

A Prospective Controlled Trial Comparing Weekly Self-testing and Self-dosing with the Standard Management of Patients on Stable Oral Anticoagulation

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Key words

Oral anticoagulation, artificial heart valves, venous thrombosis, self-management

Summary

Oral anticoagulant therapy requires frequent laboratory controls of its intensity to assure therapeutic efficacy and to prevent potentially life threatening adverse events. It is generally assumed, that increasing the frequency of testing would lead to a better control of anticoagulation. We tested this hypothesis in a prospective controlled trial comparing weekly self-testing and self-dosing (self management) with the standard-management of these patients in an anticoagulation clinic. Only patients with stable anticoagulation were included into the study. We recorded 2733 weekly determinations of the intensity of anticoagulation (INR) in 49 patients on self-testing and self-dosing and 539 determinations of the INR in 53 patients on standard-management. Two intensities of anticoagulation were used in each group: a target INR of 3.5 for patients with artificial heart valves (target range: 2.5–4.5) and a target INR 2.5 (target range: 2.0–3.0) for patients with atrial fibrillation or venous thromboembolism. The deviation from the target INR, the fraction of INR determinations within the preset therapeutic range and the difference between the target INR and the actually achieved mean INR were the three major endpoints of the study. The mean deviation from the target INR was smaller in the groups of patients on self-management compared to the patients on standard-management. Individual deviations were significantly ($p < 0.0001$) dependent on the type of management in interaction with the treatment intensity in a general linear model. Patients on weekly self-testing and self-dosing had more INR values within the therapeutic range than patients on standard-management (86.2% vs. 80.1% at INR range 2.5–4.5; 82.2 vs. 68.9 at INR range 2.0–3.0). The achieved mean INR was almost identical with the target INR in the patients on self-management but was significantly ($p < 0.005$) below the target INR in the high intensity anticoagulation group on standard-management (target INR:3.5; achieved mean INR: 3.19; CI 0.95: 3.05–3.34).

The technical equipment used for self testing in this study was provided by Roche Diagnostics, Austria

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Our data show, that weekly self-testing and self-dosing leads to a better control of anticoagulation than standard treatment in an anticoagulation clinic.

Introduction

Oral anticoagulation (OAC) is prescribed to a steadily increasing number of patients (1). It can efficiently prevent arterial embolism in a wide variety of clinical condition (2, 3) and is highly effective in the secondary prevention of venous thromboembolism (4). However, the small therapeutic range of the oral anticoagulant drugs and the potentially life threatening effects of both under-dosing and over-dosing necessitates a close control of the actual intensity of anticoagulation (5). This is usually achieved by a more or less frequent testing of the prothrombin time, which requires a lab facility for testing, a specifically educated person to perform the test and a medical doctor who prescribes the correct dosing of the anticoagulant drug. The frequency of this testing is limited by the availability of the testing facilities, the direct and indirect costs of testing and the time constraints of the patient. Thus, patients on stable OAC are seen every 4 to 6 weeks (2). In such a setting, only 40% to 60% of all prothrombin time measurements fall within the desired range (6–9).

Recently, a portable monitor for prothrombin time estimation (CaoaguChek[®], Hofmann La Roche, Indianapolis) has been introduced and has been approved for self testing by patients in the USA and in Germany. This instrument measures the prothrombin time (PT) from a capillary sample of whole blood and provides a result expressed in INR values within two minutes. It has been tested successfully for its accuracy, reliability and ease of handling in both experimental and clinical studies (10–14).

One of the major advantages of self testing at home is the possibility of increasing the frequency of testing without adding a great burden to the patient and to the health care system. From small and mainly retrospective studies it is estimated, that increasing the frequency of testing leads to a better control of anticoagulation (9, 15, 16). We therefore performed a prospective controlled trial and compared the quality of anticoagulation of weekly self testing with standard testing in an anticoagulation clinic. In addition to self testing, patients in the study group also were instructed to adjust their own coumarine dose based on their test results under specified precautions.

Patients and Methods

Patients were recruited from the anticoagulation clinic of the Department of Hematology and Hemostaseology. Between 80 to 100 patients are seen daily at

Table 1 Enrollment and follow-up of patients

Consecutive Patients included n=113	
Standard-Management n=54	Self-Management n=59
Withdrawn n=1 Lost for follow up n=1	Withdrawn n=10 Refused to participate prior to start n=7 Refused to participate after starting n=2 Deceased n=1 (melanoma)
Completed the Study n=53	Completed the Study n=49

this institution by a single physician for the estimation of the intensity of anti-coagulation and for the prescription of the subsequent coumarine dose. Patients were eligible for the study if they were on OAC therapy for at least 6 months prior to the study. In addition, more than 50% of all INR values obtained in this 6 months had to be within the specified therapeutic range. Patients with Lupus Anticoagulants, with preexisting liver disease or with addiction to drugs or alcohol were excluded from the study. Patients meeting these criteria were considered as candidates for the study if they were able to mechanically handle self testing (no major visual problems, tactile dysfunction or severe tremor), to comply with the dosage algorithm, were reliable (previous compliance) as judged by the treating physician and agreed to participate in the study. Patients for the self testing group and for the control group were taken from this pool of primarily selected patients (Table 1).

Study patients and controls were introduced into the nature of anticoagulation, the consequences of over-dosage or under-dosage, the possible alimentary and drug interactions with OACs, and the specific precautions that patients on OACs need to take when they first started on OACs (at least 6 months before entering the study). This is a routine procedure in the anticoagulation clinic and was not a specific part of the study.

Self Management Group

Consecutive patients from the primary selected patients were allocated to the self testing group (Table 1). Five out of 59 denied participation. Two patients dropped out of the study group during the training phase (one was unable to perform the finger puncture; one thought that the dosage algorithm was too complicated for him). Two patients (a couple) dropped out after participating 7 weeks. They used three different homes and felt that carrying the monitor around was too cumbersome. One patient died 3 months after the start of the study (malignant melanoma of the retina). Thus, forty nine patients completed the study in the self management group with an observation time of 12 months. Twenty-eight patients with heart valve prostheses were on a high intensity treatment regimen (INR range: 2.5–4.5). Twenty-one patients (9 venous thromboembolism, 12 atrial fibrillation) were on a low intensity treatment regimen (INR range: 2.0–3.0). The self-management group consisted of 22 female and 27 male with an mean age of 54 years (range: 28–72).

Training in testing and dosing

Patients in the study group underwent specific training for self-testing and self-dosing. Training in self-testing on the CoaguChek® monitor (10) was taught for two hours in groups of 5 to 10 patients by a lab technician who had prior experience in conventional testing and in testing with the monitor. Having been introduced to the handling of the CoaguChek® device and the use of the control substance, each patient performed a minimum of two tests on himself and was able to watch the others testing. Patients got their own monitor and were allowed to practice testing at home until the actual start of the study.

A written algorithm was explained and was handed out to the patients. It contained detailed information regarding time and frequency of testing and instructions on how to determine the correct test result in the case of a strongly diverging outcome of a test.

Self-dosing was taught in a one hour session. Patients were instructed in the use of a simple dosage algorithm. Specific dosage situations were worked up with each of them.

Specifically, patients had to aim for a target value rather than the usual target range. At the actual entry into the study, patients were reevaluated regarding their capability of self-testing and self-dosing. The begin of the study was delayed by a week when either the patient himself or the supervising physician felt uncomfortable with the patients handling of testing or dosing. Four patients had to be delayed for one week and one patient had to be delayed for two weeks for that reason. Patients had to test once a week. They were discouraged to test more frequently and were not allowed to use any additional measurement for dose adjustments. The weekly measurement was used to adjust the coumarine does, if necessary. Patients had to call the hospitals 24 h coagulation service if the INR was >5.5 or <1.5 or if they had any medical problems related to anti-coagulation. Patients were temporarily excluded from the study when a change in the therapeutic range (tooth extraction in three patients, gastroscopy with biopsy in one patient) was necessary.

Patients were seen every four weeks at the anticoagulation clinic where they had to present their documentation sheets showing the results of the previous measurements, dosage decisions, possible adverse events and possible contacts with the coagulation service.

Self-testing patients were temporarily excluded from the study when a change in the therapeutic range was necessary.

Standard Management Group

A total of 54 age and sex matched patients were recruited from the primary selected pool of patients for the standard-management group. All but one (left the area) completed the study. The whole study group included 25 female and 29 men with an mean age of 52 years.

A capillary blood test (Thrombotest®, Nycomed Pharma AS, Oslo, Norway) was performed on a KC-1 coagulometer (Amelung, Lemgo 1, Lieme, Germany) to estimate the intensity of anticoagulation in the control patients. The dosage of the oral anticoagulant was determined by a physician who was familiar with the study protocol. He specifically was instructed to aim for the target value rather than the usual target range. The frequency of testing was left to the discretion of the physician. Patients on stable anticoagulation were usually seen in intervals of 4 to 8 weeks. Patients were temporarily excluded from the study when a change in the therapeutic range (tooth extraction etc.) was necessary.

Intended INR Values

Patients in the self-management group and the physician in the standard-management group were instructed to aim the intensity of anticoagulation to a specific target INR value ("INR intended" in Table 2). Patients in the self-management group had an target INR of 3.2 for the high intensity treatment regimen and 2.4 for the low intensity treatment regimen. The respective target values in the standard management group were 3.5 and 2.5. This difference in the target value between self-management and standard-management group was necessary, because previous studies (including a pilot study in our institution) have shown a rather constant difference of 0.3 INR (at a level of INR 3.5) between the CoaguChek® values and the capillary Thrombotest® on KC1.

The difference was less pronounced at an INR value of 2.5. Adjusting the INR target values for patients in the study group obviated the need of increasing their dose once on CoaguChek®, which probably would have been executed only reluctantly by some patients and consequently would have biased our results.

Adverse Events

Clinically overt episodes of cerebral ischemia, venous thromboembolism and severe bleeding were monitored. Severe bleeding was either bleeding requiring transfusion or intracranial bleeding.

Study Medication

Patients in both management groups used phenprocoumon (Marcoumar®, Hoffmann La Roche, Vienna, Austria) as their oral anticoagulant drug.

All patients had to give informed consent. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University Vienna.

Statistical analysis. The 95% confidence intervals for the mean INR values of the different groups of patients were calculated assuming the normal distribution of the data.

A general linear model (SAS 6.12/ProcGLM) was calculated for INR values and the deviation of these values from the target value using the type of management (self/standard), the intensity of treatment (high/low) and their interaction as fixed effects and the patient within management and intensity as the random factor. Repeated measurements per patient were treated as simple random replications.

Results

Frequency of Testing

The 49 patients in the self-management group made a total of 2733 INR determinations, the 53 patients in the standard-management group made 539 INR determinations (Table 2).

Frequency of Dosage Adjustments

Patients in the self management group had a significantly higher absolute number of doses adjustments per year compared with the standard management group (22.4 vs. 3.4 changes per year, $p < 0.005$). The relative frequency of dosage adjustments (dosage changes/100 tests performed) was similar in both groups (37/100 for standard management, 42/100 for self management).

Mean Coumarine Dose

There was a borderline significant difference in the mean weekly phenprocoumon dose between the management groups in the patients with the high intensity regimen [(self management: 16.5 mg/week (range: 5.1–38.4); standard management: 13.8 mg/week (range: 4.2–32.4) ($p = 0.07$)] but not in the patients with the low intensity regimen [(self management: 17.7 mg/week (range: 4.2–32.4); standard management: 14.7 mg/week (range: 9.2–25.5) ($p = 0.13$)].

Deviation from Target Value

The mean square deviation from the target INR was considerably lower in the patients on self-testing when compared to standard management (0.32 ± 0.18 SD vs. 0.57 ± 0.40 SD, Table 2). In the general linear model of the deviations from the target value, the intensity of anticoagulation ($p < 0.0001$) and the interaction of the type of man-

Table 2 Total number of INR measurements, deviation from the target INR, number of INR measurements within the therapeutic range and intended versus achieved mean INR in patients on self-management and patients on standard-management

+ vs. ++ $p < 0.005$

	SELF MANAGEMENT		STANDARD MANAGEMENT	
Patients	49		53	
Measurements	2733		539	
Mean square deviation				
(+/-SD) from target INR	<i>total group</i>		<i>total group</i>	
	0.32+/-0.18		0.57+/-0.40	
	<i>target INR 3.2</i>	<i>target INR 2.4</i>	<i>target INR 3.5</i>	<i>target INR 2.5</i>
	0.40 +/-0.19	0.21+/- 0.11	0.61+/-0.26	0.50+/-0.54
INR-measurements within				
therapeutic range (%)	<i>total group</i>		<i>total group</i>	
	2311 (84.5)		398 (73.8)	
	<i>target range 2.5-4.5</i>	<i>target range 2.0-3.0</i>	<i>target range 2.5-4.5</i>	<i>target range 2.0-3.0</i>
	1389 (86.2)	922 (82.2)	245 (80.1)	153 (68.9)
INR intended	3.20	2.40	3.50+	2.50
INR achieved (mean)	3.15	2.42	3.19++	2.62
CI 0.95	3.06-3.23	2.36-2.48	3.05-3.34	2.46-2.78

agement with the intensity of anticoagulation ($p < 0.0001$) were statistically significant.

INR Values within Therapeutic Range

2311 of 2733 INR values (84.5%) determined in the self-management group were within the therapeutic range compared to 398 of 539 INR values (73.8%) obtained in the standard-management group. In the high intensity treatment arm of the study (INR 2.5–4.5) 1389 of 1611 (86.2%) measurements from the self-management group but only 254 of 317 (80.1%) measurements from the standard-treatment group were within the therapeutic range (Table 1). 922 of 1122 (82.2%) measurements from the self-management group but only 153 of 222 (68.9%) measurements from the standard-treatment group were within the therapeutic range in the low intensity treatment arm of the study (INR 2.0–3.0) (Table 2).

Mean INR: Intended vs. Achieved

Table 2 shows the comparison of intended target INR and the actually achieved mean INR of the four group of patients. The mean INR level of 3.15 (CI 0.95: 3.06–3.23) achieved in the high intensity group on self-management and the mean INR level of 2.42 (CI 0.95: 2.36–2.48) achieved in the low intensity group on self-management were almost exactly the intended target INR (3.2 and 2.4 respectively). The achieved mean INR of 3.19 (CI 0.95: 3.05–3.34) was significantly lower than the target INR of 3.5 in the high intensity group on standard-management and was slightly higher (2.62; CI 0.95: 2.46–2.78) than the

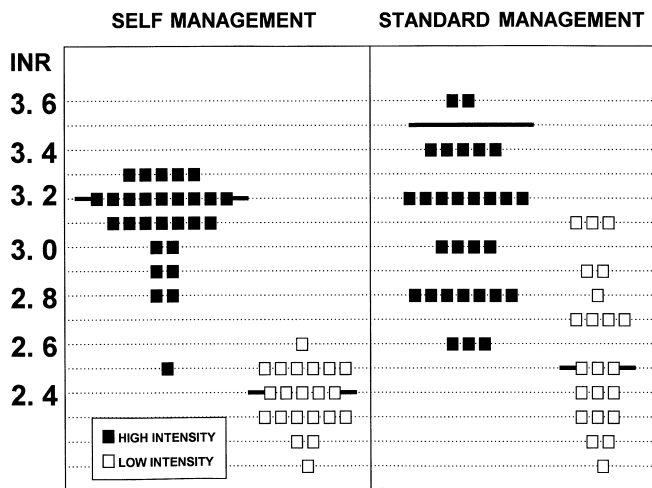


Fig. 1 Individual mean INR values of each patient in the four treatment groups. The INR target level in each group is indicated by a bold line. Mean INR values (rounded for the first decimal) are clustered around the target INR in both of the self management groups (high intensity and low intensity). In the standard management groups, in contrast, 80% of the INR values in the high intensity group are below the target value resulting in considerable under-anticoagulation of this group. Patients in the low intensity treatment group on standard management are better balanced but still have the majority of their mean INR values above the target level. This leads to a large overlap in the INR values in the standard management group and to a concentration of INR values in an range from 3.2 to INR 2.5. In contrast, INR values in the two self management groups show no overlap resulting in a statistically highly significant difference ($p < 0.001$) between the mean INR of these groups.

target INR of 2.5 in the low intensity group on standard management. The mean INR values of individual patients in the four groups are shown in Fig. 1.

Complications of Oral Anticoagulation

Two major events (major bleeding, cerebral ischemia) were recorded. A severe GI-bleed (at INR 2.9) in a patient with venous thrombosis and a TIA (at INR 2.6) in a patient with a mitral valve replacement occurred in the self management group. No complications occurred in the standard management group.

Discussion

Our study shows, that patients on weekly self-testing and limited self-dosing have a better control of anticoagulation than patients managed in a standard way by an anticoagulation clinic. This is evident from all three endpoints of our study (Table 1). Firstly, our patients on weekly self testing have a higher percentage of their INR values within the therapeutic range (84% vs. 73%). These data are consistent with results from two retrospective studies (7, 8) which show, that 67% to 88% of all INR values in patients with weekly self-testing fall within the desired range. Patients with a wider therapeutic INR range of course have a higher percentage of INR values correctly targeted which limits the generality of this parameter. We therefore used a target value as the primary endpoint in our study and calculated the deviation of the individual INR from this target value. The mean (square) deviation was almost twice as high in the standard-management group compared to the self-management group (Table 2). As can be expected from this difference, the individual INR-deviations were significantly

($p < 0.0001$) dependent on the type of management in a general linear model, albeit in interaction with the intensity of treatment only: the groups with the target INR of 3.5 and 3.2 had significantly higher deviations from their targets than the groups with the target INR of 2.5 and 2.4. A similar difference in the deviation from the target INR between self-management and standard-management has been previously reported (9).

Analysis of the mean INR in the four different treatment groups in our study showed that the mean INR actually achieved in the self-management groups (2.42 and 3.15, respectively) were almost exactly the one which were aimed for (2.4 and 3.2, respectively), while they were significantly off the desired value in the standard-management groups (Table 2): patients with the target INR of 3.5 achieved a mean INR of 3.19 and thus were significantly ($p < 0.01$) under-anticoagulated. Those with a target INR of 2.5 achieved a mean INR of 2.62 and thus were over-anticoagulated. This pattern is also evident from the analysis of the individual mean INR values. There was a considerable overlap in the individual mean INR values of the patients on standard-management due to the under-anticoagulation of the high-intensity group (target INR: 3.5) and the over-anticoagulation of the low intensity group (target INR: 2.5) (Fig. 1). There was almost no overlap in the patients mean INR values in the two self-management groups. These data suggest, that it is easily possible to generate two clearly separated groups of INR with weekly testing even when rather close INR values of 2.4 and 3.2 are targeted. This is barely possible using the conventional management, even for INR target values which are further apart (2.5 and 3.5).

The most obvious explanation for the improved outcome of the self-management group when compared with the standard management group is the higher frequency of testing in conjunction with the higher frequency of doses adjustments in the former. Weekly testing obviously allows to take action before the INR deviates too much and thus prevents strongly aberrant and widely fluctuating INR values. In addition, it is very well possible, that patients managing their own anticoagulation might be better motivated to stay on constant INR, which generates the better outcome.

The design of our study allows to rule out any selection bias influencing the study results. Stratification was performed after the inclusion of both, the self-management and the standard-management patients in the study. The training in testing and dosing, which is dispensable for the standard-management group, was provided for the self-management group only. However, careful attention was paid not to transfer any additional information on oral anticoagulation during these lessons.

Several features of our study have to be taken into account, which prevent generalization of our results to all patients on oral anticoagulant therapy. Firstly, we studied a highly selected group of patients with rather stable baseline anticoagulation. The values on percent INR within the therapeutic range and deviation from the target INR are lower in an unselected population of patients using OAC, irrespective of the type of management (8, 9). It is surprising however, that even among our stable anticoagulated patients weekly self-testing still increased the stability of the INR values. Secondly, the standard management group was managed by an anticoagulation center which generated a rather excellent control of anticoagulation. Surprisingly, patients in the self management group did still better. Thirdly, our patients were selected regarding their ability to mechanically handle self testing (no major visual problems, tactile dysfunction or severe tremor), to comply with the dosage algorithm and to be reliable as judged by a physician who had seen and treated these patients on several occasions before. We have used these clinical selection criteria because we think,

that selection of patients for self management of oral anticoagulation can not be standardized but always will, to some extent, rely on the personal judgement and experience of the treating physician. When such criteria are applied in a responsible manner, patients on weekly self testing and limited self dosing have a better control of anticoagulation than conventionally managed patients. Numerous studies have shown a clear correlation of a deviation of the INR values from the therapeutic range with bleeding or thromboembolic events (3, 17, 18). Therefore it can be expected, that the better control of therapy in the self-management patients will indeed translate into a reduction of thromboembolic episodes in patients taking oral anticoagulants.

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