Diagnostic performance of the platelet function analyzer (PFA-100) for the detection of disorders of primary haemostasis in patients with a bleeding history: a systematic review and meta-analysis

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CRD summary
This review assessed the diagnostic performance of two variants of the Platelet Function Analyzer (PFA-100) to detect disorders of primary haemostasis in patients presenting with bleeding. The authors concluded that the method using collagen/epinephrine appeared to have higher sensitivity and better predictive values than that using collagen/adenosine-diphosphate. However, further research to establish the clinical utility of the PFA-100 is recommended. These conclusions are appropriately cautious given the limitations of the data.

Authors' objectives
To assess the diagnostic performance of the Platelet Function Analyzer (PFA-100), manufactured by DADE Behring, Germany, for detecting disorders of primary haemostasis in patients presenting with a history of bleeding.

Searching
MEDLINE, EMBASE, BIOSIS Previews and the Cochrane Library were searched from January 1994 to February 2006. Additional studies were sought through contact with the manufacturer. Searches were restricted to studies published in English.

Study selection
Studies were selected if they aimed to assess the sensitivity and specificity of the PFA-100 to detect disorders of primary haemostasis; disorders of primary haemostasis were defined as platelet function disorders and von-Willebrand disease (vWD). Studies were included in the meta-analysis if they met the above criteria and, in addition, reported absolute numbers of true positives (TP), false negatives (FN), false positives (FP) and true negatives (TN); used an appropriate reference standard to establish diagnosis (composite reference standard, to include a minimum of determination of von Willebrand factor using vWF:RCo and/or vWF:Ag assays, and platelet aggregation studies with different agonists); and met the methodological quality criteria outlined (see Validity Assessment). The mean age of the participants was reported in three of the six included studies as 9.9, 46 and 53.1 years, respectively. Two studies excluded patients on non-steroidal anti-inflammatory drugs, and those with thrombocytopenia or anaemia.

Two reviewers independently assessed the titles and abstracts of all retrieved articles. One reviewer, who was not blinded to authors, authors' affiliation, or journal of publication, then assessed retrieved full-text articles for inclusion.

Assessment of study quality
The studies were assessed for methodological quality against the following criteria: inclusion of consecutive patients, or recruitment of a random sample of newly presenting patients, to ensure an unselected, clinically relevant patient spectrum (diagnostic case-control studies were excluded); absence of partial verification bias (i.e. the reference standard was applied in all patients, rather than selectively, based upon the results of the index test).

Data extraction
The numbers of TP, FN, FP and TN were extracted for the PFA-100 using either collagen/epinephrine (PFA-EPI) or collagen/adenosine-diphosphate (PFA-ADP), or derived from available data, to construct a 2x2 table. Data on study setting, methodological quality criteria and participant characteristics were also extracted.

Two reviewers independently extracted the data and any disagreements were resolved by discussion.

Methods of synthesis
Pooled estimates of sensitivity, specificity and diagnostic odds ratio (DOR) were calculated using a random-effects
model, weighted by inverse variance. The authors state that a random-effects model was chosen, based upon the results of heterogeneity testing; the method used to assess between-study heterogeneity was not reported.

Summary receiver operating characteristic (SROC) analysis, using a bivariate random-effects model, was performed for the PFA-EPI test alone and for both the PFA-EPI and PFA-ADP combined (in order to produce an estimate of relative DOR and thus comparative performance of the two tests). The dependence of this analysis upon individual studies was assessed using sensitivity analyses (each study was removed in turn).

Publication bias was assessed through construction of a funnel plot.

**Results of the review**

Six studies, with a total of 1,486 participants, were included in the meta-analysis.

For PFA-EPI, the pooled estimates of sensitivity, specificity and DOR were 82.5% (95% confidence interval, CI: 76.0, 88.9), 88.7% (95% CI: 84.3, 93.1) and 3.58 (95% CI: 2.46, 4.68), respectively.

For PFA-ADP, the pooled estimates of sensitivity, specificity and DOR were 66.9% (95% CI: 57.9, 75.9), 85.5% (95% CI: 82.0, 89.1) and 2.12 (95% CI: 1.32, 2.91), respectively.

Sensitivity was significantly higher for PFA-EPI than for PFA-ADP, but there were no significant differences in specificity or DOR between the two methods. There was significant heterogeneity between studies in both groups.

The SROC analysis for both tests combined gave a relative DOR of 3.13 (95% CI: 0.95, 10.35, p=0.061).

The sensitivity analysis showed that the removal of one study eliminated the relationship between diagnostic threshold and diagnostic performance, and hence resulted in a more symmetrical SROC curve. When this study was excluded, the estimated relative DOR changed such that PFA-EPI was found to have significantly better diagnostic performance (greater DOR) than PFA-ADP.

Funnel plots were difficult to interpret, owing to the small number of studies, but appeared symmetrical (indicative of absence of publication bias) for PFA-EPI and were considered to indicate possible publication bias for PFA-ADP.

**Authors' conclusions**

PFA-EPI appeared to have higher sensitivity and better predictive values than PFA-ADP. However, the absence of a rigorously defined reference standard for disorders of primary haemostasis, together with poor methodological quality and reporting of existing studies, mean that more research is needed to fully define the clinical utility of the PFA-100.

**CRD commentary**

The aim of the review, to assess the diagnostic performance of PFA-100 in detecting disorders of primary haemostasis, was clearly stated; criteria for including studies in the meta-analysis were itemised and these included some aspects of methodological quality. A number of relevant sources were searched in order to identify studies for inclusion, and an attempt to assess publication bias was reported. However, the restriction of searches to publications in English might have resulted in the omission of relevant data. The review process included appropriate measures to minimise error and bias. The methods used to generate SROC curves, and hence estimate relative DOR, were reasonable for the available data, though better methods of fitting SROC curves are available. However, the separate estimation of pooled sensitivity, specificity and DOR, using a random-effects model weighted by inverse variance, might be considered to be of limited value given the acknowledged presence of significant between-study heterogeneity in these parameters, as well as the clear presence of a threshold effect (relationship between differing diagnostic thresholds used in individual studies and diagnostic performance). The authors' conclusions, highlighting the need for further research, are appropriately cautious given the limitations of the available data.

**Implications of the review for practice and research**

Practice: The authors made no specific recommendations for clinical practice.
Research: The difficulties in defining a universally applicable reference standard for 'clinically relevant bleeding tendency due to a disorder of primary haemostasis' are noted, and randomised controlled trials comparing outcomes with and without application of the PFA-100 are therefore recommended to determine the clinical utility of this test.

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