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Accuracy of platelet counting haematology analysers in severe thrombocytopenia and potential impact on platelet transfusion

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Summary

Although haematology analysers provide reliable full blood counts, they are known to be inaccurate at enumerating platelets in severe thrombocytopenia. If the thresholds for platelet transfusion, currently set at 10×10^9/l, are to be further reduced, it is vital that the limitations of current analysers are fully understood. The aim of this large multicentre study was to determine the accuracy of haematology analysers in current routine practice for platelet counts below 20×10^9/l. Platelet counts estimated by analysers using optical, impedance and immunological methods were compared with the International Reference Method for platelet counting. The results demonstrated variation in platelet counting between different analysers and even the same type of analyser at different sites. Optical methods for platelet counting on the XE 2100, Advia 120, Cell-Dyn 4000 and H3* were not superior to impedance methods on the XE 2100, LH750 and Pentra analysers. All analysers except one overestimated the platelet count, which would result in under transfusion of platelets. This study highlights the inaccuracies of haematology analysers in platelet counting in severe thrombocytopenia. It re-emphasizes the need for external quality control to improve analyser calibration for samples with low platelet counts, and suggests that the optimal thresholds for prophylactic platelet transfusions should be re-evaluated.

Keywords: thrombocytopenia, platelet counting, haematology analysers, prophylactic platelet transfusion thresholds.

The optimal threshold platelet count for prophylactic platelet transfusions in patients with haematological malignancy undergoing cytotoxic therapy remains uncertain. Recent studies have suggested that for patients with no additional risk factors the clinical decision threshold may be reduced from a platelet count of 20×10^9/l to 10×10^9/l without significantly increasing the risk of haemorrhage (Heckman *et al*, 1997; Rebulla *et al*, 1997; Wandt *et al*, 1998, 2001). A major concern in lowering the threshold trigger for prophylactic platelet transfusions to the recommended level of 10×10^9/l (British Committee for Standards in Haematology, 2003) or to an even lower value, is the potential inaccuracy of standard routine automated haematology analysers for low platelet counts (Norris *et al*, 2003).

Historically, the reference method for platelet counting used in the calibration of haematology analysers was the manual phase microscopy method (Brecher *et al*, 1953; England *et al*, 1998). This is limited by being time-consuming, highly subjective and imprecise at low counts due to the low numbers of cells being counted (Harrison *et al*, 2001a). Automated haematology analysers in routine diagnostic use employ a variety of technologies to count platelets including impedance, optical light scatter and optical fluorescent staining methods. These technological principles are well-described (Harrison *et al*, 2001b). However, their precision is poor at low levels of platelets, with an increased variability of the count because of the failure of these methods to discriminate platelets from other cell fragments and debris of a similar size. This can result in spuriously high platelet counts or, as in the case of large or giant platelets, where they may not be discriminated from red cells, their exclusion would result in a false low platelet count (Ault, 1996; Harrison *et al*, 2000; Kunz, 2001; Sandhaus *et al*, 2002). To date, the accuracy of all these methodologies for severely thrombocytopenic samples in routine practice has

been difficult to assess, partly due to the lack of adequate quality control materials at very low platelet levels. The superiority of impedance platelet counting *versus* optical platelet counting has been the subject of ongoing debate, with conflicting reports in the literature as to the most accurate and precise automated method depending on the sample type (Davis & Bigelow, 1999; Stanworth *et al*, 1999; Briggs *et al*, 2000; Kunicka *et al*, 2000; Sandhaus *et al*, 2002). To overcome this, some analysers incorporate more than one platelet counting technology, such as the Cell-Dyn 4000 (Abbott Diagnostics, Santa Clara, CA, USA), which has optical and impedance platelet counting with the availability of an immunological (CD61) platelet counting technique. The XE 2100 (Sysmex, Kobe, Japan) can provide an impedance and a fluorescent optical platelet count. If both counting methods are enabled on the analyser it also has a computerized switching algorithm to give a best 'reported count'. If interference is detected in the impedance count, for example, if red cell fragments or giant platelets are present, the analyser will report the optical count; alternatively, if there is an abnormal optical platelet distribution the analyser will report the impedance count.

A major advance in platelet counting has been the development of an immunological method using flow cytometry. This method, as ratified by the International Society of Laboratory Haematology (ISLH), is now the proposed International Reference Method (IRM) for counting platelets (Harrison *et al*, 2001a). It uses two specific platelet monoclonal antibodies to label platelets and the platelet count is derived from the platelet/red blood cell ratio. This method not only compares well with the previous 'gold standard' of manual phase contrast microscopy, but also demonstrates superior precision. This method should now replace manual phase microscopy and will help to improve the calibration of haematology analysers by instrument manufacturers, quality control materials and the accuracy of platelet counting in thrombocytopenia (Dickerhoff & Von Ruecker, 1995; Norris *et al*, 2003). However, there have been very few well designed large studies comparing all available modern counting technologies at very low platelet counts to provide clear evidence of the superiority of one type of counting technology or analyser over another (Sandhaus *et al*, 2002). These limitations have therefore made it difficult to ascertain the translation of these counting errors into the degree of over or under prescription of prophylactic platelet transfusion in clinical practice. This has constrained the consideration of lowering the prophylactic platelet transfusion threshold levels to $<10 \times 10^9$/l to further reduce patient exposure to blood components and to conserve transfusion resources.

The aim of this large multicentre study was to evaluate the accuracy of different platelet counting technologies (impedance, optical light scatter, optical fluorescence and immunological platelet counting) employed by all the haematology analysers currently commercially available in the UK, and to relate this to the hypothetical use of prophylactic platelet transfusions at thresholds of 5, 10 and 15×10^9/l. Establishing the accuracy of different platelet counting technologies for evaluating severe thrombocytopenia will aid future clinical studies aimed at determining the optimal approach to platelet transfusion therapy of patients treated for haematological and other malignancies.

Materials and methods

Blood analysers used in the study

A total of nine routine haematology analysers from five different manufacturers provided the large number of platelet counts shown in Table I. A full blood count using the routine diagnostic haematology analysers *in situ* was performed on the same day as sampling and the platelet count repeated by the IRM within 24 h. The IRM utilizes two monoclonal antibodies CD41-FITC (Immunotech, Beckman Coulter, France) and CD61-FITC (Becton Dickinson, Oxford, UK) following the method as fully described elsewhere (Harrison *et al*, 2001b). The IRM is stable for at least 24 h postsampling (unpublished observations); any samples delayed in transit were not included in the study.

The quality control of the International Reference Method at the two reference centres

The IRM method was standardized using a fixed human whole blood standard (R&D Systems, Minneapolis, MN, USA). To confirm standardization, two different batches of standard material with documented platelet counts of $<20 \times 10^9$/l were analysed by the IRM at two different sites, University College Hospital (UCLH), London, and the Oxford Haemophilia Centre and Thrombosis Unit (OHTU), Oxford. Agreement of the IRM between reference centres was further assessed using the same 20 ethylenediaminetetraacetic acid (EDTA) blood samples from thrombocytopenic haematology patients at both sites.

Comparison of platelet counting methods and analysers at different sites

The EDTA blood samples from patients undergoing cytotoxic chemotherapy for haematological malignancies were obtained for routine clinical testing at five different university hospital haematology laboratories recruited to the study. Routine platelet counts $\leq 20 \times 10^9$/l from a variety of diagnostic analysers were subsequently sent to one of the two reference sites for repeat platelet counting by the IRM.

Statistical analysis

The difference in platelet counts between analysers was compared using the Bland–Altman method (Bland & Altman,

Table I. Haematology analysers and the total number of samples counted at the five sites in the study.

Analyser	Counting technology	Site number	Total number of counts
Sysmex XE 2100 (Sysmex)	Impedance and optical fluorescence	1, 2	763
	Reported count*		666
Cell-Dyn (Abbott Diagnostics)	Optical dual angle light scatter	3, 5	309
	Immunological CD61†		307
Advia 120 (Bayer Corporation, Newbury, Berks, UK)	Optical dual angle light scatter	4, 5	281
LH 750 (Beckman Coulter Miami, FL, USA)	Impedance	1	495
Pentra 120 (ABX Diagnostics Sheffield, UK)	Impedance	5	119
Bayer H3 (Bayer Corporation)	Optical single angle light scatter	5	109

*The algorithm to give the 'reported count' was not enabled at one site at the beginning of the study, resulting in a lower number of reported counts than the total number of optical and impedance counts.

†The impedance count on the Cell-Dyn was not reported on most samples with low platelet counts and was therefore not included in the final analysis. The Cell-Dyn CD61 reagent tubes, which use the same CD61 platelet monoclonal antibody as the International Reference Method (IRM), were obtained from Abbott Diagnostics, USA.

1986, 1999), which quantifies the agreement between two methods of measurement. Results were summarized as mean difference, which is the average difference between the analyser count and the IRM count for all the blood samples in the data set, with a 95% reference range for the difference, otherwise known as the limits of agreement (95% LA). Assuming the differences between the analyser and IRM follow a normal distribution, 95% of all differences will be expected to fall within the 95% LA.

The sensitivity and specificity of the analysers in comparison with the IRM around potential thresholds for prophylactic platelet transfusions of 5, 10 and 15 $\times 10^9$/l were assessed. At a transfusion trigger at a platelet count of 10×10^9/l the sensitivity and specificity were defined as:

1 Sensitivity – the probability that the analyser count is <10, given that the IRM count is <10.

2 Specificity – the probability that the analyser count is 10 or more, given that the IRM count is 10 or more.

Results

Quality control of the IRM at the two reference centres

The IRM platelet count of two consecutive batches of R&D-fixed whole blood standard material was compared at the two reference centres as shown in Table II and Fig 1. There was good agreement between the standards at the two reference sites for the range of platelet count determined by the IRM for each standard. The agreement for batch 1 was closer, with a mean difference of $0{\cdot}27 \times 10^9$/l (95% LA: −1·71 to 2·25), compared with $0{\cdot}86 \times 10^9$/l with batch 2 (95% LA: −2·48 to 4·20). This means the gold standard IRM method gave slightly different results at the two sites; overall the difference was

Table II. Platelet counts ($\times 10^9$/l) of R&D standards analysed by the International Reference Method (IRM) at the two reference sites.

Batch	R&D	*n*	Mean	Reference range*	Mean difference†	95% limits of agreement
1	Quoted			8·2–12·2		
	Oxford	26	8·6	7·3–9·9	0·27	
	UCH	26	8·3	6·8–9·8	(95% CI: −0·13 to 0·67)	−1·71 to 2·25
2	Quoted			11·4–16·7		
	Oxford	18	14·0	11·3–16·0	0·86	
	UCH	18	13·2	11·5–14·9	(95% CI: 0·03–1·69)	−2·48 to 4·20
1 and 2	Oxford	44	10·8	5·1–16·6	0·51	
	UCH	44	10·3	5·2–15·4	(95% CI: 0·11–0·92)	−2·14 to 3·16

*Reference range = (mean − 2 SD) to (mean + 2 SD).

†Mean difference for paired observations with 95% confidence interval (CI) for difference.

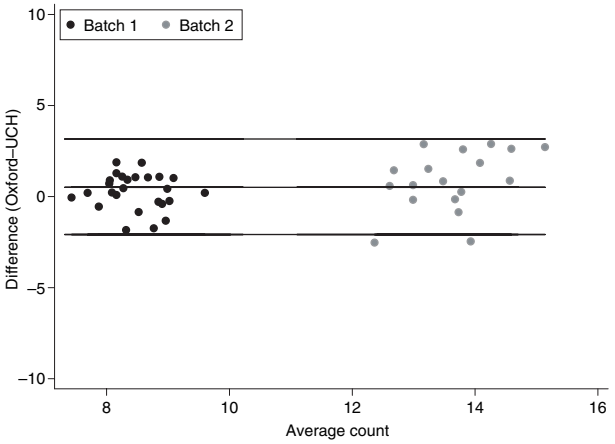

Fig 1. Bland–Altman plot of platelet count ($\times 10^9$/l) R&D standards analysed by the International Reference Method (IRM) at the two reference sites.

$0{\cdot}51 \times 10^9$/l with most differences between sites expected to lie between −2·1 and 3·2. The standard material was of undetermined stability over time once the vial was opened, which might explain some of the differences between the two sites. The IRM on the same 20 thrombocytopenic samples showed good agreement between sites, with a mean difference of $0{\cdot}57 \times 10^9$/l and 95% of the differences between −1·36 and $2{\cdot}5 \times 10^9$/l.

Comparison of platelet counting by all analysers with the IRM

The mean differences and 95% LA were calculated for all analysers, pooling data if the same type of analyser was used at more than one site. These are plotted in Fig 2. The analysers tended to over estimate the platelet count, with the exception of the Pentra, which underestimated by a mean $3{\cdot}4 \times 10^9$/l and also had poor accuracy with wide LA. The Cell-Dyn CD61 immunological method and the XE impedance and reported methods counted with the least bias, with mean differences close to zero. The Cell-Dyn immunological method was the most accurate of these, with narrower LA. The Cell-Dyn and XE optical methods and the LH750 impedance method produced similar results. The H3* machine had the narrowest LA, despite being based on the smallest number of counts. It also demonstrated only a small amount of bias, overestimating the count by a mean $1{\cdot}2 \times 10^9$/l. The least accurate analyser was the Advia, which overestimated the count by a mean $3{\cdot}5 \times 10^9$/l and had the widest LA. This was due to the fact that the platelet counts from one centre were in far greater agreement with the IRM than the other centre, a discrepancy probably caused by differences in machine calibration.

Sensitivity and specificity

The data presented in Fig 3 showed clearly that, with the exception of the Pentra, there was a tendency for all types of routine analysers used in this study to overestimate the platelet count compared with the IRM at the transfusion thresholds of 5, 10 and 15×10^9/l. This overestimation resulted in poor sensitivity at lower thresholds, but good specificity across the thresholds. Thus, there is a potential for the under-transfusion of platelets when guided by the platelet count from all analysers apart from the Pentra. However, patients with platelet counts greater than the threshold would not be over transfused.

Discussion

The results of this study highlight the inaccuracies of platelet counting methods by haematology analysers in routine clinical use in the UK and the potential clinical impact on the use of prophylactic platelet transfusions in patients with haematological malignancies. The Cell-Dyn CD61 immunological method gave the best agreement with the IRM, with small

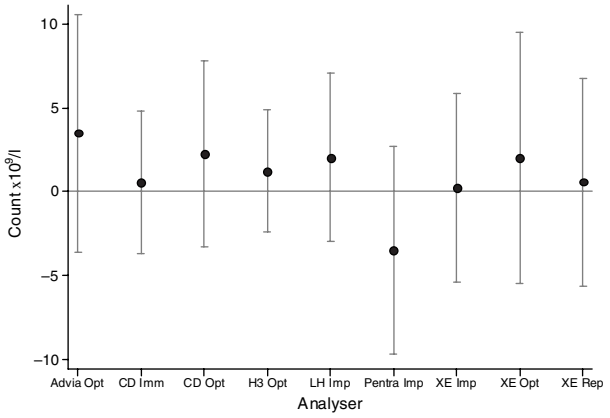

Fig 2. Summary of Bland–Altman plot of the mean difference and 95% limits of agreement of all the types of analysers used in the study to the International Reference Method (IRM).

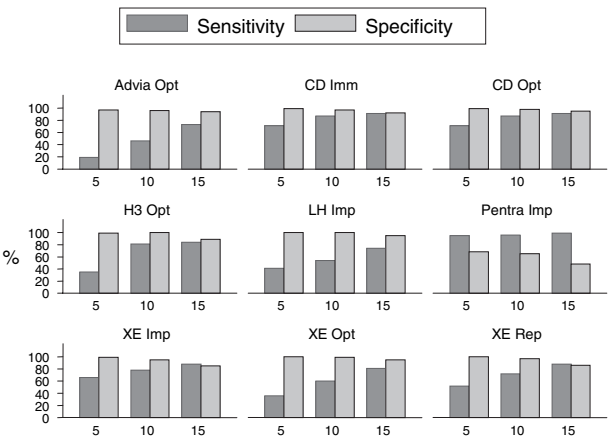

Fig 3. Summary of sensitivity and specificity of the analysers at International Reference Method (IRM) cut-offs of 5, 10 and 15×10^9/l.

LA. This was closely followed by the XE 2100 impedance platelet count, which was accurate but had wider LA. The impressive performance of the Cell-Dyn CD61 immunological method is not surprising as the methodology is very similar to the flow cytometric reference method, in that platelets are totally discriminated from other cells and debris by use of specific monoclonal antibodies and it has been reported elsewhere that the CD61 method agrees well with flow cytometry (Arroyo *et al*, 2001; Kunz *et al*, 2001). However, this method is not widely routinely utilized as it requires extra resources in terms of the CD61 tubes and is only usually performed to confirm low counts in severe thrombocytopenia.

Recent studies have suggested that various new advances in counting technologies are more accurate than conventional impedance analysis, especially in thrombocytopenia, which could have significant impact upon platelet transfusion decision making (Arroyo *et al*, 2001). The data from this study demonstrated that the various types of optical platelet counting available are not more accurate than impedance platelet counting and do not support the purported superiority of optical counting over the impedance count for thrombocytopenic samples from patients with haematological malignancies. Previously, improvements of optical platelet counting were described using the Bayer Advia (Stanworth *et al*, 1999) and the Sysmex XE 2100 (Briggs *et al*, 2000). However, these smaller studies did not use thrombocytopenic samples from patients with haematological malignancies; the samples were specifically selected with low counts from patients with autoimmune thrombocytopenia and myelodysplasia, which are disorders where impedance platelet counting is known to be problematic because of the presence of large platelets. In this study, the sample recruitment was specifically restricted to haematology patients undergoing cytotoxic therapy, as this cohort of patients has the highest demand for platelet transfusions. These samples may have white cell fragments, which are included in the optical count. Our results are in agreement with a smaller study (Sandhaus *et al*, 2002), where samples were selected by low platelet count alone from patients with a variety of diagnoses. It is often wrongly assumed that the optical platelet count on the Sysmex XE 2100 is more accurate than the impedance platelet count (Briggs *et al*, 2004). Many laboratories override the switching algorithm that will report the most 'correct count' and routinely report an optical count below a preset level, typically below 50×10^9/l. The data presented here demonstrate that this was not good practice for the samples in this study; the impedance XE 2100 platelet count was shown to be more accurate than the XE 2100 optical platelet count. Ideally, the platelet counting method used should be stated when providing results for external quality control.

An important finding was that analysers of the same type at different routine hospital laboratories gave different degrees of agreement with the IRM. Ideally, the study would have included comparisons of each analyser between two different sites; this was only possible for the Sysmex XE 2100, Cell-Dyn and Advia 120, but not for the LH750 impedance counter, the Pentra 120 or Bayer H3*, the latter two providing relatively small numbers of counts. An example of variation between the two sites was the Bayer Advia; at one site the platelet count tended to overestimate compared with the IRM and therefore would have resulted in under-transfusion of platelets, but this was not the case for this instrument at the second site.

Routine automated platelet counting techniques should be reliable for thrombocytopenia encountered in all clinical settings. These results emphasize that haematology laboratories should ideally establish the accuracy of each technology employed on the analyser used for thrombocytopenic samples at the recommended transfusion thresholds in clinical use. Given the restraints inherent in routine laboratory practice (e.g. understaffing, expertise available, workload, expense of testing), it is possible that not all the options for platelet counting available on a given analyser would be feasible for routine use. For example, the Cell-Dyn CD61 immunological count is more expensive and is therefore not designed for routine use, apart from the small number of samples where accuracy of the count may influence transfusion decision making. For the XE 2100, the optical platelet result is derived from the reticulocyte channel, so the analyser must be run in the reticulocyte count mode.

To address these issues over the last year, the United Kingdom National External Quality Assessment Scheme for Haematology have initiated some preliminary surveys of analyser performance on material with low platelet counts (Parker-Williams, 2003); coefficients of variation of 22–66% were reported, showing the considerable variation between laboratories and type of analyser. Our study further emphasizes that there is a clear requirement to develop suitable external quality control material to improve the calibration of analysers for counting severely thrombocytopenic samples. In the absence of external calibration, the results of this study indicate that most analysers, by tending to overestimate the platelet count, potentially result in the under-transfusion of platelets at the decision thresholds for prophylactic platelet transfusions of 5 and 10×10^9/l. If this practice appears not to produce an increase in significant clinical bleeding in patients with haematological malignancies, it provides further support for the re-evaluation of the optimal threshold for prophylactic platelet transfusion, and even for a re-consideration of the benefit (if any) of prophylactic transfusions in this clinical setting.

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Conflict of interest statement

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