An Evaluation of Point-of-Care Instrument for Monitoring Anticoagulation Level in Adult Cardiac Patients

M H Tay, S L Tien, T S J Chua, L L Sim, T H Koh

ABSTRACT

Introduction: Rapid point-of-care measurement of anticoagulation has become feasible with the advent of new portable devices and offers the potential for home monitoring. This study evaluates the accuracy and feasibility of such a point-of-care device, the ProTime analyser as compared with standard laboratory method (IL MCL2) for monitoring the International Normalised Ratio (INR) level in cardiac patients on oral anticoagulation therapy.

Materials and Methods: Fifty patients were studied. The majority were male (86% versus 14%). Chinese accounted for 37(74%) whereas Malay and Indian, constituted 9(18%) and 4(8%) respectively. The mean age was 55 ± 12 years. Prosthetic heart valve replacement (46%) and atrial fibrillation (38%) were among the main indications for anticoagulation. The mean dosage of warfarin was 3.0 ± 1.5 mg (range 1.0 to 6.5 mg) and the INR results ranged from 0.83 to 4.69 (based on the hospital laboratory method). Fingerstick and venous blood samples were collected from every patient and subjected to analysis by ProTime and IL MCL2 analysers.

Results: There was a good correlation of INRs between ProTime venous and IL MCL2 venous, ProTime fingerstick and IL MCL2 venous and ProTime venous and ProTime fingerstick samplings, with correlation coefficients (r) of 0.9248, 0.9403 and 0.9557, respectively. The Bland-Altman plot also showed a good correlation between the methods used without any systematic bias (limits of agreement ranged from -0.422 to +0.606 INR units on average).

Conclusion: This rapid point-of-care device appears to have an acceptable level of accuracy for measuring INR values in the recommended target ranges in adult cardiac patients on oral anticoagulation therapy.

Keywords: Point-of-care INR test, ProTime Microcoagulation System

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INTRODUCTION

Oral anticoagulation has been proven to reduce the risk of thromboembolic events in a wide range of conditions including atrial fibrillation and valvular heart disease, but it requires regular testing of International Normalised Ratio (INR) due to its narrow therapeutic range and the risk of over and under anticoagulation which can be life-threatening. Bleeding complications are directly related to the level of anticoagulation achieved and the risk of thromboembolic events is inversely related to the level of anticoagulation maintained[1,2].

Recently, a number of portable devices have been developed for rapid determination of prothrombin time (PT) and INR at locations not limited to central laboratories[3-6]. One of these portable instruments is the ProTime Microcoagulation System. This device can be potentially beneficial as INR results are available in minutes, allowing patients to shorten their outpatient clinic waiting time. As with other devices used for monitoring blood sugar and total cholesterol, this device permits fingerstick sampling. Hence, certain patients could use this under the direction of a clinician to self-test at home. Self-testing and adjusting of warfarin dosages by patients is an evolving strategy for management of oral anticoagulation. Several clinical studies have shown that patients performing self-management remain in the therapeutic target INR range a greater percentage of the time when compared to conventional testing, and tended to have a lower incidence of bleeding or thromboembolic events[7,8]. However it is essential to validate the accuracy of each device.

The aims of this trial were to evaluate the accuracy and precision of a hand-held device, the ProTime analyser, as compared with the standard hospital laboratory method; and to examine the feasibility of using it as a point-of-care test to monitor the

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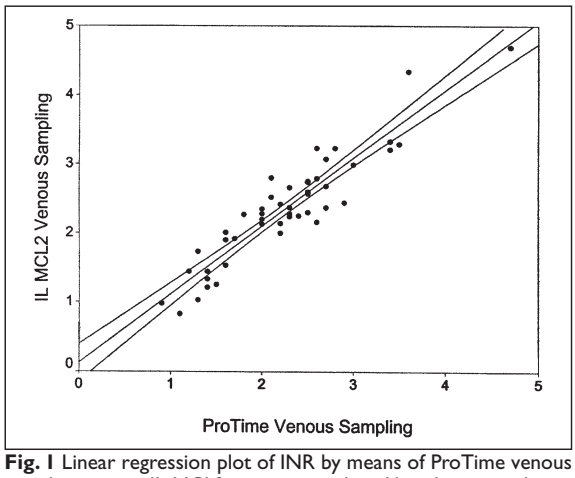

Fig. 1 Linear regression plot of INR by means of ProTime venous sampling against IL MCL2 venous sampling. Also shown are linear regression lines and 95% confidence limits.
y=0.876x + 0.198; r=0.925

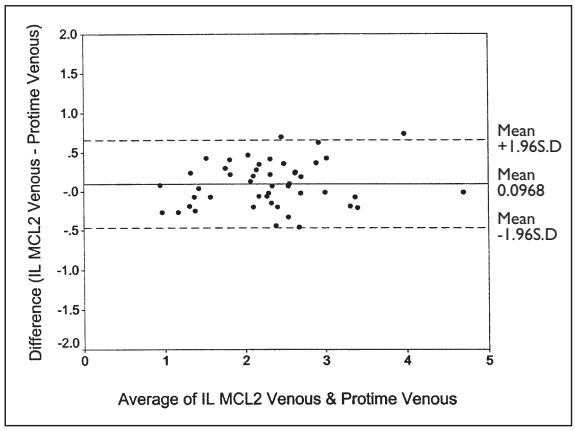

Fig. 2 Bland-Altman plot of the difference between IL MCL2 venous and ProTime venous INR results (IL MCL2 venous minus ProTime venous) plotted against mean INR values, (IL MCL2 plus ProTime venous)/2. Standard deviation (S.D)=0.2821.

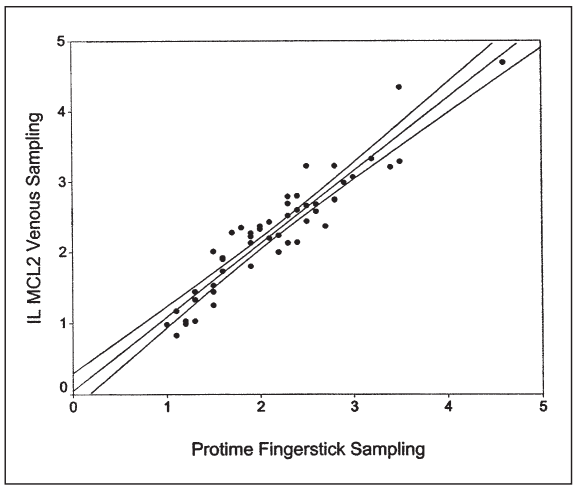

Fig. 3 Linear regression plot of INR by means of ProTime fingerstick sampling against IL MCL2 venous sampling. Also shown are linear regression lines and 95% confidence limits.
y=0.856x + 0.207; r= 0.940

INR level in adult cardiac patients on oral anticoagulation therapy. The correlation of INRs between ProTime venous and ProTime fingerstick samples was also studied.

MATERIALS AND METHODS

Study Population

We recruited 50 consecutive unselected patients who attended an anticoagulation clinic (ACC) at the National Heart Centre of Singapore into this study. As the trial coordinator was only available on certain days, recruitment was only performed on those days. All patients who agreed to undergo both venous and fingerstick samplings were consented to participate in the study. Thus the study population represents an unselected group of patients. No patients were excluded from the study based on any other clinical grounds. Fifty adult cardiac patients receiving warfarin therapy were enrolled into the study between 23 August 2000 and 12 October 2000.

Point-of-Care Testing

The ProTime Microcoagulation System (Hemochron Brand, ITC) is FDA approved. It consists of disposable 5-Channel Reagent Cuvettes, a Tenderlett Plus fingerstick device and a blood collection cup. This is a point-of-care system that reports Prothrombin Time (PT) and INR results within minutes of sampling. The device measures 23.0 x 11.0 x 5.5 cm and it weighs about 0.8 kg.

The device has a built-in function to check on temperature, timing function, battery level, and electrical and mechanical functions. According to the manufacturer, there is no need for further calibration of the instrument and it takes less than five minutes to obtain the PT/INR result. It measures the PT/INR using fibrin clot formation and detection. The instrument prompts the user through each step of the sampling process.

The study was a split sample design where patients were their own controls. Venous blood sample was collected in a sterile syringe. A drop of whole blood from the syringe (60 µI) was placed into the blood collection cup and immediately run on the ProTime analyser. (The blood sample is collected within two minutes upon incision. The process was monitored by a built-in timer in the ProTime analyser.) The remainder of the sample was placed in a standard collection tube for sampling on the Instrumentation Laboratory (IL) MCL2 machine, which is the established standard laboratory method for determining INR level at Singapore General Hospital. This was done within one hour from the time sample was collected.

With consent from the same subject, a fingerstick sample was performed with Tenderlett Plus fingerstick device and blood sample was again placed into the blood collection cup and immediately run on the ProTime analyser. The result obtained

was then correlated with the result from the hospital laboratory method.

Statistical Methods

We determined the feasibility of the ProTime analyser for anticoagulation monitoring by studying the accuracy and linear correlation of INRs between the ProTime venous and IL MCL2 venous, ProTime fingerstick and IL MCL2 venous and ProTime venous and ProTime fingerstick samplings. Regression equations were generated and a correlation coefficient was calculated from each comparison. The differences between the corresponding methods plotted against the average of the two measurements (Bland-Altman plot) were also performed to look for trends and systematic bias. The limits of agreement between the two techniques were calculated from the mean difference plus or minus 1.96 SD. Paired t tests were also used as a means of determining the two-tailed probabilities that measurements were significantly different between the two techniques, with p values of <0.05 taken as statistically significant. Statistical analysis was performed with a statistics program, SPSS for windows, Release 9.0.1, SPSS Inc.

RESULTS

Study Population

Of the 50 patients, 43 (86%) were male and 7 (14%) were female. The mean age was 55 ± 12 years (range 26 to 80 years). The majority of the patients were Chinese 37(74%) and this was followed by Malay 9(18%) and Indian 4(8%).

The indications for anticoagulation include prosthetic heart valve in 23 (46%) cases, atrial fibrillation 19 (38%), left ventricular thrombus 6 (12%), post mitral valve repair 1 (2%) and pulmonary embolism 1 (2%).

The mean dosage of warfarin was 3.0 ± 1.5 mg (range 1.0 to 6.5 mg).

INR Correlation Between the Various Methods

There was an excellent correlation of the INR between the standard laboratory IL MCL2 venous sample and the ProTime venous sample as shown in Fig. 1. The correlation coefficient, r was 0.925. The mean difference in INR measured by means of the two methods was small, only 0.097 and it was not statistically significant (p=0.282). In addition, the Bland-Altman plot of the difference between standard laboratory IL MCL2 venous and ProTime Venous INR result (IL MCL2 Venous minus ProTime Venous) plotted against the average, (IL MCL2 Venous plus ProTime Venous)/2 showed no significant trend in the difference between the two methods across the entire range of INR values (Fig. 2). The 95% limits of agreement ranged from -0.467 to +0.661.

Fig. 3 shows the excellent correlation of the INRs between the ProTime fingerstick sampling and standard laboratory IL MCL2 venous sampling with a correlation coefficient, r of 0.940. The mean difference in INR measured by means of the two methods (IL MCL2 venous minus ProTime fingerstick) was small (0.123) and it was not statistically significant (p=0.061) as shown in the Bland-Altman plot in Fig. 4. Again, no significant trend in the difference between the two methods across the whole range of INR was observed. The 95% limits of agreement ranged from -0.344 to +0.680.

Finally, the correlation of INR between ProTime venous and ProTime fingerstick samples was also studied. An excellent correlation of the INR between these two techniques was shown by means of a linear regression analysis with a correlation coefficient r value of 0.956 (Fig. 5). The mean difference in INR measured by means of the two methods (ProTime venous minus ProTime fingerstick) was also small, 0.022 and not statistically significant (p=0.364), as shown by means of Bland-Altman analysis in Fig. 6. There was no significant difference in trend throughout the entire range of INR values. The 95% limits of agreement ranged from -0.454 to +0.476.

INR results ranged from 0.83 to 4.69 (based on the hospital laboratory method). Based on the standard hospital laboratory method, 12/50 (24%) results were <2.0 and 8/50 (16%) were >3.0; whereas for ProTime venous sampling, 14/50 (28%) results were <2.0 and 5/50 (10%) were >3.0, and for ProTime fingerstick sampling, 21/50 (42%) and 5/50 (10%) results with INR <2.0 and >3.0 respectively. Using the hospital laboratory as a reference standard, 92.6% of the ProTime venous and 77.8% (p= 0.25) of the ProTime fingerstick INR results matched the patient's therapeutic range classification (INR: 2 to 3) of the standard hospital laboratory result. Ninety-four percent of ProTime venous INR results and eighty eight percent of ProTime fingerstick results were within 0.5 INR of hospital laboratory results, while 96% of either system (ProTime venous or fingerstick) were within 0.7 INR.

Rapidity and Success Rate of Pro Time Method

This portable device provided rapid measurement of PT/INR result. The time taken to obtain the PT/INR result was less than five minutes in all the study samples.

Insufficient blood sample collection was observed in about 4% of the participants. This was due to the fact that the Tenderlett Plus fingerstick device owns a rather shallow puncture needle with a puncture

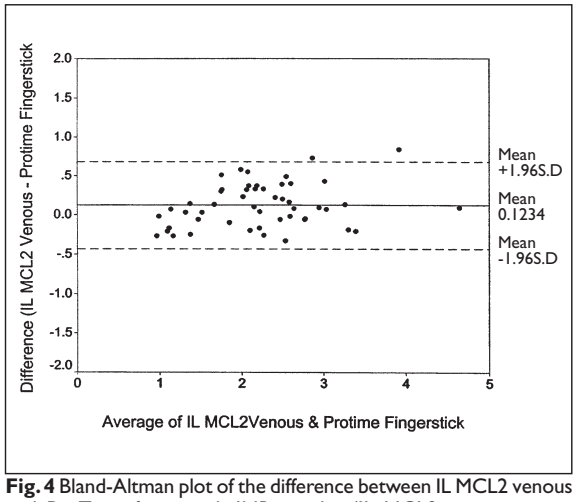

Fig. 4 Bland-Altman plot of the difference between IL MCL2 venous and ProTime fingerstick INR results (IL MCL2 venous minus ProTime fingerstick) plotted against mean INR values, (IL MCL2 plus ProTime fingerstick)/2. Standard deviation (S.D)=0.7663.

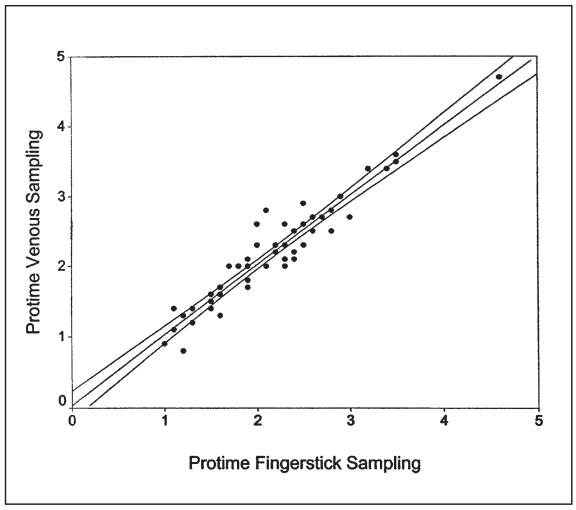

Fig. 5 Linear regression plot of INR by means of ProTime venous sampling against ProTime fingerstick sampling. Also shown are linear regression lines and 95% confidence limits.
y=0.919x + 0.155; r=0.956

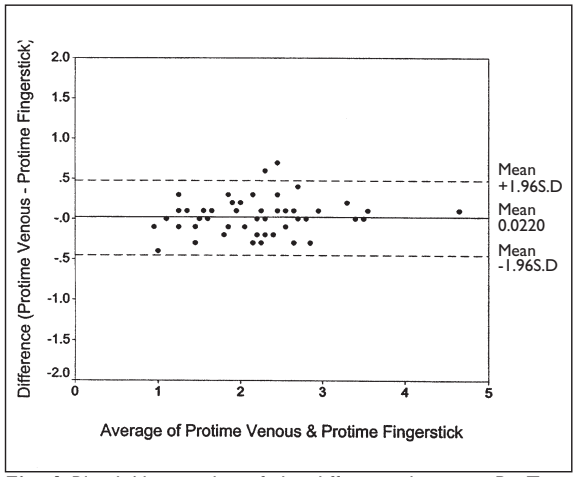

Fig. 6 Bland-Altman plot of the difference between ProTime venous and ProTime fingerstick INR results (ProTime venous minus ProTime fingerstick) plotted against mean INR values, (ProTime venous plus ProTime fingerstick)/2. Standard deviation (S.D)=0.7477.

depth of 1.75 mm which could be an important problem for blood collection especially in patients with more subcutaneous tissue. This problem was corrected with the use of the commonly used hospital fingerstick device called "Haemolance" which has a puncture depth of 1.80 mm.

DISCUSSION

The INR is the current standard test for monitoring anticoagulation therapy. One difficulty with anticoagulation is the variability of the effect of warfarin on the haemostatic system. The biologic response to warfarin is idiosyncratic and may fluctuate unpredictably. Patients may require very different doses of warfarin to reach the same level of anticoagulation. The risks of thromboembolism and bleeding depend on the intensity of anticoagulation. The results of a study by Cannegieter and her colleagues showed a U-shaped relation (INR-complication curve) between the intensity of anticoagulation and the probability of a complicating event; underanticoagulation increased the risk of thromboembolic complications and overanticoagulation may lead to haemorrhage. The risk of bleeding complication may be distressing to many patients and it can be life threatening. However, when adequately controlled, oral anticoagulant therapy is effective and safe[1,2].

Although INR is simple to determine, it requires venipuncture and proper laboratory resources for specimen handling and analysis. The quality of laboratory test results is often compromised by pre-analytical factors such as complexity of the test method and poor sample handling. The ProTime analyser is a portable point-of-care device for PT and INR testing that can be used with capillary and venous whole blood. INR assay is performed with fresh fingerstick whole blood on-the-spot, so sample transport and handling errors are eliminated. According to the manufacturer, it has been designed so that accurate and reliable results can be achieved with minimal training. Its promoted advantages include the ability to perform capillary blood sampling; a rapid turnaround time for results; relative ease of use by non-laboratory personnel; and potential for home monitoring. It requires no additional checks, controls or calibrations to assure the accuracy of the instrument.

ProTime analyser has the built-in safety measures to ensure that the system is working properly. Quality control is performed every time a test is run. Pre-set criteria are defined for the relationship between the control and the PT results. During sampling, if any of the pre-set quality criteria is violated,

a fault message will be displayed. This quality control feature which is unique in the ProTime analyser will minimise the risk of erroneous reporting. Furthermore, the thromboplastin reagent in each ProTime cuvette has an ISI of 1.0 that is in compliance with the WHO standard.

This study compared the results of INRs obtained through the venipuncture or the established standard hospital laboratory process to INRs obtained by the portable technique. Our study showed an excellent relationship of INRs between ProTime venous and the hospital laboratory IL MCL2 venous; ProTime fingerstick and hospital laboratory IL MCL2 venous; and ProTime venous and ProTime fingerstick samplings, with correlation coeffficient (r) of 0.925, 0.940, and 0.956 respectively. The regression equations and correlation coefficients were consistent, regardless of the specimen tested. The excellent correlation of the INRs was observed across a wide range of INR (Figs. 1, 3, 5). The mean difference in the INR between the each method used was small and not statistically significant as shown in the Bland-Altman plots (Figs. 2, 4, 6). The range of values define the 95% limits of agreement ranged from -0.422 to +0.606 INR units on average. In other words, for a new subject we expect the INR that generated by the two methods (Protime vs hospital laboratory IL MCL2) will give measurements that differs by less than 0.61, with any discrepancy being equally likely in either direction. The results of our study are quite similar to the previous studies on point-of-care analysers[3-5].

In our local setting, for the majority of our adult cardiac patients, the target INR range is 2.0 to 3.0. Our study showed no statistical significance in the ProTime venous and ProTime fingerstick INR results (92.6% versus 77.8%, p=0.25) in reference to the standard hospital laboratory method for INR that ranged between 2.0 to 3.0. Thus, ProTime fingerstick sampling is an acceptable alternative to venous sampling for INR measurement in adult cardiac patients on oral anticoagulation therapy. The findings of this study pose an important clinical implication. Because several conditions require long-term, if not lifelong, anticoagulation, frequent laboratory testing can become inconvenient. Self-management of INR with ProTime analyser may be feasible if it is used under the direction of a clinician. To date, few published works have demonstrated the feasibility of home monitoring of INR with portable devices[9-15]. A trial by Oral Anticoagulation Monitoring Study Group showed that 93% of point-of-care INR results were within 0.7 INR of reference laboratory results and the INR from the point-of-care device is clinically equivalent to the laboratory INR in professional and self-testing environments[15]. Self-testing would significantly enhance the convenience of monitoring for the patient which would permit more frequent testing, ensure that therapeutic drug levels are maintained more consistently and therefore reduce complications. Taborski et al[7] and Cromheecke et al[8] reported that patients performing self-management remain in the therapeutic target INR range a greater percentage of the time when compared to conventional laboratory testing, and tended to have less incidences of bleeding or thromboembolic events. Patients also overwhelmingly reported satisfaction and strongly preferred using the portable monitor to measure their INR.

Our study confirms that ProTime Microcoagulation System provides accurate and fast INR results in the clinic. The results can be achieved within minutes, allowing patients to shorten their outpatients clinic waiting time and enable the clinician to obtain the INR result on the spot and hence deliver counselling face-to-face, rather than waiting for the laboratory report and speaking to the patient by phone. Although the sample size of this study is rather small, it covers quite a wide range of INR values (0.83 to 4.69). Since most of the patients on oral anticoagulation therapy are aimed at the target INR range of 2.0 to 3.0, the results of our study is still useful and is adequate to cover most of the adult cardiac patients on oral anticoagulation therapy. ProTime analyser is a viable alternative to laboratory testing in adult cardiac patients on oral anticoagulation.

However, there are few disadvantages with the ProTime analyser. The Tenderlett Plus fingerstick device could become a potential problem in patients with more subcutaneous tissue due to its shallow puncture needle. To the best of our knowledge, this observation has not been described in other studies with the point-of-care INR devices. However this problem can easily be overcome with the used of hospital commonly-used fingerstick device called "Haemolance", which has a deeper puncture depth. Another shortcoming with ProTime analyser is the cost. The ProTime device costs about S$2,000 and each test will cost the patient S$7.50 versus S$6.00 by the conventional laboratory method. However, as with other devices, if this device is being used as a wide scale basis in future, the cost of the test might reduce significantly if not lower than the cost of the conventional laboratory method. The long term cost for patients with ProTime analyser may also be reduced in view of the fact that there will be less frequent outpatient visits and less complications

with anticoagulation from frequent INR monitoring at home.

CONCLUSION

Our study clearly shows that both the ProTime fingerstick and venous blood samples INR results were in good agreement with the standard laboratory technique. (r = 0.9403 and r = 0.9248 respectively). From the result of this study, the rapid point-of-care device, the ProTime analyser, appears to have an acceptable level of accuracy for INR values in the recommended target ranges in adult cardiac patients on oral anticoagulation therapy. Immediate test results allows for rapid appraisal of the cardiac patient's anticoagulation status. This study also demonstrates the successful use of ProTime analyser in a novel fingerstick INR measurement. Thus, the use of ProTime analyser for anticoagulation monitoring is feasible and further trial is needed to study the feasibility of using it for patient home monitoring of INR.

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