

Theme Issue Article

Point of care monitoring of oral anticoagulant therapy in children: comparison of CoaguChek Plus and *Thrombotest* methods with venous international normalised ratio

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Summary

This paper reports the outcome of a research protocol aimed at optimising warfarin monitoring in a tertiary pediatric centre. The *Thrombotest*TM INR was the standard monitoring test employed to manage oral anticoagulant therapy in children at the Royal Children's Hospital (RCH), Melbourne. This study compares the results of this standard method to the novel CoaguChek[®] INR monitor and the "gold standard" technique of venous INR sampling. The objectives were to determine 1) if point-of-care techniques of measuring the INR (*Thrombotest* and CoaguChek) are accurate and reliable compared to INR results obtained from venous sampling, processed in an accredited laboratory, and 2) if INR results generated by POC devices can be safely used to manage oral anticoagulant therapy in children. 18 children (10 females and 8 males) participated in

the study. Ages ranged from 9 months to 21 years (Mean 11.9 years; SD 5.03 years). The agreement between CoaguChek and venous INR measurements ($r = 0.885$) was shown to be higher compared to *Thrombotest* and venous INR ($r = 0.700$). Compared to the venous INR, values obtained with CoaguChek and *Thrombotest* crossed into or out of the therapeutic range in 25% and 36% of cases respectively. In 88% of the CoaguChek cases and 57% *Thrombotest* cases, the difference from the venous result was less than 0.5. The CoaguChek method of INR monitoring is a more accurate and reliable method compared to *Thrombotest*, in the pediatric population tested, and can be safely used to manage oral anticoagulant therapy in children.

Keywords

Anticoagulant monitoring, children, International Normalised Ratio (INR), Point of Care (POC), warfarin

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Introduction

Increasing numbers of children are requiring long-term oral anticoagulant therapy for either the prevention or treatment of thromboembolic disease (1). Children with complex congenital heart disease, central venous catheter-related thrombosis and cerebrovascular events represent the largest cohorts of children requiring anticoagulant therapy (2–4). Warfarin therapy is associated with several unique challenges within the pediatric pop-

ulation, including variable age-related dose response, frequent intercurrent illness and poor peripheral vasculature (2). Point-of-care (POC) monitoring offers a potential solution to one of these challenges.

A modified *Thrombotest* had been used as the standard technique for monitoring warfarin therapy in children at the Royal Children's Hospital (RCH), Melbourne since the mid-1980s. This technique consists of capillary collection of whole blood and manual determination of the prothrombin time (PT). Whilst

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this method provided an alternative to venous INR testing, it was cumbersome, time consuming and the potential for operator-error was great. The advent of POC coagulation analysers offered a potential alternative to the Thrombotest.

This study sought to determine the reliability and accuracy of INR determination by two capillary whole-blood methods (Thrombotest and CoaguChek) compared to the reference method of venous collection with laboratory analysis, in a pediatric population. For the purpose of this study, the venous method of INR determination was deemed to be the “gold standard” (23).

Methods

Patients

Patients receiving warfarin were identified through the Departments of Hematology and Cardiology at RCH. All patients presenting to the Pathology Collection Department for an INR test were eligible for this study, and informed consent was sought. The RCH Ethics in Human Research committee approved this project.

Blood sample collection

Upon providing written informed consent, three procedures for INR determination were performed: a *Thrombotest* INR, a CoaguChek INR and a venous blood INR.

Blood was obtained from a single finger prick for the *Thrombotest* and CoaguChek INRs, using an *Autolet* lancet (Ulster Scientific, Inc., Highland, NY). Staff who performed the *Thrombotest* were blinded from the result of the CoaguChek. Local anaesthetic cream was applied to the ante-cubital fossa thirty minutes prior to venipuncture, to reduce associated pain. Venous blood was drawn directly into a 3.2% citrate tube (*S-Monovette*, Sarstedt, Germany). Venous samples were delivered to the RCH Core Laboratory within 30 minutes of collection.

Blood sample analysis

Thrombotest

250 µl of the *Thrombotest* reagent ISI ≈ 1.00 (Nycomed Pharma AS, Oslo, Norway) was transferred into a small clotting tube, and placed in a water-bath at 37°C, for approximately 3 minutes. 50 µl of the capillary blood sample was added from the pipette just above the surface of the reagent. Mixing of blood and reagents initiated the clotting reaction. The time required for clot formation was recorded, and a conversion chart was used to express the result as an INR.

All clinical decisions during the study were based on the *Thrombotest* INR result, which was the current standard of care.

CoaguChek

This method has previously been reported (9). The first drop of whole blood obtained, following lancing of the finger, was

placed onto the test area. The monitor determined the PT, and displayed the result as an INR within one minute of beginning the analysis.

Venous

Platelet Poor Plasma (PPP) was obtained following centrifugation (3000g for 10min) of the venous blood sample. Analysis of the sample was performed on the ACL 100 coagulation analyser (Instrumentation Laboratory srl – Milan, Italy). The ISI of the thromboplastin reagent (*IL Test PT-Fibrinogen*, Instrumentation Laboratory- Milan, Italy) was 1.26. The mean normal PT was determined from a local population of not less than 25 individuals. The Haematology laboratory at RCH complies with the Quality Assurance Program established by the Royal College of Pathologists of Australasia (RCPA).

Statistical analysis

Values are expressed as mean and 95% confidence intervals (CI). Lin’s concordance correlation coefficient (r) was calculated as a measure of agreement between the CoaguChek, *Thrombotest* and venous INR (10). Bland-Altman analysis of limits-of-agreement was used to show the average difference between the methods compared, together with the variability of the differences and the overall trend (11). Statistical software package STATA, Release 7.0 (Stata Corporation, College station, TX) was used for data processing and analysis.

Results

18 children (10 females and 8 males) participated in the study, with an age range of 9 months to 21 years (mean 11.9 years; SD 5.03 years). A total of forty test points were performed over 6 months.

Indications for warfarin therapy included congenital heart disease (66%), cardiac arrhythmia (11%), prosthetic heart valve replacement (11%), cardiomyopathy (6%) and deep vein thrombosis (6%). There were no significant thrombotic or hemorrhagic complications during the study period.

Mean INR values for each method are summarised in Table 1. Figures 1A and 1B show the concordance curves for the comparison of *Thrombotest* and CoaguChek (respectively)

Table 1: Summary of INR values obtained using capillary (CoaguChek & Thrombotest) and venous blood samples. * $p = 0.0014$ Thrombotest versus venous INR; ** $p = 0.2292$ CoaguChek versus venous INR.

Test	INR value	
	Mean	(95% CI)
Venous INR	2.09	(1.92 – 2.26)
Thrombotest INR *	2.63	(2.36 – 2.91)
CoaguChek Plus INR **	2.25	(2.05 – 2.45)

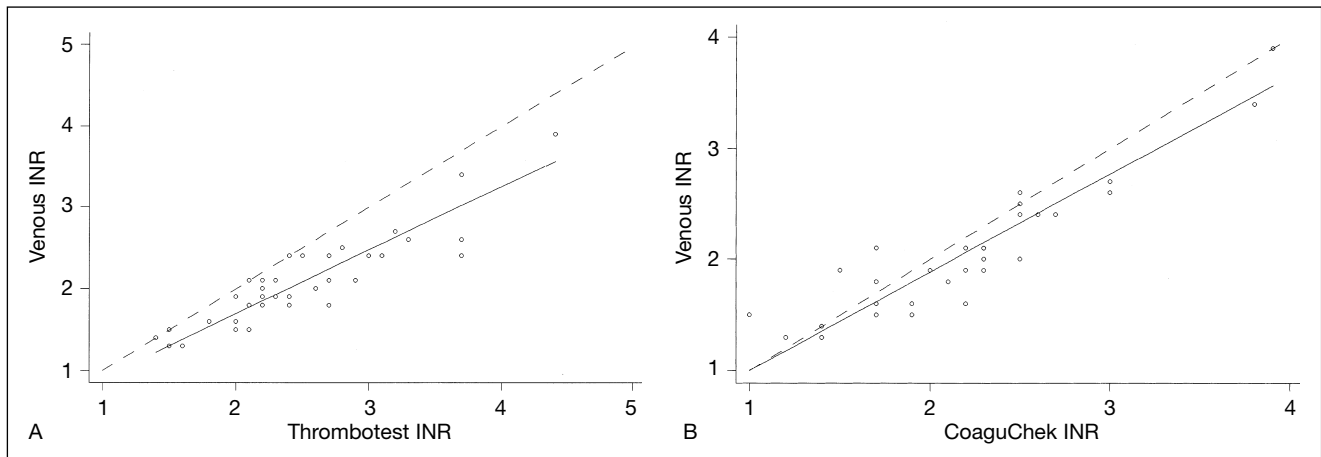


Figure 1: Concordance correlation curves for (A) Thrombotest INR ($r = 0.700$) and (B) CoaguChek INR ($r = 0.885$) versus venous INR for all patient samples.

with the venous INR. The agreement between CoaguChek and venous INR measurements ($r = 0.885$) was shown to be higher compared to *Thrombotest* and venous INR ($r = 0.700$) results. The average difference between the *Thrombotest* and venous INR was calculated to be 0.415, a value three-fold higher than the average difference of 0.138 observed between CoaguChek and venous INR. When compared to the venous INR, CoaguChek and *Thrombotest* results crossed into or out of the assigned therapeutic range in 25% and 36% of cases respectively. 88% of CoaguChek results and 57% *Thrombotest* results had a difference of less than 0.5 INR units compared to the corresponding venous result.

Discussion

Frequent blood monitoring of children requiring long-term warfarin therapy can be traumatic, particularly when venous access is difficult. Capillary whole blood monitoring of oral anticoagulant therapy offers tremendous advantages in the management of children. Overcoming the need for frequent venipuncture reduces parental and patient anxiety, with the potential to improve compliance with management plans.

We compared two capillary whole blood methods of INR measurement (*Thrombotest* and CoaguChek) with venous INR results. Capillary whole blood monitoring using a modified *Thrombotest* method had been the standard practice for INR measurement at RCH for nearly two decades. Technological advances have led to the development of user-friendly POC analysers that provide good accuracy using smaller blood samples (12). Numerous studies have shown CoaguChek to be a reliable instrument for INR determination in adult patients requiring anticoagulant therapy (13-19). In comparison, there has only been one study evaluating the clinical effectiveness of CoaguChek compared to venous INR monitoring in children (9).

This study is significant as it provides objective evidence as to the accuracy and validity of INR results obtained by POC monitoring using the CoaguChek monitor in a pediatric population. Similar studies in adults cannot simply be extrapolated to the pediatric population, and only one similar pediatric study has previously been published. The impact of developmental hemostasis, underlying disease pathology and variable age-related dose response to warfarin all make managing warfarin in children different to adult management (2, 4, 9). For this reason, investigation into strategies that optimise warfarin management in children are essential, despite the fact that similar studies have already been conducted in the adult population.

CoaguChek was found to be more precise and accurate than *Thrombotest*, when compared to our gold standard method of venous INR. Sub-analysis of results obtained from patients with a target INR of 2.5 demonstrated that CoaguChek results crossed into or out of the therapeutic range (2.0-3.0) compared to the venous INR, on 25% of samples. This compares favourably to the previously published study of CoaguChek's use in children, where 29% of CoaguChek INR results crossed into or out of the therapeutic range compared to venous results (9). Of important clinical significance, this study demonstrated that using *Thrombotest* INR results, treatment decisions would have differed from that indicated by the venous INR on eleven occasions, compared to only one difference based upon CoaguChek results.

Gosselin et al., reported a correlation coefficient of 0.900 between the CoaguChek Plus and a laboratory-based method (20). The correlation in our study was slightly reduced compared to Gosselin. This may reflect the inherent challenges of collecting any blood sample, even capillary samples, from children. It may also reflect local laboratory differences associated with calibration of the international sensitivity indices of thromboplastins. However, our correlation is significantly better com-

pared to that reported by Kemme et al. (21), who examined POC monitoring of anticoagulant therapy in patients commencing warfarin, whilst our study only enrolled patients in the maintenance phase of warfarin therapy.

The strength of this study's findings is limited by our relatively small sample size. Recruitment of children into this study was difficult as it necessitated the collection of venous blood, a procedure our patients do not usually have to endure. The staff of the RCH Pathology Collection Department performed all of the capillary punctures required during this study. They were all experienced in the collection of blood samples from infants and children, and had no difficulty in obtaining blood droplets of sufficient size to facilitate CoaguChek INR determination. Health professionals less experienced in capillary collection in infants and children may not be as successful in the use of the CoaguChek. This study only investigated the use of the CoaguChek POC monitor within a tertiary pediatric centre. One study has evaluated the CoaguChek monitor in the context of a home-monitoring program. Whilst correlation between the home INR and reference laboratory INR was acceptable ($r^2 = 0.87$; $y^2 = 1.1x - 0.2$), it was not as high as the correlation between the laboratory INR and CoaguChek INR performed by clinic staff. The accuracy of POC testing using the CoaguChek in the context of home-monitoring is yet to be validated.

This study demonstrates that INR monitoring using the CoaguChek POC device is more accurate and reliable compared to our standard method of INR testing, the *Thrombotest*. Statistical analysis demonstrated that the CoaguChek monitor achieved a high level of correlation when compared to our reference method of venous INR testing. The findings of this study offer such strong support for CoaguChek's use in INR monitoring in children that it has become the standard method of INR testing at RCH. Further study is required to determine whether the relative accuracy of CoaguChek can be maintained during home use. Anticoagulant management in infants and children presents unique challenges that do not exist in the adult population. The availability of POC monitoring options that have been validated in the pediatric population will significantly improve one aspect of this management.

Acknowledgments

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Abbreviations

International Normalised Ratio (INR); Point of Care (POC); Prothrombin Time (PT).

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