Self-monitoring of oral anticoagulation therapy in children

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Abstract

This study aimed to investigate the accuracy of home International Normalized Ratio (INR) self-monitoring in pediatric patients on long-term oral anticoagulation therapy. Statistical and clinical agreement of INR values from capillary whole blood samples measured by 2 different portable prothrombin time monitors (CoaguChek S and XS) and venous blood samples measured by a laboratory coagulation analyzer were evaluated using the Bland-Altman analysis. Eighty-three INR comparisons (56 using the CoaguChek S and 27 using the CoaguChek XS) were obtained from 35 children aged 4 months to 18 years. Mean differences between venous and capillary INR values and their limits of agreement were -0.04 (-0.63 to 0.55) overall, 0.006 (-0.63 to 0.65) for the CoaguChek S and -0.13 (-0.57 to 0.31) for the CoaguChek XS. The Pearson correlation coefficients were 0.88 overall, 0.84 for the CoaguChek S and 0.95 for the CoaguChek XS. Expanded and narrow agreements for all patients were 97.6 and 94%, respectively. In conclusion, home INR self-monitoring is accurate for children requiring long-term oral anticoagulation therapy. Our data suggest that INR self-monitoring with the newer CoaguChek XS is more accurate than with the older CoaguChek S monitor.
Self-Monitoring of Oral Anticoagulation Therapy in Children

Paolo Paioni\textsuperscript{a} Sabine Kroiss\textsuperscript{b, c} Elsbeth Kägi\textsuperscript{a} Eva Bergsträsser\textsuperscript{b, c} Margrit Fasnacht\textsuperscript{d} Urs Bauersfeld\textsuperscript{d} Markus Schmugge\textsuperscript{b} Manuela Albisetti\textsuperscript{a, b}

Divisions of \textsuperscript{a}Paediatrics, \textsuperscript{b}Hematology, \textsuperscript{c}Oncology and \textsuperscript{d}Cardiology, University Children’s Hospital, Zurich, Switzerland

Introduction

In the last few decades, the number of children requiring oral anticoagulation therapy (OAT) for prevention or treatment of thromboembolic events has increased. This is partly related to the advances in pediatric cardiac surgery and intensive care in the management of severe childhood diseases, in particular complex congenital heart diseases, prematurity and cancer \cite{1,2}. The vitamin K antagonists phenprocoumon, acenocoumarol and warfarin are the most commonly used oral anticoagulants for prolonged outpatient treatment. Close International Normalized Ratio (INR) monitoring is necessary to maintain the intensity of OAT at a level capable of preventing both thrombotic and bleeding complications.

Due to the lack of clinical trials, guidelines for anticoagulation treatment as well as current therapeutic INR ranges in children are widely extrapolated from recommendations for adults \cite{2}. However, for several reasons, management of OAT in children is more difficult and requires more frequent monitoring compared with the adult experience. Rapid INR fluctuations due to intercurrent illnesses, variation in medication and changes in diet occur more often than in adults \cite{3}. Venous blood sampling is mostly unpleasant and painful for children and can be technically demanding, especially in those children with poor venous access. Thus, capillary INR monitoring potentially offers advantages to children on long-term OAT.

Key Words
Oral anticoagulation · Portable prothrombin time monitor · Self-monitoring

Abstract
This study aimed to investigate the accuracy of home International Normalized Ratio (INR) self-monitoring in pediatric patients on long-term oral anticoagulation therapy. Statistical and clinical agreement of INR values from capillary whole blood samples measured by 2 different portable prothrombin time monitors (CoaguChek S and XS) and venous blood samples measured by a laboratory coagulation analyzer were evaluated using the Bland-Altman analysis. Eighty-three INR comparisons (56 using the CoaguChek S and 27 using the CoaguChek XS) were obtained from 35 children aged 4 months to 18 years. Mean differences between venous and capillary INR values and their limits of agreement were –0.04 (–0.63 to 0.55) overall, 0.006 (–0.63 to 0.65) for the CoaguChek S and –0.13 (–0.57 to 0.31) for the CoaguChek XS. The Pearson correlation coefficients were 0.88 overall, 0.84 for the CoaguChek S and 0.95 for the CoaguChek XS. Expanded and narrow agreements for all patients were 97.6 and 94\%, respectively. In conclusion, home INR self-monitoring is accurate for children requiring long-term oral anticoagulation therapy. Our data suggest that INR self-monitoring with the newer CoaguChek XS is more accurate than with the older CoaguChek S monitor.
In the 1980s, portable prothrombin time (PT) monitors using capillary whole blood and providing an INR result within minutes have been introduced to allow patients to monitor OAT by themselves. The successful use of these devices in adults has been demonstrated in several large studies showing very good correlations between venous and capillary INRs and indicating that the quality of OAT is even better than with conventional management [4–9].

Unfortunately, only few studies evaluating capillary INR monitoring in children have been conducted so far [10–16]. In particular, very few pediatric data are available on the newer PT monitor, CoaguChek XS. This study aims to investigate the accuracy of home INR self-monitoring in pediatric patients on long-term OAT, comparing the newer CoaguChek XS with the older CoaguChek S monitor.

**Patients and Methods**

**Patient Population**

Since 2002, pediatric patients on long-term OAT with phenprocoumon followed at the University Children’s Hospital of Zurich, Switzerland, and/or their parents have been offered the possibility of self-monitoring oral anticoagulation at home using a portable PT monitor. All patients, who have been willing to perform home INR self-monitoring, constitute the cohort for this study, without exclusions.

To be able to perform home INR self-monitoring, all patients and/or parents were educated and trained by a specialized team consisting of a physician and a pediatric nurse. The training program involved theoretical aspects of OAT (interpretation of home INR results, dosing and dose adjustment, interaction with other medication, influence of nutrition and intercurrent illnesses, as well as documentation of home INR results and adverse effects), and repeated practical demonstrations on the use of the portable PT monitor. Patients and/or parents were given the possibility to contact the team at any time when home INR values were outside the target range, or by uncertainties. On a regular basis, home INR records were discussed with the patients and/or parents, and a comparison between capillary and venous INR was performed.

Patient characteristics including sex, age, indication for OAT, INR target ranges and documented home INR values were collected from the medical records. This study was approved by the Research Ethics Boards of the University Children’s Hospital, Zurich, Switzerland.

**Portable PT Monitor**

All patients used the portable PT monitor CoaguChek S or XS (Roche Diagnostics, Rotkreuz, Switzerland), depending on when they started OAT. Both are capillary whole blood, battery-powered analyzers functioning with single used, thromboplastin-coated test strips to activate the coagulation cascade. For the determination of the PT, the CoaguChek S uses rabbit brain thromboplastin [International Sensitivity Index (ISI) 1.6–1.8] and a photometric method, whereas the CoaguChek XS uses recombinant human thromboplastin (ISI value close to 1) and an amperometric (electrochemical) method.

**Blood Collection and PT Measurements**

Capillary whole blood samples were obtained by fingertip puncture using an Accu-Chek Softclix Pro lancet system (Roche Diagnostics). One drop of at least 10 μl capillary blood was directly applied on the test strip, which was already inserted into the portable PT monitor.

Venous blood samples were drawn by venipuncture into 1.4-ml plastic tubes in the proportion of 9 parts blood to 1 part 0.106 mol/l sodium citrate for a final sodium citrate concentration of 10.6 mmol/l. Venous citrated blood was analyzed in the laboratory at our institution after centrifugation at 3,000 g for 15 min at 18°C on a STA Compact coagulation analyzer (Roche Diagnostics). Between 2002 and 2007, the thromboplastin used by the laboratory was Neoplastin Plus (thromboplastin 1), ISI 1.3 (Roche Diagnostics). Since 2007, a new thromboplastin, Neoplastin R (thromboplastin 2), with an ISI close to 1, has been used (Roche Diagnostics). The manufacturer’s ISIs and mean normal PT were used to determine venous INR values.

The PT values from both capillary whole blood samples measured by the portable PT monitor and venous blood samples measured by the laboratory coagulation analyzer were expressed in INR units according to the recommendations given by the International Committee of Standardization in Hematology in 1985 and by the World Health Organization.

**INR Comparisons**

Comparisons between venous and capillary INR were performed 1–2 times per year for each patient. The time between the venous and capillary blood collection did not exceed 15 min.

Clinically relevant agreement was defined based on whether or not the difference between venous and capillary INR measurements would be likely to influence clinical management of OAT. Two types of clinical agreement were used. Expanded agreement was achieved if both INR values were either within, above or below the target therapeutic range, or if 1 of the 2 INR values was within the therapeutic range and the pair within 0.5 INR units. Narrow agreement was achieved if both INR values were within 0.5 INR units [17].

**Statistical Analysis**

The proportion of home INR values falling within the therapeutic range was assessed for each patient from the collected data, and the mean and its 95% confidence interval (CI) were calculated in order to determine the time in therapeutic range. Agreement between venous and capillary INR values was analyzed using a Bland-Altman plot. The mean difference between venous and capillary INR was calculated for overall comparisons and for comparisons before and after changing the laboratory thromboplastin in order to assess the limits of agreement (mean difference ± 1.96 times the standard deviation) [18]. Significant mean differences of venous and capillary INR were tested by the Mann-Whitney test. A p value <0.05 was considered significant. In addition, the correlation between venous and capillary INR was determined using the Pearson correlation coefficient. Analysis was performed using Microsoft Excel 2004, version 11.3.5, and GraphPad InStat for Windows (GraphPad Software, San Diego, Calif., USA; version 3.05).
Results

Patient Population

Between 2002 and 2008, 35 pediatric patients received a portable PT monitor for a total of 89 self-monitoring years (range 2 months to 6 years). Demographic and clinical characteristics of patients are depicted in table 1. Of the 35 patients, 23 received a CoaguChek S and 12 a CoaguChek XS monitor. Two of 23 patients were switched to the CoaguChek XS monitor for no particular reason after 6 and 12 months, respectively.

Capillary INR Measurements

During the study period, a median of 3.3 capillary INR measurements per month was performed by the 35 patients for a total of 3,706 capillary INR measurements. In 70.1% (95% CI 65.4–74.8), capillary INR measurements were within, in 13.6% (95% CI 10.3–16.8) above and in 16.4% (95% CI 12.8–19.9) below individual INR target ranges.

INR Comparisons

Thirty-three of the 35 patients had 1 or more INR comparison measurements for a total of 83 comparison values. Of the 83 capillary INR measurements for comparison, 56 were performed using the CoaguChek S and 27 using the CoaguChek XS.

For all comparisons, mean differences between venous and capillary INR values and their limits of agreement were −0.04 (−0.63 to 0.55) overall, 0.006 (−0.63 to 0.65) for the CoaguChek S group and −0.13 (−0.57 to 0.31) for the CoaguChek XS group (p = 0.02). The Pearson correlation coefficients were 0.88 overall, 0.84 for the CoaguChek S group and 0.95 for the CoaguChek XS group. Overall expanded and narrow agreements were 97.6 and 94%, respectively.

Mean differences between venous and capillary INR values, their limits of agreement and the expanded and narrow agreements before and after changing the laboratory thromboplastin are summarized in table 2. While the CoaguChek S showed narrower limits of agreements after changing the thromboplastin, no differences were

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<th>Table 1. Characteristics of 35 pediatric patients</th>
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<td>Indication for oral anticoagulation, n</td>
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<td>Prosthetic aortic or mitral valve</td>
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<td>Dilated cardiomyopathy</td>
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<td>History of repeated thrombosis</td>
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<td>Giant aneurysm after Kawasaki disease</td>
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<td>INR target range, n</td>
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<th>Table 2. INR comparisons before (thromboplastin 1) and after (thromboplastin 2) changing the laboratory thromboplastin</th>
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<sup>a</sup> p = 0.03, significant mean differences of venous and capillary INR before and after changing the laboratory thromboplastin.
<sup>b</sup> p = 0.02, significant mean differences of venous and capillary INR between the CoaguChek S and XS.
observed for the CoaguChek XS before and after changing the thromboplastin. The corresponding Bland-Altman plots of the differences between venous and capillary INR values plotted against their means before and after changing the thromboplastin are shown in figures 1 and 2. The Pearson correlation coefficients before changing the thromboplastin were 0.84 for the CoaguChek S and 0.95 for the CoaguChek XS. The Pearson correlation coefficients after changing the thromboplastin were 0.87 for the CoaguChek S and 0.93 for the CoaguChek XS.

**Discussion**

Only few studies evaluating self-monitoring of OAT in pediatric patients have been conducted so far. The aim of this study was to assess the statistical and clinical agreement between capillary INRs measured by 2 portable PT monitors and venous INRs measured by a standard laboratory method in children. The results of this study validate home INR self-monitoring to be accurate for children on long-term OAT, especially when the newer CoaguChek XS monitor is used.

**Fig. 1.** Bland-Altman plots showing the differences between capillary (INR cap) and venous (INR ven) INR values plotted against their means for INR comparisons with capillary INR performed using the CoaguChek S (n = 36) (a) and comparisons with capillary INR performed using the CoaguChek XS (n = 13) (b) before changing the laboratory thromboplastin (thromboplastin 1). The straight line indicates the mean difference between capillary and venous INR values, while the dashed lines indicate their limits of agreement (mean difference ± 1.96 times the standard deviation).

**Fig. 2.** Bland-Altman plots showing the differences between capillary (INR cap) and venous (INR ven) INR values plotted against their means for INR comparisons with capillary INR performed using the CoaguChek S (n = 20) (a) and comparisons with capillary INR performed using the CoaguChek XS (n = 14) (b) after changing the laboratory thromboplastin (thromboplastin 2). The straight line indicates the mean difference between capillary and venous INR values, while the dashed lines indicate their limits of agreement (mean difference ± 1.96 times the standard deviation).
The challenges associated with the management of OAT in children require more frequent INR measurements and dose adjustments compared with adults. The use of a portable PT monitor, which measures thromboplastin-mediated clotting times using capillary whole blood, allows rapid testing at the patient’s convenience as well as prompt attention to critical values and drug dosage adjustment. A more rapid correction of out-of-range INR values may play a critical role in reducing the incidence of thrombotic and hemorrhagic complications during OAT, particularly in children [3]. However, for this purpose, a high grade of accuracy of the portable PT monitor needs to be demonstrated.

In the present study, the overall average difference between venous and capillary INR results was −0.04 INR units. Almost all previous studies evaluating portable PT monitors in children have used correlation coefficients to assess the correlation between venous and capillary INR measurements. However, correlation coefficients measure the strength of a relation between 2 variables, not the agreement between them. Thus, high correlations for 2 given methods do not mean that the 2 methods agree [18]. Besides very few other small reports, only our study and the one by Baumann et al. [10] have assessed agreement between venous and capillary INR measurements in a substantial number of children using the Bland-Altman analysis. While both studies indicate that capillary INR measurements using the portable PT monitor are very accurate, the negative values in our study show that the capillary INR was on average lower than the venous INR. As far as the negative mean difference measured for the CoaguChek XS is concerned, our findings indicating an underestimation of capillary INRs are consistent with results of previous studies in adults [19].

One important clinical issue when comparing 2 methods of measurement is whether or not the difference between the 2 methods would likely influence the clinical management. In this study, the overall expanded and narrow agreements were 97.6 and 94%, respectively, indicating that the differences between capillary and venous INRs were not sufficient to change clinical management decisions.

In 2006, the CoaguChek S monitor was replaced by the new generation of portable PT monitors, the CoaguChek XS. This new monitor offers several innovative practical and technical features, including smaller size and weight, side and top blood dosing options, the use of a recombinant human thromboplastin with a lower ISI, and internal quality control included on the test strip. Recent data from an ongoing study in 16 pediatric patients have suggested that the CoaguChek XS may be less accurate than the CoaguChek S monitor [20]. By contrast, the CoaguChek XS in our study showed an increased correlation coefficient and narrower limits of agreement as compared with the CoaguChek S, suggesting increased accuracy. Our results also indicate that, when using the CoaguChek XS, INR agreements are not dependent on the type of thromboplastin used by the laboratory. This seems not to be the case when the CoaguChek S is used. The inferior number of children using the CoaguChek XS compared with the number of children using the CoaguChek S monitor may limit the interpretation of our study results. However, our findings are consistent with results of recent studies in adults, also showing that the newer CoaguChek XS is more precise and accurate than the older CoaguChek S monitor [21–23]. Our results are also consistent with the results of another recent pediatric study showing a much more satisfactory performance of the CoaguChek XS compared with the CoaguChek S [16]. However, in this study, laboratory INR measurements were performed not on venous but on capillary specimens, which may potentially influence comparisons of INR results [16].

In conclusion, results of this study show a very good agreement between venous and capillary INR measurements. Portable PT monitors provide an accurate and simple method for home INR self-monitoring of long-term OAT in children, in particular when the newer CoaguChek XS monitor is used.

References


Paioni/Kroiss/Kägi/Bergsträsser/
Fasnacht/Bauersfeld/Schmugge/Albisetti


