Self management of oral anticoagulant therapy after heart valve replacement

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Abstract

Objective: Patients with mechanical heart valves require lifelong oral anticoagulant treatment which entails frequent blood sampling and dosage adjustment. The purpose of this study was to investigate the feasibility of letting heart valve operated patients manage blood specimen analysis and dosage adjustment themselves. Methods: A total of 21 patients were enrolled in the study and followed for at least 9 months postoperatively. Immediately after the heart valve operation they were trained in operating a CoaguChek® international normal ratio (INR) monitor to analyze capillary whole blood samples. Subsequently training in dosage adjustment was accomplished and all patients were considered fully capable of self management after 30 weeks. In the training period, parallel laboratory INR measurements were made at 3–4 week intervals for reference. A control group of 20 patients was matched, respectively, to the study group. The INR target range was 2.0–3.0. Results: Out of the 21 study patients 19 continued self management beyond 9 months. The median INR value obtained with the monitor was within therapeutic target range for all study patients and only 15 out of 20 control patients were within this range. The mean systematic deviation between laboratory and CoaguChek® INR was 7.8% but each patient had a constant characteristic deviation from −11 to +21%. The study patients were within therapeutic target range 77% of the time compared with 53% for the control patients. Conclusions: Self management of oral anticoagulation is feasible for selected patients and constitutes a significant service improvement compared with conventional management. The CoaguChek® monitor seems sufficiently accurate and reliable for self testing and the treatment quality is comparable or even better than conventional management. Assessment of the rate of bleeding and thrombo-embolic events shall be settled in studies comprising larger number of patients. © 1997 Elsevier Science B.V.

Keywords: Self management; International normalized ratio; Anticoagulants

1. Introduction

Oral anticoagulation treatment with vitamin-K antagonists is required by patients with mechanical heart valve prostheses, atrial fibrillation and other indications. The treatment constitutes a delicate balance between two potentially fatal complications: haemorrhage and thrombosis. Therefore, frequent analyses of the blood's coagulatory status is mandatory. In many countries INR (International Normalized Ratio) is used as an indicator of this status and constitutes the basis for appropriate dosage adjustment of the medication. [4,14,17].

In the interest of optimizing the use of resources for both the patient and the health system, blood specimen analysis which balance both safety and economy shall be made at intervals. The time span between blood sampling varies between patients, institutions and coun-
ties with a range from 2 to 12 weeks [9]. Regardless of the blood sampling frequency the treatment restricts the patient’s mobility in terms of, e.g. work, travels and holidays. Thus, patients on long-term oral anticoagulation treatment have an impaired quality of life.

Due to the high risk and the need for laboratory blood specimen analysis, management of oral anticoagulant therapy has always strictly been considered a physician’s task but the treatment quality depends on the level of doctoral and institutional experience [2,5,6,12]. In spite of this there is a considerable diversity in frames of responsibility for anticoagulant therapy, even in the Nordic countries [9].

With the same approach as for diabetic patients who often manage the insulin treatment themselves, the feasibility of letting oral anticoagulated patients exhibit self management has been addressed in previous studies [1,3,8,13,15,18]. Although these studies indicate that self management of oral anticoagulation treatment is feasible, the concept has not yet gained widespread use.

The purpose of the present study was, therefore, to explore the concept of self management of oral anticoagulation treatment further by implementing a training and monitoring setup for a group of patients immediately after heart valve replacement.

2. Material and methods

2.1. Study population

In total, 21 patients (15 male and 6 female; age range: 19–70 years) who were admitted to our department for open heart surgery and had indicators for lifelong oral anticoagulation treatment were included in the study between December 1994 and August 1995, and were followed for at least 9 months. The inclusion criteria were:

- Implantation of a bileaflet mechanical heart valve (St. Jude Medical or CarboMedics).
- Age between 18 and 70 years.
- Address less than 100 km from the hospital.
- Anticipated high level of patient compliance judged from interview.

The exclusion criteria were:

- Coagulopathies.
- Addiction to drugs or alcohol.
- Liver disease.

Patients were included in the project after oral and written consent. The study protocol was approved by the county ethical committee and complied with the Helsinki II declaration.

After completion of the self management study we extracted a group of 20 patients from our department’s clinical files matching the study group by: valve position, valve type, age, sex, and time of operation (listed according to priority). In retrospective fashion we studied the INR data, medication adjustments and made a telephone interview asking for oral anticoagulation treatment related complications. Thus the control group served as a reflection of the clinical routine performance refrained from study conditions.

2.2. INR-analysis equipment

A finger puncture was made by a dedicated puncture device (Softclix®) to release a small sample of capillary whole blood (approximately 25 μl) placed on a test strip (CoaguChek® PT-test) which is inserted in a portable CoaguChek® analysis apparatus (shown in Fig. 1). After less than 2 min of analysis the INR value was presented in the apparatus display. The test strip contains iron oxide particles which are incorporated on the strip together with rabbit brain thromboplastin (International Sensitivity Index (ISI) value = 1.0). Blood contact with the thromboplastin triggers the coagulation cascade. The instrument measures the time from the first contact of the blood sample with thromboplastin to the completion of coagulation process and converts this measure to the INR value.

Fig. 1. The CoaguChek INR-analysis apparatus with a test strip mounted. The apparatus is operated by four press buttons and the display. Power supply is accomplished by AD/DC adaptor or batteries. Each lot of test strips are accompanied by a small calibration code chip which is inserted in the apparatus front end.
The claimed INR-measuring range is 0.7–13.0. The physical measures of the apparatus (height × width × depth) are 5.6 cm × 14 cm × 22 cm, and the weight (including batteries) is 600 g.

In order to aid review of data the CoaguChek® apparatus has a facility to store the previous 30 INR values. These can be downloaded to a personal computer via an adapter cable or reviewed in the apparatus display. Time and date are stored along with each INR value.

Each production lot of test strips are calibrated separately by the manufacturer. In order to assure consistent data each package of test strips are accompanied by a calibration code chip which is inserted into the apparatus’ front end. Evaluation of the equipment’s performance quality is made by the patient through periodic analysis of a standardized control solution dripped on a test strip.

Previous investigations have proven that the CoaguChek® equipment is sufficiently accurate to allow decentralized monitoring oral anticoagulation treatment [11,16]. Our own institutional technical evaluation of the apparatus is will be published elsewhere [7].

Hospitalized blood sampling and analysis was performed as reference at Skejby Sygehus, Aarhus University Hospital, for all patients throughout the entire study period. INR was analysed on blood obtained from cubital vein puncture succeeded by centrifugation at 2720G for 10 min. The plasma sample obtained in this way was analysed on a Coag-A-Mate X-C instrument (Organon Teknika) Simplastin-A tissue factor preparation with an International Sensitivity Index (ISI) calibrator supplied by the Danish Institute for External Quality Assurance in hospital laboratories. The ISI value assigned to the ISI calibrator to the WHO tissue factor preparation.

2.3. Study protocol

A survey of the study protocol is schematized in Fig. 2. In the immediate pre- or postoperative days patients commenced blood specimen analysis based on capillary blood samples as described above using the CoaguChek® Monitor. Training in self analysis was undertaken by two dedicated nurses. In this initial training period oral anticoagulation treatment was regulated into a stable level with INR-values between 2.0 and 3.0 as the therapeutic target range. This initial regulation of INR level was performed by the study group doctors. After the hospital stay, weekly hospitalized INR analyses were performed during the first 6 study weeks. In this period daily CoaguChek® measurements were performed and registered by each patient on a dedicated record form. After 3 weeks the patients were individually interviewed for dedicated teaching about medication and analysis technique. The purpose for of this visit was also to adjust possible flaws in the patient's INR analysis technique.

At a new interview after 6 weeks the patient’s ability to perform analysis was subject to final evaluation and a decision on continued project participation was made. When approved, the hospitalized INR frequency was reduced to once every 3 weeks and the patients own analysis was performed weekly. In this second study phase anticoagulant dosage adjustments were suggested by the patient and followed by doctoral approval or correction, before the patient actually took the medication.

After having passed this phase in a satisfactory and confident way the patients were allowed to adjust the anticoagulant dosage themselves and subsequently report the dosage taken along with the measured INR
values. The frequency of hospitalized INR measurements was reduced to once every 4 weeks. At the end of this 12 week period the patients had to display their skills in a practical and multiple choice test to be allowed full scale self management without hospitalized INR measurements. This implied that the patients were reporting INR values along with information on anticoagulation medication at 3 months intervals.

In the final self managing phase the patients made dosage adjustment without consultation as long as INR values were within a safety range of 1.5–4.5. (This safety range was intuitively settled for the purpose of practical handling of the oral anticoagulation treatment). They were instructed to consult the study group if their dosage adjustment did not have the anticipated effect or INR was outside the safety range. They were also instructed in detail about signs of bleeding or thrombo-embolism.

During the course of the study two meetings were arranged to allow the patients to exchange personal experience and to provide further theoretical information from the study team.

Once every month the patient dripped a standard control solution (provided by the manufacturer) on a test strip to verify apparatus function and correct display of calibration value. This control procedure was performed in an extended version every 3 months by a hospitalized check-up to inspect apparatus cleaning and test analysis accuracy at 3 INR levels: 1.0, 2.5 and 3.8. This control procedure was accomplished by letting the patient send the instrument to the hospital.

2.4. Data handling

INR-values obtained from the hospital and patients were typed on a personal computer into a conventional spreadsheet (Microsoft® Excel). This allowed time courses on INRs to be displayed for each patient. Also differences between CoaguChek® and laboratory INR values were displayed as a function of the laboratory INR value both for each individual patient and for the entire study group. The initial 25 days were discarded due to a significant scatter in the patient’s initial analytical operation performance. Box and whiskers plots were made for both self managing and conventional treated patients in order to reveal median values, upper and lower quartiles, 1.5 times the distance between upper and lower quartile. Outliers are marked with data points on the plots. Data variation is expressed as coefficient of variation in percent (CV%). Furthermore, time within therapeutic INR target level as measured with the monitor by laboratory analysis was used as a parameter for quality assessment.

3. Results

Fig. 3a and b shows the box and whiskers plots for the self management group and the control group. The median value for all CoaguChek® INR recordings was within therapeutic range in all 20 patients (patient No. 13 and 19 had therapeutic ranges adjusted as described below). For comparison the mean median values of laboratory INR in the control group were inside therapeutic target range in 14 out of 20 patients. Boxes and whiskers are obviously smaller for the self management group compared with the control group.

The laboratory monitor control disclosed calibration values which in all cases but one were within the ranges

![Fig. 3. Box and whiskers plot of median INR value line in box for each patient. Corresponding upper/lower quartile (box) and 1.5 times the upper and lower quartiles (whiskers) are indicated as well. Outliers are marked as data points. All INR-values are recorded after the 126th study day. In the self managing group the therapeutic interval was 2.0–3.0, except for patient no. 13 and no. 19, who had 1.5–2.5 and 2.5–3.5 as the therapeutic target range, respectively. In the conventionally treated group the INR target range was 2.0–3.0 for all patients.](image-url)
given for each control solution with a tolerance of 0.1 INR value. One monitor which exceeded the calibration range by 0.3 INR value was returned to the manufacturer and replaced. Inspection of the monitors showed that maintenance and cleaning was properly performed by the patients in all cases.

Out of the 21 patients enrolled in the study one patient (No. 11) chose to discontinue (due to several postoperative problems—not related to the anticoagulant treatment—which made him unwilling to undertake an additional procedure). Another patient was excluded from the study after 8 months due to irregular blood analysis and failure to submit data. She was returned to conventional management of oral anticoagulation treatment. All remaining patients expressed unanimous satisfaction and comfort with the technique. In fact, all 19 patients wanted to continue self management after the study period and chose to buy the monitor and testing disposables out of their own pocket.

None of the patients experienced major bleeding events leading to hospitalization or contact to physician. One patient (No. 13) had a transient episode of blurred vision with no sequela. This event could have been caused by a small embolus, but could not be otherwise verified. Since INR was within therapeutic range at the time of this incident acetylsalicylic acid treatment was added as supplemental thrombosis-prophylaxis. No other patients experienced signs of embolic events.

All patients could operate the instrument properly at the time of the performance test after 30 weeks. They all appeared capable of adjusting anticoagulant medication based on understanding of the specific pharmacology and biochemistry which is necessary to manage the treatment.

Two patients were allowed to operate outside the preset therapeutic target range. Patient no. 13 (mentioned above) had the therapeutic target range changed to 1.5–2.5 since she experienced an event of prolonged menstrual bleeding and tendency to subcutaneous hematomas when INR was above 2.5–3.0. After 13 months on self management she became pregnant and was converted to heparin treatment. She had a spontaneous abortion but was kept on heparin treatment due to continued wish for pregnancy.

Another patient (no. 19) repeatedly claimed physical discomfort whenever INR was below 2.5. He was allowed to change target range to 2.5–3.5. He had no bleeding tendency.

After the 18th study week (where all patients made dosage adjustment themselves) they spent an average of 77% of the time within the therapeutic target range. For comparison the control group of patients were within therapeutic target range for 53% of the time. The maximum INR measured by CoaguChek® after 25 days was 4.1 in average for all patients. Likewise the average minimum INR value was 1.7.

Within the period of initial training (from 25 days and until hospital INR was no longer analysed) a total of 189 parallel INR analyses were obtained from venous puncture (CoagMate) and capillary blood specimen (CoaguChek®). The deviation from the ideal zero line of difference between the two analysis techniques is displayed for all 20 patients in Fig. 4. The median difference between all simultaneously drawn blood samples at the laboratory and CoaguChek® monitor was 7.8% (0.16 INR-value) or approximately 0.16 INR-value at INR = 2). The total CV% was 15.4. The between patient CV% was 8.9 and the within patient CV% was 12.6.

Each patient seem to maintain a fairly constant mean relative deviation between INR measured on CoaguChek® and Coag-A-Mate. This relative difference ranged from −0.3 (−11%) (CoaguChek® overestimation) to +0.5 (+21%) (CoaguChek® underestimation). The relative difference between CoagMate and CoaguChek® remained fairly constant over time for each patient and for the entire group of patients (one example shown in Fig. 5).

The graphic display in Fig. 4 could give the impression that the CoaguChek® monitor exhibits increasing underestimation with increasing INR levels. However, plots of differences versus sums show, that only the variation of the difference in INR between the two techniques increases with increasing INR level.
Fig. 5. The time course of INR values analysed on blood plasma (lab-INR) and whole blood capillary blood samples (CoaguChek® INR). This example from one patient has the same overall pattern as the other study patients.

4. Discussion

Self management is an attractive feature for some patients on lifelong oral anticoagulation treatment, since the conventional treatment requires frequent blood sampling to allow proper dosage adjustment. Letting patients do their own blood analysis and dosage adjustment alleviates the need to go to a hospital laboratory or the family doctor to have blood sampling and subsequent dosage adjustment performed. It saves time and efforts for the patient and it requires less resources for these routine tasks in the health care system. Furthermore, being the primary caretaker of the treatment gives the patient a much better insight into the impact different food items, trivial infection diseases etc. may have on the INR level. These daily life changes are seldom reported to the doctor who is responsible for the dosage adjustments. Thus, the patient is in a better position to respond appropriately to INR changes with a much more differentiated approach than the doctor. Being aware of the potential risks of oral anticoagulation treatment and having first hand control of the management will, therefore, most likely accentuate the patient compliance.

A precondition for self management is a reliable and accurate monitor which is easily operated. The monitor used in this study has been evaluated by several centers [11,16,10] and considered reliable for near patient testing. Kaatz et al. 1995 reported that the difference between INR data obtained in different laboratories was larger than the difference between one laboratory and the CoaguChek® monitor. Flensted et al. 1995 reported that with a therapeutic target of INR = 2.5 the biological variation is 0.7. Accordingly, a difference between serial measurements below this level should not lead to dosage adjustment. To put this figure in perspective we found that the CoaguChek® monitor underestimated INR by 0.16 (or 7.8%) (0.2 INR of a target value of INR = 2.5) compared with our laboratory.

Our findings indicate a patient specific deviation in INR data obtained on the monitor and by the laboratory. Since this deviation was fairly constant over at least 6 months it could justify either a patient specific calibration against the patient’s reference laboratory or an individual adjustment of the therapeutic target range in order to retain the conventional level of anticoagulation. From our experiences we estimated suggest that at least ten simultaneous laboratory and CoaguChek® recordings should be made to estimate this level of difference.

The reason for the patient specific deviation between the two analyses cannot be clarified from this study but an obvious difference between the technique is the use of plasma and capillary whole blood, respectively. It might even be speculated whether assessment of the patients coagulatory capacity in whole blood with (e.g. thrombocytes) is a more precise reflection of the patients tendency to bleed or develop thrombi. This question must obviously be addressed in studies of much larger number of patients.

In a Nordic survey [9] 67% of INR values from patients on conventional oral anticoagulation treatment were within therapeutic level. Specialized centers generally obtain better results with INR values in therapeutic level for approximately 80% of the time [2] In this context our self managing patients have a satisfactory performance bearing in mind that they started training immediately after open heart surgery. The frequent blood sampling also prevented excessive excursions...
from the therapeutic target range since proper action was taken earlier than is feasible with conventional management. The limited number of patients and the short study period does not allow any interpretation of the clinical outcome in terms of bleeding and thrombo-embolic complication rates. The only indication of better treatment quality is the higher percentage of time within therapeutic target range.

Supported by other reports our data allows us to conclude that self management of oral anticoagulation treatment is feasible for selected patients with prosthetic heart valves.

Practical training in blood analysis and monitor maintenance is undertaken by a dedicated nurse in our department. For quality assessment and optimization of the oral anticoagulation treatment it is essential to acquire INR recordings, medication dosages and information about clinical signs of complications for centralized data handling. In order to validate the performance of the monitors quality assurance is valuable tool for external verification of analysis reliability.

5. Conclusion

Self management of oral anticoagulant therapy is feasible for selected patients with prosthetic heart valves. Studies comprising larger number of patients and longer study periods are needed to assess the bleeding and thrombo-embolic complication rates.

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References

Appendix A. Conference discussion

Dr B. Messmer (Aachen, Germany): Did you have in your series mitrals or aortics or both?
Dr M. Hasenkam: Yes, both mitral and aortic valves.
Dr B. Messmer: And you didn’t make any difference in the INR values you wanted to have?
Dr M. Hasenkam: No. We have a Danish convention that patients with these types of valves—the bileaflet valves—should be kept within an INR target range of 2–3; and actually in our study group of patients we did not have any major complications.
Dr F. Fontan (Bordeaux, France): Did you advise the patient differently if he was not in atrial fibrillation for the level of INR required?
Dr M. Hasenkam: No. We kept all of them with a preset target value. Two of the patients were allowed to operate outside: one of them had a combination of acetylsalicylic acid INR target range was 1.5–2.0 and another patient was allowed to be slightly above (INR target range 2.5–3.5).
Dr M. O’Brien (Brisbane, Australia): I might have missed this point, but what was the difference in the frequency of the tests between the control group and the patient group?
Dr M. Hasenkam: The control group was collected in a retrospective fashion and managed according to our daily routine in the department, and blood sampling was not at a preset frequency. It was depending on the value of the patients.
Dr M. O’Brien: What I ask is did the patients do the tests more frequently than the control group who would have had it done by the doctor?
Dr M. Hasenkam: Yes.
Dr M. O’Brien: What was that difference?
Dr M. Hasenkam: The patients took an INR value at least every week, and the control group of patients had an increasingly longer period between their measurements, up to about 8 weeks.
Dr M. O’Brien: Did the patients not do it more frequently than weekly? Diabetic patients often do several tests, some far more frequently.
Dr M. Hasenkam: That probably depends on what kind of medications that you use. We used phenprocoumon, which has a very long half-time and therefore it probably is not necessary to do measurements more frequently than once a week.
Dr J. Szecsi (Szeged, Hungary): Have you done a comparison between the expenses of the two techniques?
Dr M. Hasenkam: The initial expense is a slightly more because the patients have to buy the monitor themselves. After having bought that monitor, the maintenance cost is cheaper than having blood specimens analyzed in the public system. But it’s very difficult to compare that from country to country because the systems are very different.
Dr J. Szecsi: Is it reimbursed by insurance companies?
Dr M. Hasenkam: In Denmark it is not. I know that in Germany, for example, it is reimbursed by the insurance companies.
Mr R. Williams (Glasgow, Scotland). You say the patients have to be quite well disciplined and motivated to do this. What proportion of your overall valve patients did you think were suitable to run this machine at home in this way?
Dr M. Hasenkam: We have speculated quite a lot about that and it’s very difficult to predict. Some, very optimistic, say that up to about half of the patients can manage that. I don’t know whether that is a realistic figure. I would estimate about 30%, but it’s a very rough guess.
Dr B. Messmer: Well, I feel that one disadvantage is that when you have unreliable patients and they are doing their self-adjustment, then they disappear from the doctor’s control, then I think that you really have to be careful also from the side of the doctor which patient to select for his self-adjustment.
Dr M. Hasenkam: You are absolutely right, we have to be careful. As I said during my presentation, it is extremely important not to loose contact with these patients. You should always monitor their performance and interfere if something seems to drift away from the correct course. Actually one of the patients in our study group seemed to lose consistency in taking the specimens, and then we asked the patient to go back to conventional treatment.