

Oral Anticoagulation Therapy in Children: Successfully Controlled by Self-Management

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ABSTRACT

Background: Children with congenital heart disease and who are on oral anticoagulation therapy present special challenges due to, for example, rapid fluctuations in international normalized ratio (INR) values, interruption in daily life due to frequent hospital/doctor visits, and difficulties and pain to the child in the performance of venipuncture. We hypothesize that oral anticoagulation therapy can be successfully controlled by self-management for this subset of patients. The aim of this study was to assess the treatment quality of self-managed oral anticoagulation therapy as the proportion of time within the therapeutic INR target range in children with congenital heart disease.

Methods: Children (N = 22) with a mean age of 10.6 years (range, 1.8-18.6 years) and their parents were trained in home blood analysis of INR and in coumarin dosage adjustment. After training, the children were monitored by weekly INR measurements. The therapeutic range in target INR values was ± 0.5 . The indications for initiating oral anticoagulation therapy were the presence of a mechanical heart valve (n = 16) and total cavopulmonary connection (n = 6). The children had no physical restrictions.

Results: The mean observation time was 3.6 years (range, 0.9-5.8 years), and the total number of patient-years was 75.4. The patients were within the therapeutic INR target range for a median of 73.1% (range, 30.3%-91.0%) of the observation time. Two children died for reasons not related to the oral anticoagulation therapy. None of the patients experienced thromboembolic or bleeding complications requiring doctor intervention.

Conclusion: Self-management of oral anticoagulation therapy is safe and provides a good quality of treatment for selected children with congenital heart disease.

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INTRODUCTION

Oral anticoagulation therapy (OAT) with a vitamin K antagonist is used as thromboprophylaxis in adults for the treatment of many conditions that entail an increased risk of thromboembolism. Although OAT is used rarely in children [Andrew 1994, Buck 1996], the spectrum of its indications has expanded during the last several years [Spevak 1986, Michelson 1995]. The most frequent indication is implantation of a mechanical heart valve because of congenital heart disease [Spevak 1986, Andrew 1994, Buck 1996]. Even though the number of children on OAT is small compared with that of adults, children contribute many treatment years because the condition is often permanent and OAT is started early in life.

Because OAT increases the risk of bleeding, using this therapy implies a necessity to create a delicate balance between thromboembolic and bleeding events, and OAT must therefore be tightly controlled to obtain the lowest possible risk of complications. This goal is conventionally accomplished by laboratory analyses of the international normalized ratio (INR) of plasma samples obtained by venipuncture. The patient's doctor or the hospital then uses the INR value to decide on the dosage of the vitamin K antagonist.

Compared with adults, children present special problems because their INR values show greater fluctuations as a result of higher metabolic rates and greater susceptibilities to medication, infection, and food complications [Andrew 1994, Buck 1996]. The younger these children are, the more profound these fluctuations become [Streif 1999]. Therefore, frequent analysis of blood specimens [Marzinotto 2000] of up to 4 times a month is recommended, with dosage adjustments made, if needed, 1 or 2 times each month [Andrew 1994]. Hence, only 10% to 20% of these children can be safely monitored by taking monthly samples [Michelson 1995]. A relatively low quality of treatment continues to be present [Streif 1999], and many of the clinical complications seen in children with congenital heart disease are due to the OAT [Andrew 1994, Cabalka 1995, Vosa 1995]. The quality of the OAT is the most important factor for the prognosis of pediatric patients with a mechanical heart valve [Cabalka 1995].

There are also practical problems for children who undergo OAT in terms of difficulties in performing venipuncture, interruption of attendance at school and/or parental professional engagements, problems with traveling

abroad, and compliance in puberty [Stewart 1987, Andrew 1994, Massicotte 1995, Marzinotto 2000].

Today, there are different methods of managing OAT, including routine care, hospital outpatient clinics, specialized/pediatric anticoagulation clinics, computer-generated dosaging, patient self-testing (PST), and patient self-management (PSM). PSM implies a self-analysis using a portable coagulometer of a drop of blood obtained by finger stick. The patient then uses the displayed INR value to decide on the dosage adjustment of the vitamin K antagonist. PST implies that the patient merely performs blood sampling and analysis and that a health care provider decides on the dosage adjustment.

The CoaguChek coagulometer (Roche Diagnostics, Rotkreuz, Switzerland) has been evaluated extensively in adults [van den Besselaar 2001] and children [Marzinotto 2000], and various studies have concluded that it possesses adequate precision and accuracy for clinical use.

Three published studies [Massicotte 1995, Streif 1999, Marzinotto 2000] have concluded that the quality of OAT with PST is better than with conventional management, that PST is feasible, and that patients and their parents are pleased with the concept.

PSM has been shown to provide a better quality of OAT for selected adult patients than conventional management [Cromheecke 2000, Körtke 2001]. Two studies have reported the use of PSM in children. One study [Günther 2000] included 6 patients. However, PSM was not the main topic of this report, and no description of the results for the children performing PSM was presented.

In another study [Christensen 2001], we reported on the feasibility and short-term results of using PSM. This study included 14 patients with a mean follow-up time of 1.5 years, resulting in a median percentage of time within the therapeutic INR target range of 65.5%. We concluded that PSM provides a good quality of treatment and is safe and feasible for selected children with congenital cardiac disease. Long-term results for a larger population of patients have not been reported. In the present study, we hypothesize that OAT can be successfully controlled with self-management by children with congenital heart disease. The aim of this study was to assess the treatment quality of self-managed OAT in terms of the time within the therapeutic INR target range for children with congenital heart disease.

MATERIALS AND METHODS

Study Population

The study population comprised children (N = 22) with a mean age of 10.6 years (range, 1.8-18.6 years). All had undergone surgery in our department for treatment of congenital cardiac disease. Inclusion criteria consisted of a long-term indication for OAT because of congenital heart disease, an age between 0 years and 18 years, and an interest in and an anticipated high level of compliance with PSM, as judged from interviews with the patient and their parents. Patients with coagulopathies or hepatic disorders were excluded.

The study protocol complied with the Helsinki II declaration and was approved by the local scientific ethical committee. The patients and their parents gave both oral and written

Table 1. Patient Demographics (N = 22)

| | |
|--|-----------------|
| Male/female sex, n | 12/10 |
| Age, y* | 10.6 (1.8-18.6) |
| Indication for oral anticoagulation therapy, n | |
| Mechanical heart valve prostheses | |
| Aortic position | 8 |
| Mitral position | 8 |
| Total cavopulmonary connection | 6 |
| Therapeutic INR target range, n† | |
| 2.0-3.0 | 16 |
| 2.5-3.5 | 6 |
| Coumarin used, n | |
| Phenprocoumon (Marcoumar) | 16 |
| Warfarin (Marevan) | 6 |

*Data are presented as the mean (range).

†INR indicates international normalized ratio.

consent. The children had no physical restrictions. Demographic data for the patients are displayed in Table 1.

Study Design

The study consisted of a case series study of clinical data for children with congenital heart disease who were conducting PSM. All of the patients were trained and monitored by the Center for Self-Managed Oral Anticoagulation, Skejby Sygehus, Aarhus University Hospital, Denmark.

INR Analysis Methods and INR Values

Patients used the CoaguChek coagulometer and the CoaguChek PT test strips. A finger-puncture device (Softclix; Roche Diagnostics) was used to release a drop (10-25 μ L) of capillary whole blood, which was applied to the test strip and inserted into the coagulometer. The INR value was displayed after 1 to 2 minutes and was recorded by the patient on a dedicated data sheet. The working principle and the operation of the CoaguChek coagulometer have been described earlier [Hasenkam 1997]. The INR was measured once a week.

During the training phase (see below), blood samples for INR were taken and analyzed in a hospital for the purpose of comparison with patient-analyzed INR values. The hospital blood sampling was performed at the Department of Clinical Biochemistry, Skejby Sygehus, Aarhus University Hospital, or at a hospital laboratory nearest the patient's home. The INR was analyzed for plasma obtained by centrifugation of a blood sample obtained from a cubital venipuncture.

Study Protocol

The training concept for PSM is shown schematically in the Figure.

The involvement required by the parents strongly depends on the age of the patient. The younger the patient, the greater is the involvement required from the parents in conducting PSM. We emphasize that regardless of the age of the patient, the parents were always involved to some extent. When we refer to the patient, therefore, we implicitly include parental involvement.

| | | | | | | | | | | | | | | | | | | | |
|--------------------|----------|---|----------------|---|----|----------------|----|----|----------------------------|----|----|----|----|----|----|----|----|----|---|
| Week number | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | |
| Hospital INR | Weekly | | Every 3rd week | | | Every 4th week | | | None | | | | | | | | | | |
| CoaguChek® INR | Daily | | Weekly | | | | | | | | | | | | | | | | |
| Anticipated skills | Training | | Approval first | | | Check after | | | Self-management and report | | | | | | | | | | |
| Interview | ? | ? | | | | ? | | | | | ? | | | | | | | | ? |
| Examination | | | | | | | | | | | + | | | | | | | | |
| Self control | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Laboratory control | ✓ | | | | | | | | ✓ | | | | | | | | | | ✓ |

Training program for self-management of oral anticoagulation therapy. The patient and the parents start with 3 weeks of daily measurements of the international normalized ratio (INR) on the CoaguChek coagulometer and with weekly hospital INR measurements. After these 3 weeks of daily training, INR measurements are made weekly, and hospital INR measurements are obtained every third or fourth week for another 24 weeks. In this 24-week period, co-responsibility for dosage adjustment is gradually transferred from the doctor to the patient and the parents. During the entire period, self-control analyses and laboratory control of the CoaguChek coagulometer are made every fourth week and sixth month, respectively.

Each patient commenced the training program by practicing the analysis of blood specimens. The patient then gradually took over the management of OAT, initially by suggesting the dosage of coumarin and subsequently by assuming responsibility for the adjustment of the dosage monitored by the study group. After 27 weeks, the patients demonstrated their knowledge in a multiple-choice performance test. The analysis of the INR conducted by the laboratory was terminated once this test had successfully been completed, and at that point the patients were considered self-managing. Home analysis was performed once a week throughout the entire study, and the patients reported their values and selected therapeutic doses to the training center on a quarterly basis. Any complications were reported by the patient or the managing physician to the study group.

During the entire study, the CoaguChek coagulometer was monitored every fourth week, when the patients performed a control procedure using a standard control solution provided by the manufacturer. Every sixth month, the coagulometer was mailed to the hospital for a checkup performed at the Department of Clinical Biochemistry, Skejby Sygehus, Aarhus University Hospital.

Data Handling and Statistics

All data obtained from the patients and from the hospital were recorded and analyzed in a spreadsheet (Excel; Microsoft, Redmond, WA, USA). The relative amount of time within the therapeutic INR target range was estimated for each patient by means of linear interpolation, and this parameter was used to assess the quality of treatment.

Quality of treatment was defined as the time within the therapeutic INR target range and was assessed following the 28th study week, that is, after the patients had passed the examination and had begun to make dosage adjustments themselves.

RESULTS

Two patients died during the study. One patient died suddenly at 6 months after inclusion, probably because of arrhythmia. The INR value was 2.7 the day before this patient died. The other patient died from progressive heart failure 26 months after inclusion. A third patient underwent

heart transplantation, and the OAT was therefore terminated. The overall results are shown in Table 2.

No child died for reasons related to the OAT, and none of the patients experienced any major thromboembolic or bleeding complications requiring doctor intervention.

The mean observation time was 3.6 years (range, 0.9-5.8 years), and the total number of patient-years was 75.4.

The patients were within therapeutic INR target range for a median of 73.1% and a mean of 70.2% (range, 30.3%-91.0%) of the observation time. There was no statistically significant difference in the mean time within the therapeutic INR target range between the 2 types of coumarin used.

The distribution of the patients in various therapeutic INR target range intervals (in percent) is shown in Table 3.

The age distribution of the patients and the time within the therapeutic INR target are displayed in Table 4.

All children and their parents were able to learn blood specimen analysis and became capable of managing coumarin dosage adjustments.

All of the patients and their parents expressed full satisfaction with the treatment, especially because of the minimal interruptions in daily life and the less painful finger-stick method compared with conventional venipuncture.

Table 2. Overall Results

| | |
|--|---------------------|
| Observation time, y* | 3.6 (0.9-5.8) |
| Patient-years | 75.4 |
| Percentage of time within INR target range† | |
| Median | 73.1% |
| Mean* | 70.2% (30.3%-91.0%) |
| Coumarin used and percentage of time within therapeutic target range | |
| Phenprocoumon (Marcoumar) (n = 16) | 68.7% |
| Warfarin (Marevan) (n = 6) | 70.8% |
| Deaths, n | 2 |
| Major clinical complications, n | |
| Thromboembolism | 0 |
| Bleeding | 0 |

*Data are presented as the mean (range).

†INR indicates international normalized ratio.

Table 3. Distribution of Patients in Various Therapeutic International Normalized Ratio (INR) Target-Range Intervals

| Percent Time within Therapeutic INR Target Range | Patients, n |
|--|-------------|
| 30%-40% | 1 |
| 40%-50% | 1 |
| 50%-60% | 2 |
| 60%-70% | 4 |
| 70%-80% | 9 |
| 80%-90% | 3 |
| 90%-100% | 1 |

DISCUSSION

Optimized management of OAT reduces the number of thromboembolic and bleeding complications significantly [Ansell 1996], and PSM seems to be one of the methods for achieving this goal. In randomized clinical trials, PSM was found to be better than conventional management of OAT, both in terms of lowering thromboembolic and bleeding events and in increasing the time within the therapeutic INR target range [Horstkotte 1996, Cromheecke 2000, Körtke 2001].

The optimum way of assessing treatment quality is to register the number of clinical complications. However, such studies require a large number of patients to provide a clear outcome. Several studies have clearly demonstrated that the number of complications parallels the amount of time patients spend outside the therapeutic INR target range [Steffensen 1997], and it is considered reasonable to use the time within the therapeutic INR target range as a surrogate measure for assessing the quality of treatment [Samsa 2000].

Estimation of the time within the therapeutic INR target range has been done in a very limited number of studies with children. Spevak et al [1986] found that only 64% of treated children maintained a prothrombin time within the desired range for at least 50% of the measurements.

The time within the therapeutic INR target range is inversely related to the age of the child and the therapeutic INR target range. Streif et al [1999] found in a pediatric OAT clinic study of 319 children that the mean (±SD) percentage of time patients aged less than 1 year were within the therapeutic INR target range was 37% ± 16%. The percentage rose to 53% ± 19% for patients between the ages of 13 years and 18 years. With respect to the percentage of time within the therapeutic INR target range, the figures were 49% ± 21%, 47% ± 18%, and 61% ± 20% for therapeutic INR target ranges of 1.4 to 1.8, 2.0 to 3.0, and 2.5 to 3.5, respectively [Streif 1999].

For PST, the percentage of time within the therapeutic INR target range was between 63% and 68%. PST is safe and, compared with the usual care, has practical advantages, including minimal trauma to the child, minimal interruption of school schedules, ease of operation, and portability [Massicotte 1995, Streif 1999].

Regarding PSM, we found a median percentage of time of 73.1% within the therapeutic INR target range over a

Table 4. Patient Age and Time within Therapeutic International Normalized Ratio (INR) Target Range

| Patient Age, y | Proportion of Time within Therapeutic INR Target Range* |
|----------------|---|
| 0-5 | 70.4%, 69.0%, 64.7%-77.5% |
| 6-10 | 78.8%, 79.9%, 67.5%-91.0% |
| 10-15 | 68.4%, 73.1%, 56.9%-79.2% |
| >15 | 58.1%, 60.9%, 30.3%-80.4% |

*Data are presented as the mean, median, range.

mean measurement period of 3.6 years. This frequency is at least as good and perhaps better than that reported with conventional management. In a previous publication, we reported that 14 patients with a mean follow-up time of 1.5 years had a median frequency of time within the therapeutic INR target range of 65.5% [Christensen 2001]. We can therefore conclude that these short-term results also hold after a longer follow-up period including a larger group of patients.

The poorest results are obtained in adolescents between the ages of 15 years and 18 years with a median percentage of time within the therapeutic INR target range of 60.9% (range, 30.3%-80.4%). This result is consistent with the results of other studies, in which compliance in puberty was found to be a predictor for the quality of the OAT [Stewart 1987, Massicotte 1995].

Patients conducting PSM acquire a much more detailed knowledge about OAT and the influence of medication, food, and so forth than do patients on conventional management. The impact of all these factors are evaluated by each patient to a much higher level of detail than is practically possible for the average professional anticoagulation manager. Thereby, it is possible to predict and react adequately to the rapid changes in INR values normally seen in children on OAT.

We found that both children and their parents expressed significant satisfaction with PSM and that the degree of satisfaction was unrelated to the age of the children. This result is consistent with the results obtained with PST [Massicotte 1995]. The patients and their parents avoided the interruptions to their daily lives imposed by conventional management in terms of visits to the hospital or to the family doctor for blood sampling and adjustments of the drug dosage. PSM reduces patient dependence on the system of health care and thereby minimizes the social impairment of both the children and their parents. That obtaining blood samples by finger stick is less painful than venipuncture also enhanced the satisfaction.

Today, several coagulometers are on the market. The US Food and Drug Administration has approved 3 of these instruments, and one of these instruments is the CoaguChek coagulometer used in the present study. It has been used in many of the conducted studies (eg, [Hasenkam 1997], [Cromheecke 2000], and [Körtke 2001]) in adults for both PST and PSM. The CoaguChek coagulometer has a satisfactory precision (a coefficient of variation of approximately 5%)

and an accuracy of less than ± 0.2 INR relative to an INR value measured in a laboratory using a standardized method [Attermann 1998, van den Besselaar 2000, van den Besselaar 2001].

There is also an acceptable correlation in children between values obtained with the CoaguChek coagulometer and laboratory INR values [Marzinotto 2000]. The small difference in INR values has no clinical consequences. This result is consistent with our previously reported results [Christensen 2001].

We consider that although patients are labeled as “self-managing,” it is important that they be followed and have their quality of OAT monitored by a specialized training and monitoring center.

The fraction of children and parents eligible for PSM is difficult to assess. In our study, none of the patients initially included had to be subsequently excluded for a lack of ability to accomplish the training program. However, this lack of exclusion is partly due to selection bias. Large-scale studies and/or more experience are required to estimate this figure precisely.

It is important that the interest and motivation of the patients and their parents are present. These qualities are essential to facilitate the enthusiasm required to keep up the high quality standards for treatment.

Our study has some inherent limitations in being a case series study, and only a randomized controlled trial can clarify sufficiently whether PSM provides a better treatment quality than conventional management. However, we consider our data powerful enough to provide a valid message.

PSM is feasible for a selected group of patients, and the results seem promising on a long-term basis for a relatively large group of patients. This study provides a benchmark for further studies. We conclude that self-management of OAT is safe and provides a good quality of treatment in selected children with congenital heart disease.

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