Original Article

Evaluation on the Use of a Portable Unit Versus the Laboratory for the Monitoring of International Normalized Ratio (INR) in Orally Anticoagulated Patients

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Abstract

***Introduction**: Measuring the International Normalized Ratio (INR) through a laboratory requires venipuncture and takes about 1 hour for results to be available. A portable monitor (CoaguChek Plus System), which measures the INR using fingerstick samples, is evaluated in this study to determine its clinical significance in anticoagulated and non-anticoagulated individuals. The hospital's outpatient and inpatient laboratories were also compared in the study. **Materials and Methods**: Paired venous and capillary blood INRs were performed on anticoagulated patients using the monitor and the Singapore General Hospital (SGH) outpatient and inpatient laboratories (OPS and IPS labs). Paired INRs of control samples were also performed using the monitor and the IPS lab. **Results**: We plotted the difference in INR by the 2 methods (monitor and OPS lab, n = 91) against their mean, and calculated the limits of agreement (95% of the difference would lie between -0.90 to 0.70). After a logarithmic transformation on the data, we found that for 95% of the cases, the OPS lab would differ from the monitor by 13% below to 14% above. There was also a marginal difference (95% limits of agreement of -0.14 to 0.10) when we compared the INR obtained from OPS and IPS laboratories (n = 43). Our control sample (n = 19) showed that the 95% confidence interval for the bias was -0.04 to 0.10. **Conclusion**: The monitor should be used with caution in patients with INR >3. We suggest use of the monitor in situations where the non-anticoagulated state of a patient needs to be measured. There is a difference in INR measured by laboratories within the same institution.*

***Ann Acad Med Singapore* 2002; 31:145-9**

Key words: Anticoagulation, Fingerstick, INR, Monitoring, Portable Unit

Introduction

Oral anticoagulation therapy is used for a number of conditions, namely deep venous thrombosis, pulmonary embolism, mechanical heart valves, embolic stroke as well as atrial fibrillation.[1] Patients receiving this therapy are carefully monitored in order to maintain the intensity of anticoagulation in the appropriate therapeutic range.[2]

The current preferred method of monitoring warfarin therapy is by monitoring the International Normalized Ratio (INR) through the traditional laboratory method which requires venipuncture, a costly and time-consuming procedure.[3] At the Outpatient Anticoagulation Clinic in the Singapore General Hospital, patients often spend long hours waiting for the test results. This can discourage patients from complying with frequent follow-up appointments, in addition to being a hindrance to the workflow process within the organisation.

The availability of a portable monitor unit that uses a drop of whole blood obtained by fingerstick to determine the INR and prothrombin time (PT) has brought about the possibility of using it as a substitute.[4,5] Thus, to determine the accuracy of both portable unit and clinical laboratory INR determinations, comparisons were done with the criterion standard method of INR determination. Any significant difference in the INR measurements between the inpatient and outpatient laboratory anticoagulation equipment[6,7] was also determined.

Materials and Methods

The Department of Haematology, Singapore General Hospital operates a weekly outpatient anticoagulation clinic managed by a haematologist, pharmacist and nurse. This was a randomised, prospective, self-controlled study carried out over 2 months. Patients, who received oral anticoagulation therapy for a variety of thromboembolic conditions, were consecutively enrolled into the study based on their INR value performed using the hospital's

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outpatient laboratory equipment. They were categorised based on their initial laboratory-determined INR into the range values of 1 to 1.5, >1.5 to 2, >2 to 2.5, >2.5 to 3, >3 to 3.5 and >3.5 respectively. Patients were not included into the study if their INR value fell in the range that already had sufficient numbers of patients enrolled. All enrolled patients gave both verbal and written consent to the study.

A separate control sample of healthy individuals who were not receiving any anticoagulation therapy was included into the study. This was to determine if there was any discrepancy between the CoaguChek Plus (Boehringer Mannheim, GmbH, Mannheim, Germany) monitor and the IPS lab in this patient subgroup.

Venous blood was drawn from patients, citrated and centrifuged to form citrated plasma. Human thromboplastin (Thromborel S) with an international sensitivity index (ISI) of 1.22 was then added to the plasma and the coagulation time measured and converted to the INR. At the same time when the venous samples were drawn, another aliquot was kept aside for INR measurement using the Inpatient Laboratory (IPS lab) equipment (for 43 samples), to ensure consistency in the INR readings obtained from OPS and IPS laboratories. The patients were then referred to the pharmacist, before or after consultation with the doctor, for INR check using the CoaguChek Plus portable system (the test strips of which had an ISI of 1.9).

The PT test was initiated by inserting a CoaguChek Plus PT test cartridge into the CoaguChek Plus Coagulation monitor. The monitor read a code on the test cartridge to determine test identity and to obtain calibration information. Upon heating up the cartridge, a drop of fresh, whole blood was placed on the test cartridge sample application well. Blood was drawn by capillary action into the reagent chamber where it mixed with the thromboplastin to initiate coagulation. The blood sample moved along the reaction path until a clot formed. The laser optical system detected the clot by monitoring blood flow; endpoint was reached when the blood stopped moving. The time from applying sample to detecting the clot was the PT. After the PT was converted to INR and displayed, a new cartridge was inserted for the next test. Each test required approximately 3 minutes.

Results

Ninety-one subjects agreed to participate and were enrolled into the study. The number of pairs of INR measured for each INR range is shown in Table I.

For each patient, the two procedures occurred within a one and a half hour period. Analysis on 91 blood specimen pairs from anticoagulated patients were measured using the CoaguChek Plus monitor and the outpatient laboratory. A plot on the difference between the methods (INR obtained from CoaguChek Plus minus the INR from the OPS lab) against their mean was made as this is a more accurate method of comparing two methods of clinical measurement.[3,6-8] The agreement between the monitor and the outpatient laboratory results is illustrated in Figure 1.

TABLE I: NUMBER OF PAIRS OF BLOOD SPECIMEN PER INR RANGE AND THEIR MEAN DIFFERENCE AND STANDARD DEVIATION

INR	No. of patients	Mean difference	SD
1–1.5	13	0.165	0.340
>1.5–2	15	0.165	0.285
>2–2.5	16	-0.010	0.152
>2.5–3	18	-0.003	0.390
>3–3.5	15	-0.235	0.161
>3.5	14	-0.734	0.249
Total no. of patients	91		

Figure 2 shows that since the differences are normally distributed (Gaussian)[8] (Fig. 2), 95% of the differences will lie between these limits[8] of mean +2SD and mean -2SD, i.e. -0.90 to 0.70.

Figure 1 also shows that the differences tended to deviate from this range and toward a negative difference when the INR values increased above 3. The mean differences for INR >3 and >3.5 were -0.235 and - 0.734, respectively (as shown in Table I). This meant that the INR obtained for the same patient by OPS lab was relatively higher (compared to the other INR ranges) than that from the CoaguChek Plus monitor, when the INR was >3.

The limits of agreement are only estimates of the values which apply to the whole population.[8] Hence, to show precision of the estimates of the values which apply to the whole population, standard errors and confidence intervals[8] were used. The standard error of the difference in mean by the 2 methods was 0.0424. The 95% confidence interval for the bias was -0.03 to -0.17 (90 degrees of freedom and t = 1.6645); for the lower limit it was -0.77 to-1.02 and for the upper limit it was 0.57 to 0.81. The scatter of the differences increases as the average INR increases and this cannot be ignored as the limits of agreement would be wider apart than necessary for small INRs and narrower than they should be for large INRs.[8] Since the differences were proportional to the mean INR, the same analysis was applied to the logarithmic transformed data[8] (Fig. 3). On the log scale, the mean difference was -0.008 and the limits of agreement were -0.14 to 0.13. To relate this limit of agreement to the original scale of measurement,[8] antilogs of these limits were taken. For 95% of cases, the INR from OPS will be 0.87 to 1.14 times that from CoaguChek Plus; i.e., the OPS lab may differ from the CoaguChek Plus by 13% below to 14% above.

Fig. 1. Plot of the difference against mean for the INR obtained by CoaguChek Plus monitor and outpatient laboratory. Where there is agreement between the CoaguChek Plus and the outpatient laboratory, the difference would distribute evenly about the reference line (i.e. where the difference in INR = 0.0). The mean difference calculated was –0.103 and the standard deviation was 0.405. The reference lines are the mean and +2SD.

Fig. 2. Histogram of the difference between the methods, i.e. INR obtained from CoaguChek Plus minus the INR from the outpatient laboratory. The distribution seems normal because numerous variations between subjects have been removed; only the measurement error is left 9. The standard normal curve is shown.

The control sample (n = 19) showed a mean difference of 0.03 (SD 0.168) between the 2 methods (95% confidence interval for the bias was -0.04 to 0.10).

When 43 INRs measured by OPS lab and IPS lab were analysed, there was marginal difference (95% limits of agreement -0.14 to 0.10).

A quality control (QC) system on the CoaguChek Plus monitor was established by using a set of control solutions with PT values in the high intensity range of 49 to 21 seconds, as provided by the manufacturer. Before starting each session (up to 31 tests done per session), QC was done. At each QC check, the CoaguChek Plus monitor displayed control values within the accepted range as indicated by the manufacturer.

Discussion

In this study, it was demonstrated that the CoaguChek Plus monitor was moderately less precise when compared to the OPS lab. Accuracy was best at INR <3 (especially

Fig. 3. Plot of the difference of log (INR by CoaguChek Plus monitor, -INR by outpatient laboratory) against the average INR obtained by outpatient and inpatient laboratories. Where there is agreement between the CoaguChek Plus and the outpatient laboratory, the difference would distribute evenly about the reference line (i.e. where the difference in INR = 0.0). The mean difference calculated was –0.008 and the standard deviation was 0.069. The reference lines are the mean and +2SD.

when the INR was between 2 to 3). Above this level, the CoaguChek Plus monitor tended to underestimate the INR. This is of concern, as INR at this range would include patients who have heart valve replacements, a group of patients who are at high risk for thrombosis. In a study by Douketis et al,[9] it was also shown that for INR >3, the CoaguChek monitor consistently underestimated the INR when compared with the laboratory method. Other portable monitors showed a similar trend.[6,7,10] In contrast, the study by Cosmi et al[11] showed an overestimation of INR values above 3.

It must be noted that the difference in INR from CoaguChek Plus monitor and the OPS lab analysis could have been due to patient-related differences (e.g. tissue activation and thrombocyte activity) rather than differences in analysis technique between the 2 test systems.[6]

Not only that, in a study by Morrison et al,[12] the authors tested 2 different reagents (using both capillary and venous blood samples) and showed that to check INR values of ≥5.0, venous blood samples should be used, and not capillary blood.

Converting the PT to INR takes into account the different sensitivities of thromboplastins reagents,[6] thus it is likely that the difference is intrinsic to the measurement technique employed by the monitor rather than a lot-related idiosyncrasy with the thromboplastin reagent.[6] The INR determination can be improved by using more responsive thromboplastins with ISIs in the range of 1 to 2.[13-15] The thromboplastin in the CoaguChek Plus reagent strips is from rabbit brain whereas that from the laboratories is from human brain. This could account for the CoaguChek Plus monitor being less sensitive to the anticoagulant effects of warfarin[15] with increasing INR.

The control sample showed minimal difference between

the 2 methods (CoaguChek Plus and IPS lab), suggesting possible use of the monitor in situations where the non-anticoagulated states of patients are required.

It is interesting to note that when the INR obtained from the OPS lab was compared with that from the IPS lab, there was a mean difference of -0.21 (with a standard deviation of 0.474). The 95% CI for the bias was -0.143 to 0.101. This showed that even within the institution, the INR may vary marginally with the laboratory used. In this study, both the OPS and IPS laboratories used the same thromboplastins, and the only differences were in the machines used in the 2 laboratories respectively (semi-automatic in the OPS lab and fully automatic in the IPS lab), and in the laboratory technicians doing the tests.

Our study has several limitations. Two different pharmacists did testing of the INR using the CoaguChek Plus monitor, and although both were sufficiently trained in the technique, there was still a possibility for inter-personnel variation in obtaining the patient's blood sample and performing the test.

Although repeatability is relevant to the study method comparison, repeatability on both CoaguChek Plus monitor and the OPS lab machine was not examined. It is possible that either or both machines had poor repeatability, thus suggesting considerable variation in repeated measurement on 1 sample.

As with many other studies,[3-7,16] this study did not address several other important issues, including the variation in functional accuracy of the lot of cartridges or strips provided by the manufacturer, intra-subject variation in the accuracy of measurements, and durability of the monitors and test strips (this is especially so in hot and humid climates).

It is of concern that at INR values >3, the CoaguChek Plus monitor produced lower values. This means that patients may be over-anticoagulated without the physician's knowledge. A study to show the significance of this would have to be carried out with a much larger patient group size.

Conclusion

Although previous studies have shown that portable systems (including systems similar to that of the CoaguChek Plus)[3-7,17] are satisfactorily accurate in measuring the INR for anticoagulated patients, our study seems to show that this is true only when the INR measured is <3.5.

The study results suggest that the CoaguChek Plus monitor should be:

1. used by healthcare personnel trained in doing the test;
2. calibrated regularly;
3. used for INR values between 1.0 and 3.5;
4. used with caution in patients with INR >3.5.

It must be noted that the CoaguChek Plus monitor needs to be calibrated regularly to maintain the quality of INR results.

Many studies have shown the feasibility and cost effectiveness of patients doing home INR monitoring, when they are on long-term therapy.[16,18-25] However, our results show that this should be proceeded with caution, since most of these long-term patients are heart valve replacement patients who require higher INR maintenance levels.

The ease and convenience of a portable system would perhaps prevent patients from failing to show up at appointments. In addition to using these monitors in patients on long-term maintenance anticoagulation, appropriate patients who had just started on therapy may also benefit. Such systems may help to lower the risks of early thromboembolic or haemorrhagic episodes. It remains obvious that patients need to be trained sufficiently in order for such monitors to work effectively.[11,23-27]

To summarise, the accuracy of the CoaguChek Plus monitor appears to be satisfactory when the INR values of patients are <3. With the use of more responsive thromboplastins by the manufacturer, perhaps the accuracy would improve for these higher INR values.[7,10,15,17] If it is accepted that CoaguChek Plus may underestimate the INR by 13% or overestimate by 14%, then use of the monitor in place of the laboratory method could be implemented for clinical purposes in the Singapore General Hospital. However, it needs to be used with caution in patients with INR >3. As the control samples show that the difference in INR is minimal, it appears safe to use the monitor in situations where the non-anticoagulated state (i.e., low INR) of a patient needs to be measured e.g. pre-surgeries or pre-dental procedures.

There is a marginal difference between the 2 laboratories within the same institution, even though the same thromboplastins (ISI = 1.22) were used. This should be investigated further as theoretically, there should not have been a difference.

Acknowledgements

The authors would like to thank Ms Tai Bee Choo, Medical Statistician, National Medical Research Centre; Ms Stephanie Fook Chong, Biostatistician, Singapore General Hospital; and Ms Jennifer Lee, Statistician, Singapore General Hospital for their expert advice in the statistical analysis of this study. This study was funded by Boehringer Mannheim.

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