New Technologies, Diagnostic Tools and Drugs

Point-of-care monitoring of oral anticoagulation therapy in children

Comparison of the CoaguChek XS® system with venous INR and venous INR using an International Reference Thromboplastin preparation (rTF/95)

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Summary

Point-of-care (POC) monitoring of oral anticoagulation has been widely adopted in both paediatric and adult patients. A new POC system, the CoaguChek XS® has recently been developed to measure the international normalised ratio (INR) and may offer significant advantages. The CoaguChek XS® utilises a new method of electrochemical clot detection based on thrombin generation. This system has not been previously evaluated in children with reference to the laboratory gold standard, the prothrombin time using reference thromboplastin. It was the objective to compare values obtained by the CoaguChek XS® system with both the venous INR and the gold standard for anticoagulant monitoring, prothrombin time with reference thromboplastin (rTF/95). To evaluate the impact of testing using the CoaguChek XS® on clinical anticoagulant dosing decisions. Fifty paired venous INR and capillary CoaguChek XS® results were obtained from 31 children (aged up to 16 years). The laboratory gold standard, a manual prothrombin time with reference thromboplastin (rTF/95) was additionally performed on 26 samples. Correlation between the CoaguChek XS® result and the venous INR was r= 0.810. Agreement between the CoaguChek XS result and the reference INR was shown to be higher (r=0.95), in the subset analysed by this method. Correlation between the venous INR and reference INR was r=0.90. Despite changes to the methodology of testing with the CoaguChek XS® POC monitoring system, the accuracy of this method when compared with both the venous INR and gold standard reference INR was satisfactory. This resulted in infrequent changes to clinical decision making regarding anticoagulation

Introduction

Over the last decade, increased survival as a result of improved cardiac surgery techniques and advances in neonatal and intensive care support has been associated with an epidemic of thromboembolic disease in paediatric patients (1). This, in turn, has led to an increased frequency in the use of warfarin anticoagulation in this population (2). Point-of-care (POC) systems, for monitoring warfarin therapy, that utilise a finger-prick whole blood sample as opposed to a more invasive venous sample, offer significant advantages to anticoagulated children in whom venous access is often problematic and traumatic.

The new generation POC anticoagulant monitoring system the CoaguChek XS® (Roche Diagnostics, GmbH, Mannheim Germany) will shortly supersede the previous version, CoaguChek S®. This system has the potential to offer significant benefits to patients and providers through increased portability achieved by improved stability of the monitor and test strips. In addition, the inbuilt quality control system which is performed with each test and the use of a superior human recombinant

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thromboplastin (International Sensitivity Index, ISI =1.01) aims to improve accuracy of the testing (3).

The CoaguChek XS® uses an electrochemical clot detection method (4, 5) which is activated by the generation of thrombin. This represents a change in test methodology, where the previous version of this monitoring system (CoaguChek S®) used mechanical clot detection (6). Important age-related differences in the coagulation system (7–9), including differences in thrombin generation potential dictate that the safe use of this system (CoaguChek XS®) in paediatric population must be established and confirmed prior to widespread clinical use.

A small number of paediatric studies have considered the CoaguChek XS®; however, these studies have determined accuracy relative only to the venous INR (5, 10). Prior to widespread use of POC anticoagulant monitoring, the venous international normalised ratio (INR) was the clinical standard of care, and continues to be used as the confirmatory test when there are concerns regarding accuracy of POC anticoagulant monitoring. The venous INR, however, does not represent the laboratory gold standard, where despite a universal system of calibration of thromboplastins (11) significant interlaboratory variation of results can occur. The gold standard for oral anticoagulant monitoring is testing using a World Health Organization (WHO) reference thromboplastin (from the same species) (12). Precision for the CoaguChek XS® system has been previously determined and ranges from 1.1 to 5.0% (3, 5).

To better evaluate the system we performed a study which not only compared results of POC monitoring of warfarin in paediatric patients using the CoaguChek XS® monitor to standard monitoring using venous INR, but also compared the performance of the CoaguChek XS® system with the gold standard for oral anticoagulant monitoring, the venous INR using a manual tilt tube prothrombin time (PT) with WHO reference thromboplastin (rTF95). Finally we determined the safety of use of the CoaguChek XS® monitor for clinical management of children receiving Warfarin therapy, by considering the effect on clinical anticoagulant dosing decisions.

This study is the first study in children to provide data on the accuracy of the CoaguChek XS® POC system relative to the true laboratory gold standard for anticoagulant monitoring.

Methods

Paediatric patients under the age of 16 years taking oral warfarin therapy, who were being managed by the anticoagulation service at The Royal Children's Hospital (RCH), Melbourne, Australia were eligible to participate. Patients on additional anticoagulants including heparin or antiplatelet agents such as aspirin were excluded from this study. Data collection included: indication for warfarin, target therapeutic range, current dose of warfarin, weight and other medications. Patients were eligible to participate on more than one occasion during the study period.

Written informed consent was obtained from parents and patients using a protocol approved by the RCH Ethics Committee in Human Research Committee (26057A) in accordance with the National statement on conduct in research.

Sample and data collection

A capillary blood sample followed by a venous sample was obtained from each patient. A single finger stick was performed and the first drop of whole blood obtained was then applied to the CoaguChek XS® test strip, according to manufacturer's instructions (Roche Diagnostics GmbH).

The CoaguChek XS® uses an electrochemical clot detection method. Following activation of coagulation with human recombinant tissue factor the thrombin that is generated is active against the substrate Electrocyme TH® contained within the test strips. The thrombin activity of the patient sample generates an electrical signal which is then converted by the CoaguChek XS® monitor to PT. This result is then converted to an INR with reference to the ISI of the thromboplastin within the test strip, 1.01 (3). Following successful completion of the CoaguChek XS® test, a single venepucture was performed, with 3 ml of venous blood drawn directly into a 3.2% S-Monovette® citrate tube (Sarstedt, Mawson Lakes, SA, Australia). The venous sample was sent to the RCH Core laboratory within 30 minutes (min) of collection.

Platelet-poor plasma (PPP) was obtained from the venous sample following centrifugation in Heraeus Megafuge 1.0R at 10°C for 10 min at 3,000 g. The PT was performed using the STA Compact or STA-R Evolution analyser, with STA Neoplastine C1 Plus reagent (Diagnostica Stago, Asnieres, France). The result was reported as a venous INR with reference to the ISI of the reagent. Immediately following completion of the automated venous INR the remaining PPP was frozen in 300 µl aliquots for testing of the manual PT using rTF95. Grau et al. have previously shown no significant effect from freezing plasma samples prior to PT testing (13).

Manual PT was performed according to previously published methods (14, 15). A CV of 4.9% was established by the authors (data not shown) for the manual tilt tube method using pooled normal adult plasma. The International Reference Thromboplastin, human recombinant (rTF95) was made available for the purpose of this study. A manual PT was obtained for a subset of the study subjects (n=26), and reflected the demographic characteristics of the overall study population including age-group and gender. The results of the PT were then converted to an INR using the standard calculation, incorporating the ISI of the reagent and the mean normal PT (20 normal adult plasma samples tested in duplicate) of 14.8 seconds for this reagent established using the tilt tube method.

The venous INR was used for clinical decision making regarding the patients ongoing warfarin dose. The medical officer responsible for anticoagulant dosing was blinded to the CoaguChek XS® result.

To assess the impact of the CoaguChek XS® result on clinical care, the number of occasions where variation in the results would have resulted in a differing clinical decision regarding anticoagulant management was determined. The results have been assessed using a previously established nomogram for warfarin dosing which is currently in use in our institution (16). This nomogram allows up to 10% variation in INR results above or below the target therapeutic range before a dose change is required. Using these criteria, altered clinical management was defined when one of the pair of results was outside the target

range and also qualified for a dose change according to the nomogram.

Statistical analysis

Lin's concordance correlation (r) coefficient was used to measure the agreement between the venous INR and the Coagu-Chek XS® result, between the venous INR and the reference INR, and between the CoaguChek XS® result and the reference INR (p<0.05 significant) (17). Bland-Altman 95% limits of agreement were calculated as the mean difference between measurements (18).

Proportions of values within 0.5 units of the laboratory or reference INR were also determined, as were the proportion of results which would have resulted in a different clinical decision regarding anticoagulant dosing for the patient.

The statistical software package STATA, release 10.0 (StataCorp, College Station, TX, USA) was used for data processing and analysis.

Results

Thirty-one children participated in this study (16 male/ 15 female; 0.5–16 years of age), with a total of 50 paired CoaguChek XS® results and venous samples obtained during this study. Samples obtained were not evenly distributed across the age ranges (4% for <1-year-olds, 6% from 1– to 5-year-olds, 32% for 6– to 10-year-olds, and 58% for 11– to 16-year-olds). For 26 samples, results were available for all three methods of testing.

The indications for oral anticoagulation for the study population included: congenital heart disease (45%), prosthetic heart valve (13%), venous thromboembolic disease (13%), neurological disorders (including Moya Moya disease, vertebral dissection and arterial ischaemic stroke) (10%), primary pulmonary hypertension 16% and cardiomyopathy (6%).

Correlation between the CoaguChek XS® result and the venous INR was r= 0.810. In the subset of patients who had a reference INR performed, agreement between the CoaguChek XS®
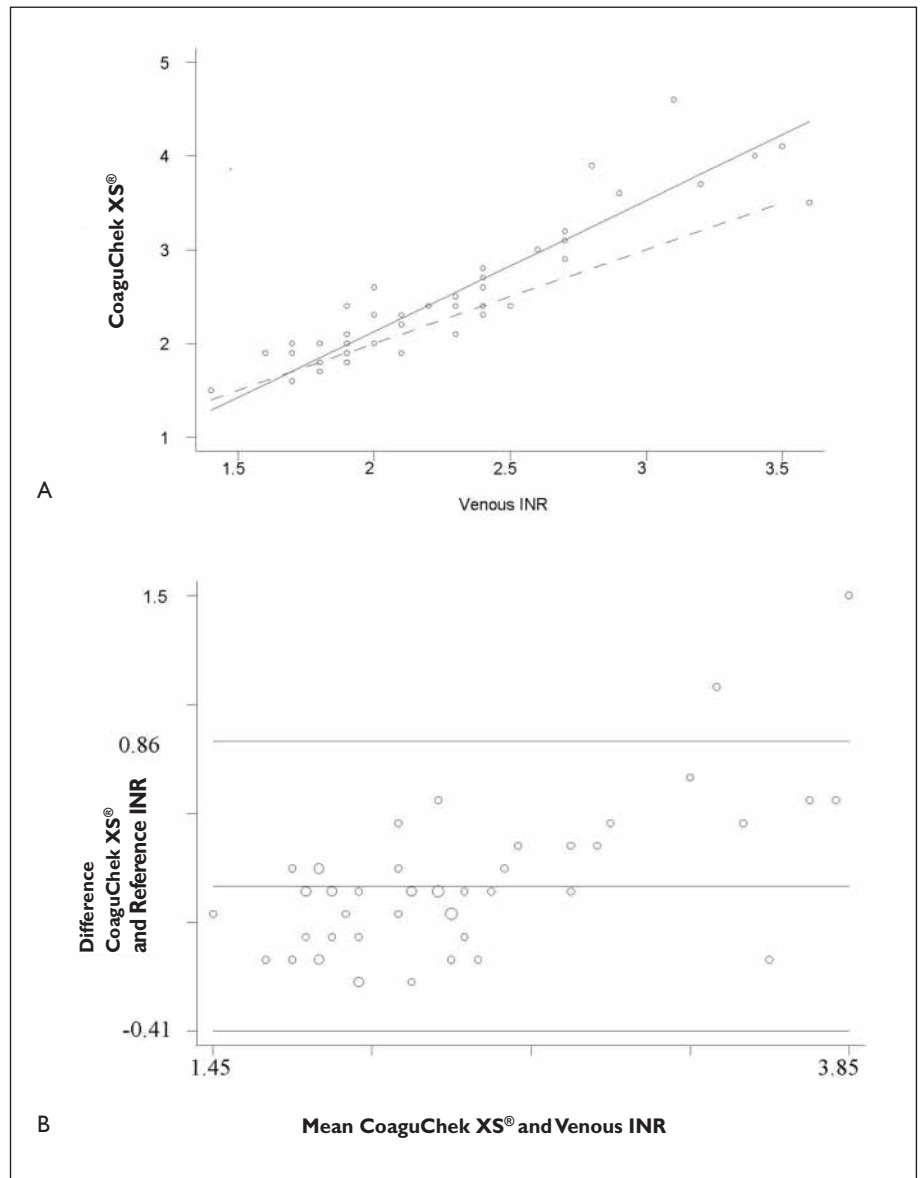

Figure 1: Correlation curve (linear regression) and Bland Altman graph of CoaguChek XS® and venous INR (RCH laboratory). A) Correlation curve (r=0.81, SE 0.038). Dashed line indicates perfect concordance between variables. B) Bland Altman graph. Mean difference 0.22 INR units (95% confidence interval 0.13 to 0.32. Limits of agreement (reference range for difference): -0.41 to 0.86.

result and the reference INR was shown to be higher (r=0.95). Correlation between the venous INR and reference INR in the subset tested was r=0.90 (Figs. 1–3A).

The CoaguChek XS® result was on average 0.22 INR units above the corresponding venous INR result. The Coaguchek XS® result was on average 0.07 INR units above the reference INR result, while the venous INR result was on average 0.13 INR units below the reference INR result (Figs. 1–3B).

A total of 12% (6/50) of venous INR results differed by >0.5 INR units, when compared with the CoaguChek XS®. None of the CoaguChek XS® results differed by >0.5 INR units when compared to the reference INR. When the CoaguChek XS® result was compared with the venous INR a different clinical decision regarding oral anticoagulant dosing would have been made on 20% of occasions. A different clinical decision would have been made on 3.8% of occasions when the CoaguChek XS® result was compared to the reference INR.

Discussion

POC monitoring of anticoagulation is now well established in the management of adults (4, 19) and children requiring anticoagulation (5, 6, 10, 20) . This form of management has been particularly beneficial in the paediatric population as it uses a capillary whole blood sample, and therefore provides an alternative to frequent venesection for safe monitoring of warfarin.

This study is the first in children to compare the CoaguChek XS® monitoring system with the gold standard, the PT with reference thromboplastin (rTF/ 95). Whilst it is not possible to make this comparison during routine clinical care of patients due to limitations of the reference thromboplastin (unsuitable for automated analysers), the superior correlation of the CoaguChek XS® result when compared to the gold standard PT provides important additional supportive evidence that this methodology is safe and appropriate for use in the paediatric population. Similar accuracy has been shown by Plesch et al. when CoaguChek XS® was compared with the gold standard, reference thromboplastin
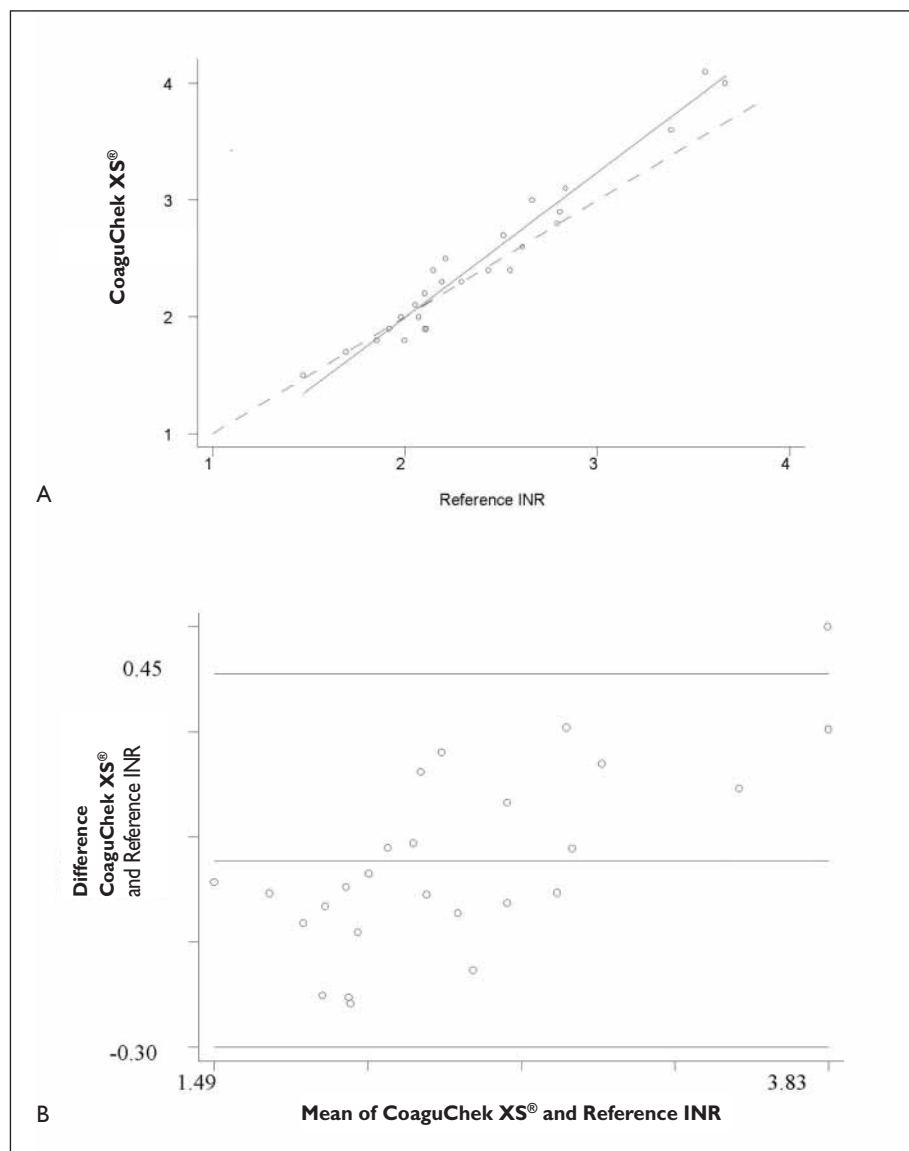

Figure 2: Correlation curve (linear regression) and Bland Altman graph of CoaguChek XS® and reference INR (venous INR with rTF/95). A) Correlation curve (r=0.947, SE 0.016). Dashed line indicates perfect concordance. B) Bland Altman graph. Mean difference 0.07 INR units (95% confidence interval -0.002 to 0.15. Limits of agreement (reference range for difference): -0.30 to 0.45.

(rTF/95), in a single adult cohort (anticoagulated and normal donors) (21). Results of the original multicentre calibration study in adult patients for the CoaguChek XS® system were also similar (3).

Accuracy of the CoaguChek XS® when compared to the reference INR (r= 0.95) was slightly better than that observed between with the venous laboratory INR and the reference INR (R=0.90). This is likely to reflect the ISI of the thromboplastin used in the CoaguChek XS® monitor. A multicentre calibration study, according to WHO guidelines for determination of the ISI (3) has determined the ISI of the CoaguChek XS® PT test strip to be 1.01. The system of INR calibration using the ISI has been developed such that the lower the ISI the more sensitive the reagent is to deficiency of the vitamin K-dependent coagulant proteins (22). The ISI of the international reference thromboplastin rTF95 has been reported as 0.94 (23), indicating its superior sensitivity. The superior ISI of the thromboplastin in the CoaguChek

XS® test strips improves the accuracy of this monitoring system when compared with the venous INR in our laboratory, using a commercial thromboplastin (STA-Neoplastine C1 Plus, ISI 1.26 and ISI 1.22).

The clinical implications of the study findings, including projected dosage changes that would result from differences in CoaguChek XS® and venous INR results are similar to those observed in a previous paediatric CoaguChek XS® study (10). The number of projected dosage changes when the CoaguChek XS® was compared with the reference INR was significantly less, 3.8% or one of 26 encounters. INR monitoring in children is undertaken more frequently compared with anticoagulated adult patients due to the inherent difficulties with warfarin management; however, this would still represent an infrequent clinical occurrence at this rate (2). This assessment has been performed using the validated nomogram for warfarin dosing used within our institution, and therefore reflects the true clinical outcome
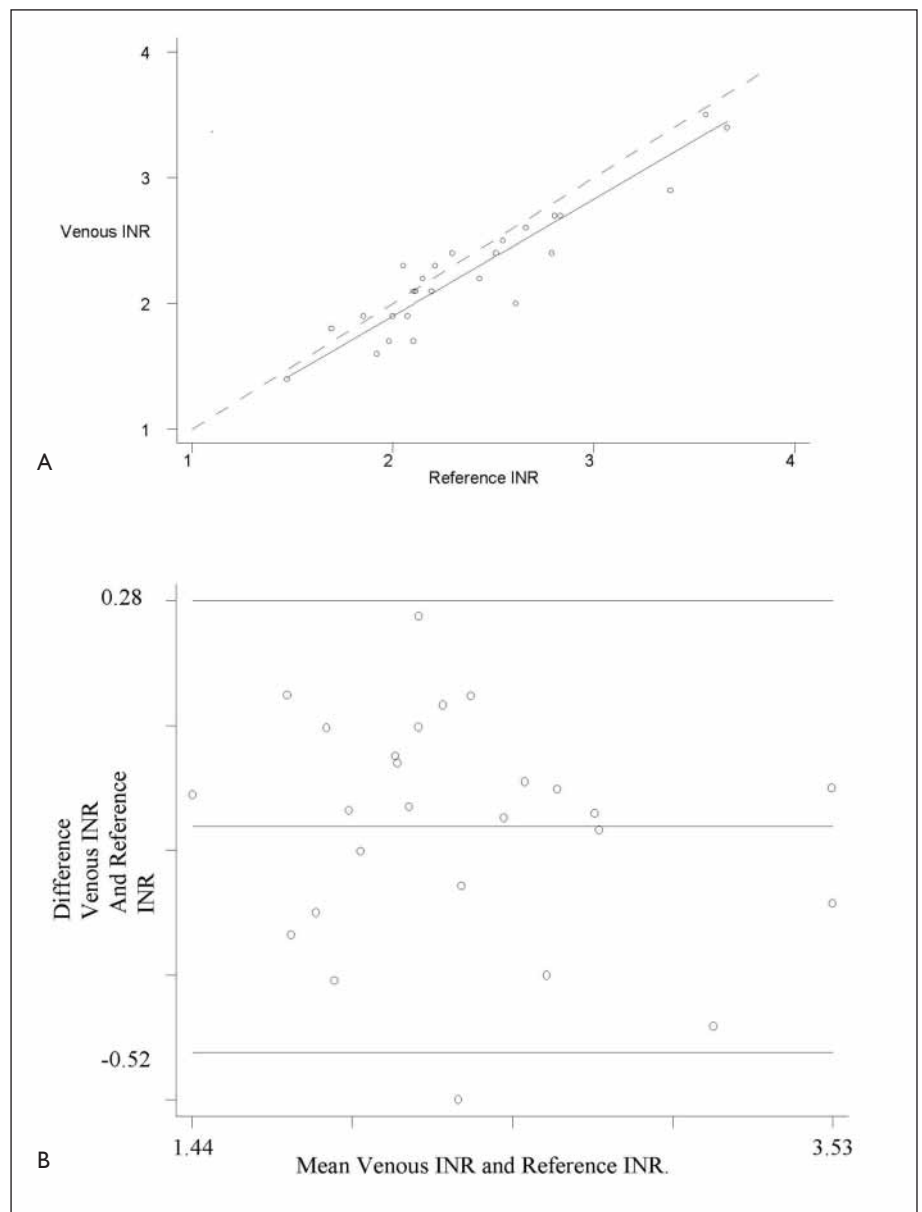

Figure 3: Correlation curve (linear regression) and Bland Altman graph for venous INR result and reference INR (venous INR using rTF/95). A) Correlation curve (r=0.90, SE 0.037). Dashed line indicates perfect concordance. B) Bland Altman graph. Mean difference 0.13 INR units (95% confidence interval -0.21 to -0.05. Limits of agreement (reference range for difference): -0.52 to 0.28.

for the individual patient. The lower number of projected dosage changes in the reference INR subgroup is in keeping with the higher correlation seen between this and the CoaguChek XS® result, however the smaller sample size for this subgroup may also have contributed to this finding.

In addition the accuracy of the CoaguChek XS® when compared to venous INR in this study (r= 0.81) is similar to the accuracy of the previous CoaguChek system, the CoaguChek S® (r= 0.885) (20), which was established prior to introduction of POC testing at RCH. This was an important comparison to ensure no deterioration in accuracy had occurred despite the change in methodology of the CoaguChek XS® to a thrombin-dependent electrochemical method. Thrombin generation is suppressed relative to normal adult levels throughout childhood, although levels are most significantly reduced in early childhood, prior to age 10 years (7). It was essential to establish that this variation in thrombin generation with age would not impact on accuracy of the CoaguChek XS® result, and ultimately the safety of this POC testing system in the paediatric population.

What is known about this topic?
– The CoaguChek XS® point-of-care (POC) system offers convenient and accurate anticoagulant monitoring in adult patients. This testing system uses an electrochemical clot detection method which is dependant on the generation of thrombin.
– Important age-related differences in the coagulation system, including thrombin generation, have been documented.
– Very few studies have considered the accuracy of the CoaguChek XS system in children on oral anticoagulants. These studies have suggested good correlation with the venous INR.

What does this paper add?
– Good correlation was seen between the new POC system (CoaguChek XS) and the laboratory gold standard (venous INR with reference thromboplastin).
– This is the first study to compare the CoaguChek XS with the gold standard, the PT with reference thromboplastin, in a paediatric cohort. This provides more robust data than the previous paediatric studies, which have compared the CoaguChek XS system only to venous or capillary INR measures.
– Due to the change in test methodology it is essential that new technology such as the CoaguChek XS is validated against the gold standard prior to introduction into clinical care.
– The findings of this study are able to confirm those of the only other large paediatric cohort, recently published by Bauman et al. (Thromb Haemost 2008; 99:1097–1103), with additional data using the laboratory gold standard for oral anticoagulant monitoring.

The limitations of this study include the small numbers of children in the infant (<1 year) and small child (1–5 years) age groups. This reflects the less frequent use of oral anticoagulants in the infant age group, due to the potential for fluctuations in anticoagulant levels with dietary changes and intercurrent illness. In addition as the current clinical standard of care in our institution is the CoaguChek S® system, there is moderate parental and patient resistance to additional venous testing particularly in the younger age groups. Further limitations include the paucity of results in the higher INR range, with only three of fifty CoaguChek XS® results greater than or equal to 4.0. Analysis of this small subgroup does not reach statistical significance; however, the correlation curves (Figs. 1–3) suggest reduced concordance between the CoaguChek XS® and the venous or reference INR with increasing INR values. This trend has been also been observed by previous researchers (5, 10), although again overall numbers have failed to reach significance. The implications of inaccuracy at high INR values, which are exponentially associated with an increased risk of bleeding at INR results >4.5 (24, 25) can be significant. At a clinical management level, this trend suggests that the common practice of confirming a high POC result with a supplementary test such as a venous INR is appropriate to reduce the risk of haemorrhagic complications, and to minimise thrombosis risk due to inappropriate reversal or dose reduction (10).

The findings of this study indicate the accuracy of the CoaguChek XS® point of care anticoagulant monitoring system, when compared with the gold standard venous INR with reference rTF/95 thromboplastin and with venous INR is adequate for safe clinical use in the paediatric anticoagulant population. The superior accuracy when correlated with the gold standard reference INR is likely to reflect the ISI of the recombinant thromboplastin used in the CoaguChek XS®. Ideally future advances in point of care technology should consider paediatric populations in the earliest possible phases of development, as the potential benefits for children are significant (26, 27). Caution should still be exercised at high CoaguChek XS® results due to a trend to reduced correlation with the reference or venous INR. Confirmatory testing should be considered in this instance (5, 10).

Our future focus is to consider the effects of anticoagulation on thrombin generation in children across the paediatric age range. This may provide useful insight into correlation of target anticoagulation ranges between adults and children, and in turn improve anticoagulation efficacy and safety in the paediatric population.

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