Pediatr Cardiol 21:347–352, 2000
DOI: 10.1007/s002460010078

Pediatric
Cardiology

Capillary Whole Blood Monitoring of Oral Anticoagulants in Children in Outpatient Clinics and the Home Setting

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Abstract. A whole blood prothrombin time/international normalized ratio (PT/INR) monitor (CoaguChek, Roche Diagnostics Corp., Indianapolis, IN) was assessed in children for its accuracy, reliability, safety, and acceptance by health care personnel and patient's families. The PT/INR values measured by the CoaguChek monitor showed an excellent correlation with PT/INR values measured by the Hospital for Sick Children (HSC) laboratory ($r = 0.96$) and Hamilton Civic Hospitals Research Centre (HCHRC) laboratory ($r = 0.92$) in clinic patients and a close correlation with PT/INR values measured by the HSC laboratory ($r = 0.76$) and HCHRC laboratory ($r = 0.74$) in patients at home. Reduced correlation in the home setting did not adversely affect clinical management. The whole blood PT/INR monitor is safe and accurate for children requiring oral anticoagulation therapy in either the outpatient clinic or home setting.

Key words: Pediatrics — Anticoagulants — Thrombosis

Increasing numbers of children with major primary illness such as complex congenital heart disease are at risk for, or have developed, thromboembolic disease and require anticoagulation therapy for variable periods of time [2]. Coumadin in North America and phenprocoumon in Europe are the most commonly used oral anticoagulants for prolonged outpatient treatment of pediatric patients [1]. The activities of oral anticoagulants must be closely monitored to ensure safety and avoid both hemorrhagic and thromboembolic complications. Unfortunately, oral anticoagulants require more frequent monitoring in pediatric patients compared to adults because of the complexity and labile nature of primary diseases in children [2]. The increased difficulty of safely managing anticoagulation in children has resulted in the formation of specialized thrombophilia clinics at some tertiary pediatric centers [9].

Venepuncture in children is frequently difficult, particularly in the presence of primary medical problems that necessitate frequent venous access. Also, the recent emergence of thromboembolic complications in children who are now surviving major primary illnesses, such as congenital heart disease and childhood cancer, means there is limited experience in managing anticoagulation in children, especially outside of large tertiary pediatric institutions. The problem of safely monitoring oral anticoagulants is often a deterrent to optimal anticoagulation therapy.

Recently available portable monitors that measure prothrombin time (PT) values using capillary whole blood have been tested in adults receiving oral anticoagulants [3, 5, 16, 18]. Whole blood PT monitors offer potential advantages for the management of oral anticoagulant therapy in children, including the reduced need for venepuncture and the ability to monitor children geographically distant from the tertiary care pediatric centers. Therefore, we prospectively evaluated a whole blood PT monitor in children requiring oral anticoagulant therapy.

Methods

Patient Population

There were two phases to the clinical study. Phase 1 was an outpatient study in pediatric anticoagulation clinic ("clinic") and phase 2 was a study conducted at home ("home"). All children (newborn to age 18 years) receiving oral anticoagulant therapy and who were monitored through the pediatric outpatient anticoagulation clinic at the Hospital for Sick Children (HSC) (Toronto, Ontario, Canada) were eligible for

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the phase I clinic study. The same patient population was also eligible for the phase 2 home study if they met the following criteria: the parent and/or child understood the instructions, were willing to perform the test at home with confirmation in the laboratory on at least three occasions during the study period, were able to adequately perform finger pricks to obtain blood samples, and were able to operate the CoaguChek. In each phase children were monitored for a period of 8 weeks. The frequency of monitoring during the study period was at least weekly, and it was more frequent if clinically indicated. The protocol was approved by the HSC institutional ethical review board. Informed consent was obtained from all parents and, where appropriate, children prior to enrollment in the study. Patients were monitored with one of three target international normalized ratios (INR): therapeutic range for venous thromboembolic disease (INR 2.0–3.0), therapeutic range for patients with prosthetic heart valves (INR 2.5–3.5), and prophylactic range for children at risk for a thromboembolic complication (INR 1.4–1.9).

Whole Blood Sampling

All whole blood PT monitor measurements were made on blood obtained by finger prick. All INR values determined in the laboratory were performed on blood obtained by venepuncture. Platelet-poor plasma was obtained from whole blood anticoagulated with sodium citrate (9 parts blood to 1 part sodium citrate), followed by centrifugation at 3000*g* for 20 minutes. Laboratory PTs were measured in the HSC clinical coagulation laboratory (clinic values) and in a research laboratory (research values) located at the Hamilton Civic Hospital's Research Centre (HCHRC) (Hamilton, Ontario, Canada). Clinic PTs were measured on an Electra 1400 (MLA, Pleasantville, NY) using Ortho Brain Thromboplastin (Ortho Diagnostics, New York) [International Sensitivity Index (ISI) 1.87]. Research PTs were measured on an Automated Coagulation Laboratory (Instrumentation Laboratory S.P.A., Milan, Italy) using Thromborel S (Behring Diagnostics, Inc., Montreal, Quebec, Canada) (ISI 1.02). A second blood sample was anticoagulated with EDTA to measure hematocrit and hemoglobin (Coulter, Inc., Hialeah, FL). Capillary blood samples were collected with an automated device, either the Tenderlet device (International Technidyne, Edicon, NJ) or the Soft Touch (Roche Diagnostics Corp., Indianapolis, IN). Samples were obtained from either a finger prick in older children or a heel prick in young infants. For some younger children direct application of the blood drip onto the application zone of the test strip was difficult. In such cases the method adopted was to collect the blood drop into a capillary tube and then transfer the blood sample immediately onto the application zone. This method of blood collection has been validated previously in our clinic (unpublished data). In the home study, all patients routinely performed a level 2 control at study entry (week 1), week 4, and study completion (week 8) on the same day that venous INRs were performed.

Whole Blood Prothrombin Time Monitor

The whole blood PT monitor was the CoaguChek. Briefly, after the monitor is turned on, a test strip containing a reaction zone of iron oxide particles and rabbit brain thromboplastin (lot-specific ISI between 1.9 and 2.2) is inserted into the monitor and warmed to 37°C. A drop of capillary blood is applied to the test strip application zone. Capillary forces draw the blood to the reaction zone, where the thromboplastin activates the coagulation cascade. Two magnets are directly below the reaction zone within the CoaguChek. The iron oxide particles are aligned horizontally by a permanent magnet and are forced into vertical alignment by a pulsating electromagnet at a frequency of 2 Hz. A photocell, situated above the test strip, records the regular pulsation pattern by reflectance photometry. As a fibrin matrix is formed the iron oxide particle movement is inhibited and eventually stopped. The time from the first contact of blood with the thromboplastin to the cessation of movement (clot formation) is measured and the INR calculated using a calibration code stored in the lot-specific code chip.

Patient Education for the "Home" Study

The nurse coordinator (V.M.) of the anticoagulation clinic taught parents or older children to use the CoaguChek. The educational program consisted of an overview of the study, an explanation of the parent/patient requirements, a brief demonstration of the monitor, viewing of a training video, and one-on-one instruction on the finger-prick procedure and use of the CoaguChek. Before home use, parents or older children were required to demonstrate their ability to use the CoaguChek successfully on at least three separate occasions. The assessment of the ability to use the Coaguchek included assessing parents or children's ability to use the control materials that come with each box of test strips. In accordance with our current clinical practice, all parents or children were trained to perform a quality control check (level 2 control) each time they commenced a new box or lot of test strips if the INR was markedly abnormal or if they suspected improper storage of the test strips. Families recorded all PT/INR values and any coumadin dose changes in a calendar. The nurse coordinator was in contact with families at least weekly by telephone and after every home test.

Questionnaires

All home study patients were asked to complete a detailed questionnaire about the study training program, ease of monitor use, the user's manual, and the package inserts for the test strips and controls.

Statistical Analyses

Correlation between the CoaguChek and laboratory PTINR reference values were statistically evaluated by linear regression. Results from home and clinic patients were compared separately. Single-factor ANOVA was used to compare PT and INR values obtained using the CoaguChek and by the HSC and the HCHRC laboratories. If there was a statistically significant difference between the three groups, multiple paired Student's *t*-tests with Bonferroni correction were used to analyze the differences. Unless otherwise indicated, *p* values less than 0.05 were considered statistically significant. Proportions of values within 0.5 of the laboratory INR were also determined for all patients, as was the relationship of these differences to the INR therapeutic range. Clinical demographic information and results of the home patients' questionnaire are presented descriptively.

Results

Patient Population

Sixty children (27 girls and 33 boys) participated in the outpatient clinic study and 20 children (12 girls and 8 boys) in the home study. The demographic information for both the clinic and the home patient populations were

Table 1. Comparison of PT/INR values obtained with CoaguChek versus laboratory values

	CoaguChek	HSC	HCHRC
Outpatient clinic			
Mean (95% CI) PT (sec)	17* (16.6–18.7)[a]	16* (15.4–17.4)[a]	22 (19.9–24.7)
Mean (95% CI) INR	2.2** (2.0–2.6)[b]	1.9** (1.6–2.1)[b]	2.0 (1.8–2.3)
Home setting			
Mean (95% CI) PT (sec)	18* (17.2–19.2)[a]	18* (17.5–19.3)[a]	24 (22.6–26.2)
Mean (95% CI) INR	2.4** (2.1–2.6)[b]	2.3** (2.1–2.5)[b]	2.3 (2.1–2.4)

[a] Comparison of the measured PT between the CoaguChek and HCHRC and between HSC and HCHRC using single factor ANOVA and confirmed with multiple-paired Student's *t*-tests with Bonferroni correction. * $p < 0.001$.
[b] Comparison of the INR between the CoaguChek and HCHRC and between HSC and HCHRC using single factor ANOVA. ** No significant difference.

similar and therefore combined. The ages of the 80 children enrolled in both studies ranged from 3 months to 18 years. The underlying diseases which necessitated anticoagulation therapy were prosthetic heart valve replacement (29%), congenital heart disease (27%), deep vein thrombosis (8%), nephrotic syndrome (8%), and a spectrum of other diseases (18%). The average number of INRs performed per month ranged from 9.5 in children <1 year old to 4.3 in children aged 11 to 18 years. The average number of changes in warfarin dose per month ranged from 4.5 in children <1 year old to 1.8 in children aged 11 to 18 years. There were no significant clinical complications, neither thrombotic nor hemorrhagic, during the clinic or home study.

Comparison of Laboratory and CoaguChek PT and INR Values

As expected, average PT values measured at the HSC and HCHRC laboratories differed and from values measured by the CoaguChek, reflecting different thromboplastin reagents. In contrast to PT values, average INR values measured at the HSC and HCHRC laboratories were similar to each other and to INR values measured by the CoaguChek (Table 1). The INR values measured by the HSC and HCHRC laboratories showed similar correlation (by linear regression) in the clinic ($r = 0.95$) and in the home setting ($r = 0.95$). The patient's INR values measured by the CoaguChek monitor showed an excellent correlation with INR values measured by the HSC laboratory ($r = 0.96$) and HCHRC laboratory ($r = 0.92$) in clinic patients and a close correlation with INR values measured by the HSC laboratory ($r = 0.76$) and HCHRC laboratory ($r = 0.74$) in patients at home. Figure 1 shows the correlation curves for the INR values reported by CoaguChek versus the HSC INR values in both the clinic and the home patients.

Warfarin monitoring is aimed at maintaining the patient's INR within a therapeutic range. Figure 2 shows

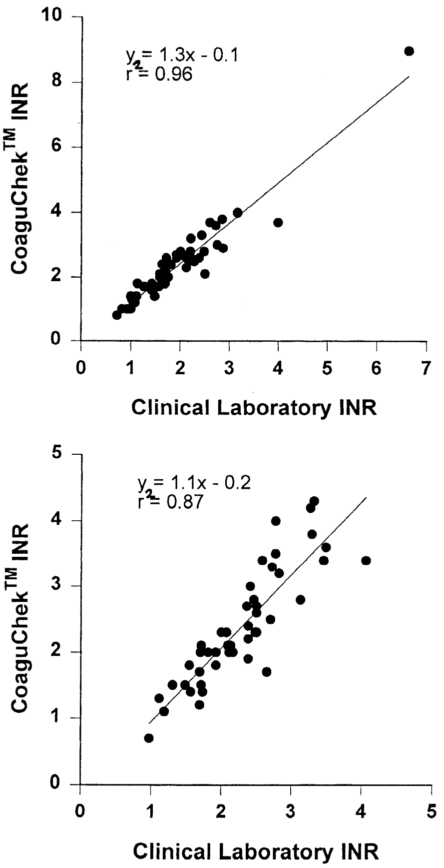

Fig. 1. Correlation curves (linear regression lines) for CoaguChek INRs versus paired INRs determined in the clinical laboratory at the Hospital for Sick Children, Toronto, for children monitored in the outpatient clinic (*top*) and the home setting (*bottom*).

the paired CoaguChek versus HSC INR values for the three target ranges used in the study for both clinic and home patients. When compared to the HSC INR, the INR value obtained with CoaguChek crossed into or out of the therapeutic range in 29% of cases. In the majority of these cases (58%), the INR values obtained by CoaguChek and the HSC laboratory differed by less than 0.5.

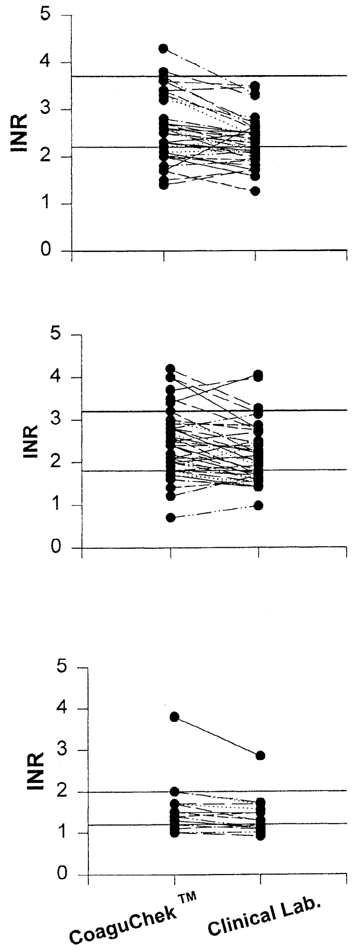

Fig. 2. Paired INR values obtained with CoaguChek and in the clinical laboratory at the Hospital for Sick Children, Toronto, for the target INRs of 2.5 to 3.5 (*top*), 2.0 to 3.0 (*middle*) and 1.4 to 1.8 (*bottom*). The horizontal lines represent the upper and lower critical clinical decision INR values (defined as the INR at which warfarin dosing may be modified due to deviation from the target range).

The accuracy of CoaguChek INR values compared to HSC INR values was compared by plotting delta INR (CoaguChek INR − HSC INR) versus HSC INR (Fig. 3). The INR obtained from CoaguChek was within 0.5 of the HSC INR for 71% of paired patient samples and within 0.9 in 92% of paired patient samples. Similar results were obtained when the CoaguChek INR values were compared to the HCHRC INR values (data not shown). There was no correlation between increasing INR and delta INR.

Questionnaires

All patients found the training program to be helpful, and the majority of patients required no further review of training materials. All parents/patients stated that the CoaguChek was easy to use and preferable to venepuncture INRs.

Discussion

The use of warfarin in children presents several unique problems. Children requiring warfarin frequently have complex underlying disorders, necessitating frequent monitoring. However, obtaining venous access is often difficult [2, 9]. The need for weekly visits to the clinic for anticoagulation monitoring is a difficult burden on many families, especially those who live in remote areas. Frequently, children rely on community laboratories, which are often unable to provide optimal facilities for the care of small children. Capillary whole blood monitoring of oral anticoagulation potentially offers a major step forward in the management of children requiring oral anticoagulation, especially if monitoring can be safely performed at home. The current study evaluated the accuracy, reliability, and acceptability of the CoaguChek monitoring system in a cohort of pediatric patients in the outpatient clinic and at home. The CoaguChek was shown to be easy to use, accurate, and reliable in a pediatric population.

Dramatic improvements in tertiary pediatric care, particularly in pediatric cardiac surgery and childhood cancer, have led to improved survival for many children with previously lethal diseases [14]. The increased survival in children with serious diseases has been associated with an increase in secondary complications, of which thromboembolic disease is very common [14]. One of the mainstays of treatment and prevention of thromboembolic disease is oral anticoagulation therapy. A medline search of the English literature from 1980 to 1996 identified 51 publications describing the use of warfarin in children (references available upon request). More than 80% of reported pediatric patients received warfarin for primary prevention of thromboembolism secondary to prosthetic heart valves. The literature likely reflects reporting bias and fails to reflect the increasing use of therapeutic warfarin for thromboembolic disease. Currently, <50% of the children attending our anticoagulation clinic receive warfarin for prosthetic valve prophylaxis (unpublished data).

Warfarin has a relatively narrow therapeutic window and requires close monitoring to ensure effective prevention of thrombosis, with minimal bleeding risk [2, 9, 14]. The PT is the most commonly used test to monitor oral anticoagulation therapy. Commercially available thromboplastin reagents used to measure PTs have differing sensitivities to decreased plasma concentrations of vitamin K (VK)dependent coagulant proteins, necessitating standardization of PTs [15]. To overcome this problem, thromboplastins are compared to the World Health Or-

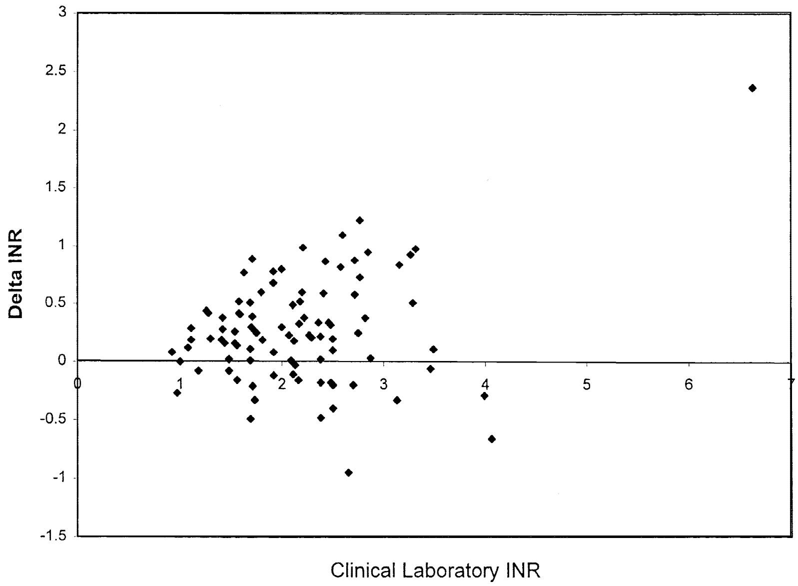

Fig. 3. Delta INR, defined as the CoaguChek INR minus the paired INR value obtained in the clinical laboratory at the Hospital for Sick Children, Toronto, plotted against the HSC INR.

ganization reference thromboplastin and assigned an ISI, which is a measure of a reagent's responsiveness to low plasma concentrations of VK-dependent factors. The INR is then calculated as follows: (patient PT/control PT)^{ISI}. The INR is accepted internationally as a standardized form of the PT and is recommended for monitoring all patients requiring oral anticoagulants, irrespective of age [8]. For venous thromboembolic disease, the usual target range for the INR is 2.0 to 3.0, and for prosthetic heart valves the usual target range is 2.5 to 3.5 [14]. Current practice is to monitor patients frequently until the INR has reached a steady state within the therapeutic range. The frequency of subsequent measurements of the INR is dictated by the clinical circumstances. For most children weekly monitoring is necessary [7, 9]. Until recently, warfarin monitoring using the INR system required venous blood to be taken at regular intervals. Obtaining venous access in children is frequently difficult and distressing. The increasing use of warfarin for treatment of thromboembolic disease in children, as distinct from primary prophylaxis, has increased the complexity of warfarin monitoring. Children with serious underlying disorders, increased number of intercurrent illnesses, and usually multiple drug interactions require frequent monitoring of warfarin therapy [2]. Although the relative number of children requiring warfarin is small compared to the number of adults receiving warfarin, the increased complexity of managing children on warfarin therapy has led to the development of specialized pediatric anticoagulation clinics at major tertiary pediatric centers. Many children are unable to attend such clinics for each INR measurement due to geographical distance.

Capillary whole blood monitoring of oral anticoagulation has been tested previously in adults. Randomized prospective studies have shown that portable INR monitors achieve superior anticoagulation control compared to standard anticoagulation clinic care [17]. Adult patients requiring oral anticoagulation monitoring strongly prefer using portable INR monitors [1]. The use of portable INR monitors has led to the development of programs for self-monitoring/self-adjustment of oral anticoagulation therapy for adult patients requiring long-term oral anticoagulation [4, 6].

Capillary whole blood monitoring of oral anticoagulation potentially offers tremendous advantages in the management of children requiring oral anticoagulation. Reducing the need for frequent venepuncture greatly improves the ability to monitor oral anticoagulant therapy, reduces parent/patient anxiety, and probably improves compliance. The ability to monitor children at home, without the need for weekly visits to the laboratory or hospital, reduces the burden on children and their families. Initial studies in children suggest that portable monitors are safe and offer practical advantages in the long-term management of oral anticoagulation [12]. However, prior to widespread use of capillary whole blood monitoring, especially in the home setting, the safety and effectiveness must be assessed, as must the acceptability of use of home monitors to both families and physicians.

We assessed the CoaguChek capillary whole blood monitoring system in a cohort of children in the outpatient clinic and at home. In the outpatient clinic, the correlation between the CoaguChek INR values and the laboratory INR values was excellent. The correlation between the CoaguChek and laboratory INR values in the home setting was very good, although not as close as observed in the clinic patients. Possible reasons include operator variability in the use of the CoaguChek at home and variable timing of CoaguChek samples compared to laboratory samples. All patients were using a CoaguChek for the first time during the study, and operator variability may be reduced with longer term use of the monitor.

Correlation curves can be misleading because correlation does not necessarily confirm accuracy [10, 12]. We plotted delta INR versus the laboratory INR values to determine the accuracy of the CoaguChek monitor. For the entire cohort, of both clinic and home patients, the CoaguChek INR was within 0.5 of the laboratory INR in more than 70% of cases. Our results compare favorably with those of studies of portable INR monitors in adult patients [13]. Ultimately, accuracy and precision must be considered together in the clinical context of the patient and the result obtained. The aim of warfarin therapy is to maintain the INR within a predetermined target range, which optimizes therapeutic benefit for the lowest bleeding risk [12]. In our study, the CoaguChek INR differed from the laboratory INR in terms of being inside or outside the target range in 29% of cases. However, many factors are involved in the decision to alter warfarin dose—not just the INR value in isolation. The clinical impact of the observed differences is difficult to ascertain. In the majority of cases, the CoaguChek INR differed from the laboratory INR by less than 0.5, implying that any dose adjustments were likely to have been minor and not substantially altered the patient's risk of bleeding or thrombosis due to under- or overanticoagulation.

All patients entered into the home phase of the trial were required to satisfy many criteria and demonstrate adequate ability to use the CoaguChek monitor following a comprehensive educational program. Although all parents/patients in our study were satisfied with the educational program and preferred using the CoaguChek monitor to having laboratory INRs, not all patients will be suitable for home monitoring. Patient screening, education, and ongoing support by health professionals experienced in anticoagulation monitoring will be crucial to maintaining a home monitoring program.

In conclusion, the CoaguChek monitoring system, when combined with a comprehensive educational and support program, is an effective and safe method for monitoring anticoagulation in children. The INR values obtained are of acceptable reliability and accuracy in the home and especially in the clinic setting. Clinically, there were no bleeding or thrombotic complications throughout the study period suggesting that the minor differences in results obtained by the CoaguChek do not alter the risk of bleeding or thrombosis due to over- or underanticoagulation. Importantly, the CoaguChek monitor makes reliable INR monitoring more accessible and is much preferred by patients compared to laboratory monitoring. Home monitoring programs for oral anticoagulation in children offer an attractive alternative to laboratory monitoring.

Acknowledgments. This work was supported by a grant-in-aid from the Heart and Stroke Foundation of Canada and a research grant from Roche Diagnostics, Corp. Dr. Andrew is a Career Investigator of the Heart and Stroke Foundation of Ontario.

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