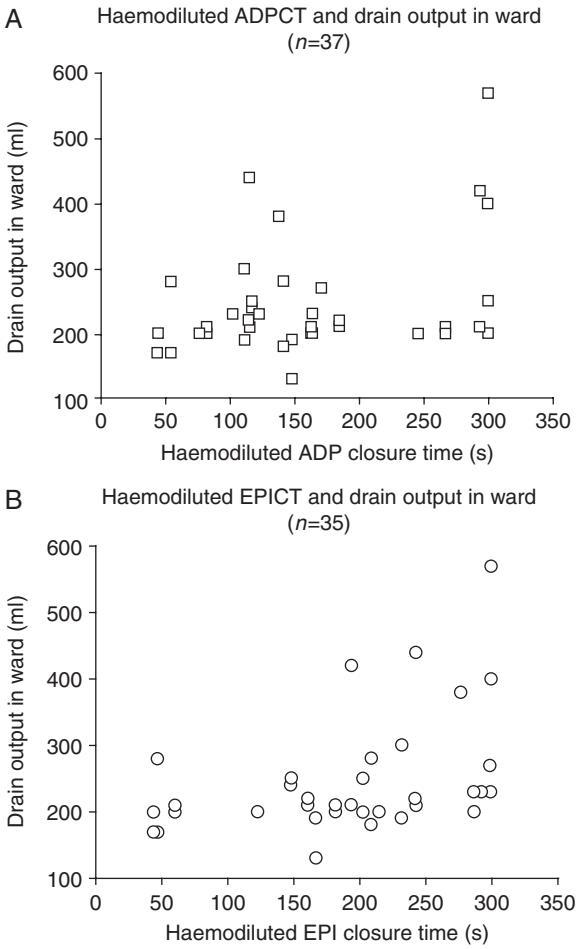

Fig 2 Correlation of preoperative (A) ADPCT (n=37) and (B) EPICT (n=35) with 20% haemodilution *in vitro*, measured using the PFA-100® with drain output in the first 24 h after operation. (A) r=0.35, P=0.04; (B) r=0.42, P=0.01. ADPCT and EPICT refer to PFA-100® closure times measured with adenosine-5'-diphosphate and epinephrine cartridges, respectively.

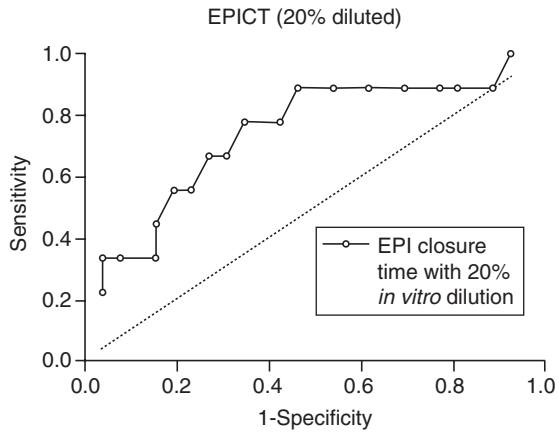

Fig 3 Receiver-operating characteristic (ROC) curve for predicting excessive drain output in the first 24 h after operation, using the preoperative EPICT with 20% haemodilution *in vitro* [area under the curve, 0.74 (95% CI 0.54–0.94)]. Excessive output is defined as output above the top 25% in this study, which is 270 ml.

Discussion

Our study confirms the usefulness of a single preoperative PFA-100® measurement in predicting postoperative drain output in patients who are taking COX inhibitors and undergoing total knee replacement. As far as we know, this is the first study in the literature which demonstrates the usefulness of the PFA-100® in this aspect.

Koscielny and colleagues[17] retrospectively reviewed the preoperative PFA-100® in more than 5000 surgical patients and found that those with abnormal results received more transfusions. However in that retrospective review, neither the type of surgery nor the anaesthetic and surgical techniques are specified. The actual blood loss and the transfusion trigger are also unknown. Similarly, the value of the PFA-100® in predicting intraoperative and postoperative blood loss in open heart surgery has produced conflicting results.[10–13] The design of this study allows a more stringent evaluation of the PFA-100® in relation to perioperative bleeding in non-cardiac surgery. Although the best diagnostic performance comes from a diluted sample in this study, we believe that this arbitrary 'treatment' of the sample allows the best approximation of intraoperative and postoperative conditions. Taking into account that saline dilution changes the concentration of coagulation factors and platelets, saline and not plasma dilution is used in this study as this reflects better the actual clinical situation. However, our dilution results may or may not approximate dilution by other crystalloids, such as Ringer's lactate which may be used more commonly.

Table 3 Diagnostic performance of different test for predicting postoperative drain output in excess of 270 ml (top 25% percentile) (area under receiver-operating characteristic curves, aROC). Values in parentheses are 95% CI. ADPCT and EPICT refer to PFA-100® closure times measured with adenosine-5'-diphosphate and epinephrine cartridges, respectively. *0.8 closure times are closure times measured after *in vitro* 20% haemodilution with saline

Test	aROC
0.8EPICT (s)*	0.74 (0.54–0.94)
0.8ADPCT (s)*	0.58 (0.35–0.80)
EPICT (s)	0.56 (0.39–0.73)
ADPCT (s)	0.55 (0.37–0.72)
Platelet count ($\times 10^9$ litre^{-1})	0.56 (0.37–0.75)
Prothrombin time (s)	0.59 (0.40–0.78)
Activated partial thromboplastin time (s)	0.57 (0.37–0.77)
Fibrinogen concentration (mg dl^{-1})	0.57 (0.37–0.76)

Interestingly in our study, preoperative PFA-100® measurement is not correlated with intraoperative blood loss. However, the diluted EPICT is found to correlate with surgeons' assessment of the difficulty in achieving haemostasis. We believe this indicates that patients with more prolonged EPICT are detectably more 'oozy', although this may not have translated into differences in intraoperative blood loss. One possible explanation is that as the surgeons detect some patients are more 'oozy', they take more care and are more meticulous with respect to haemostasis. On the other hand, postoperative output from the wound drain is much less affected by all these factors, and is probably a lot more dependent on platelets.

In our study, patients who took COX inhibitors before operation were recruited to provide us with a convenient mix of subjects exhibiting variable PFA-100® measurements, so that correlation can be sought between the PFA-100® measurements and the clinical outcome of bleeding. This study is not intended to answer the question whether or when COX inhibitors, including aspirin should be stopped before elective operations. However, because aspirin and the COX inhibitors evaluated in this study inhibit platelets via the same mechanism, namely inhibition of thromboxane synthesis by platelets, our results suggest the PFA-100® may also be useful in guiding the management of patients taking aspirin before operation, but further studies in the appropriate context are required.

There are a few limitations of this study. PFA-100® measurements only correlate with drain output, but not intraoperative loss. Not surprisingly, the PFA-100® measurements also do not correlate with outcome measures generally considered important, such as transfusion requirement (data not shown). There were also more female than male patients in this study, and therefore the results may be affected by gender bias. Further, this study is not performed in 'high-risk' patients, for example, neurosurgery, where even a mild or moderate increase in postoperative bleeding could be dangerous. Further studies in these areas are warranted.

In conclusion, this study demonstrates for the first time the usefulness of the PFA-100® in predicting bleeding during and after surgery. A CT of >188 s, using the epinephrine cartridge and in a 20% diluted sample predicts more bleeding after operation but not intraoperatively. It may suggest that PFA-100® can detect subtle impairment in primary haemostasis, which is manageable with more meticulous surgical haemostasis but nonetheless causes

Table 4 Diagnostic performance of different cut-off values for EPICT on a 20% haemodiluted sample (0.8EPICT) for predicting postoperative drain output in excess of 270 ml (top 25% percentile). Values in parentheses are 95% CI. EPICT refers to PFA-100® closure times measured with epinephrine cartridges. PPV, NPV, and LR+ refer to positive predictive value, negative predictive value, and positive likelihood ratio, respectively

0.8EPICT cut-off value (s)	Sensitivity	Specificity	PPV	NPV	LR+
165	88.9 (51.8–99.7)	38.5 (20.2–59.4)	33.9 (18.3–45.9)	90.9 (54.8–99.8)	1.44 (0.98–2.11)
188	88.9 (51.8–99.7)	53.9 (33.4–73.4)	40.0 (21.2–56.5)	93.4 (66.7–99.9)	1.93 (1.20–3.10)
300	22.2 (2.8–60.0)	96.2 (80.4–99.9)	66.5 (4.7–99.5)	78.1 (70.5–87.8)	5.78 (0.59–56.38)

more bleeding after operation. The significance of such increase in postoperative bleeding would depend on the clinical context.

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