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ORIGINAL ARTICLE

Comparison of initial loading doses of 5 mg and 10 mg for warfarin therapy

Comparação da dose inicial de 5 mg ou 10 mg para o início da terapia com varfarina

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Abstract

Context: The question of what is the best loading dosage of warfarin when starting anticoagulant treatment has been under discussion for ten years. We were unable to find any comparative studies of these characteristics conducted here in Brazil. **Objective**: To compare the safety and efficacy of two initial warfarin dosage regimens for anticoagulant treatment. **Methods**: One-hundred and ten consecutive patients of both sexes, with indications for anticoagulation because of venous or arterial thromboembolism, were analyzed prospectively. During the first 3 days of treatment, these patients were given adequate heparin to keep aPTT (activated partial thromboplastin time) between 1.5 and 2.5, plus 5 mg of warfarin. From the fourth day onwards, their warfarin doses were adjusted using International Normalized Ratios (INR; target range: 2 to 3). This prospective cohort was compared with a historical series of 110 patients had been given 10 mg of warfarin on the first 2 days and 5 mg on the third day with adjustments based on INR thereafter. Outcomes analyzed were as follows: recurrence of thromboembolism, bleeding events and time taken to enter the therapeutic range. **Results**: Efficacy, safety and length of hospital stay were similar in both samples. The sample that were given 10 mg entered the therapeutic range earlier (means: 4.5 days vs. 5.8 days), were on lower doses at discharge and had better therapeutic indicators at the first return appointment. **Conclusions**: The 10 mg dosage regimen took less time to attain the therapeutic range and was associated with lower warfarin doses at discharge and better INR at first out-patients follow-up visit.

Keywords: anticoagulants; warfarin; dose-response drug relationship; thrombosis; treatment outcomes.

Resumo

Contexto: A melhor dose para o início do tratamento anticoagulante com varfarina vem sendo debatida nos últimos dez anos. Em nosso meio, não observamos nenhum estudo comparativo quanto a estas características. **Objetivo**: Comparar segurança e eficácia de dois esquemas de dosagem inicial de varfarina para tratamento anticoagulante. **Métodos**: Foram estudados prospectivamente 110 pacientes de ambos os sexos, consecutivos, com indicação de anticoagulação por tromboembolismo venoso ou arterial. Durante os três primeiros dias de tratamento, estes pacientes receberam doses adequadas de heparina (RT - razão dos tempos - alvo entre 1,5 e 2,5) e 5 mg de varfarina, cuja dose foi reajustada a partir do quarto dia pelo Razão Normatizada Internacional - RNI (alvo entre 2 e 3). Esse grupo foi comparado com série histórica de 110 pacientes que receberam 10 mg nos dois primeiros dias, 5 mg a partir do terceiro dia, com ajuste posterior de dose baseado no RNI. Os desfechos foram: recorrência do tromboembolismo, sangramentos e tempo para alcançar níveis terapêuticos. **Resultados**: A eficácia, a segurança e o tempo de internação foram similares entre os grupos. O grupo que recebeu 10 mg atingiu níveis terapêuticos mais precocemente (média de 4,5 dias × 5,8 dias), sendo as doses na alta menores e os níveis terapêuticos mais adequados na primeira visita de retorno. **Conclusão**: O esquema de dosagem de 10 mg proporcionou menor tempo para alcançar nível terapêutico, com menores doses de varfarina na alta e RNI mais adequado no retorno.

Palavras-chave: anticoagulantes; varfarina; relação dose-resposta à droga; trombose; resultado de tratamento.

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INTRODUCTION

Classic anticoagulant treatment for venous thromboembolism (VTE) or arterial thromboembolism (ATE) is well-established and should be initiated with parenteral anticoagulants (unfractionated heparin [UFH], low molecular weight heparin [LMWH] or fondaparinux) in combination with warfarin, withdrawing the parenteral component when INR has been successfully maintained within the therapeutic range (2 to 3) for 2 consecutive days[1-3].

The initial warfarin dose is usually a 10 mg loading dose for 2 consecutive days followed by 5 mg, and is adjusted thereafter on the basis of INR. An alternative approach is to start with 5 mg per day until the target INR of 2 to 3 is achieved[2]. This option may offer the advantage of provoking less severe reduction in serum C and S protein levels, making an initial hypercoagulable state less likely[2]. The objective of the treatment regimen employing a 10 mg loading dose is to get within the 2 to 3 INR range as early as possible. However, this approach may occasionally provoke transitory hypercoagulability states[4].

Review studies have shown that both posologies were equally effective and safe, but studies that recommended an initial warfarin posology of 10 mg excluded patients at high risk of bleeding[5]. One systematic review compiled information from 11 randomized studies, showing that there is still considerable uncertainty surrounding the benefits of initial dosages of 5 or 10 mg of warfarin, although there is greater consensus around using 5 mg doses with elderly patients. This review did not make it clear whether genetic characteristics may offer indications to which initial warfarin dose is preferable[6].

The lack of consensus on the ideal initial oral anticoagulant dose, the biases that have been identified in the designs of previous studies (such as excluding patients at high risk of bleeding) and the lack of Brazilian studies on the subject that have been conducted within Brazil all justify conducting this study.

PATIENTS AND METHODS

This was a non-randomized prospective study of 110 consecutive patients treated at our unit after admission for VTE or ATE and given parenteral anticoagulation with UFH in combination with an initial warfarin dosage of 5 mg for the first 3 days, adjusting the dose thereafter on the basis of INR. This set of patients was compared with a retrospective historical sample of 110 patients, who had been treated previously at the same service and for the same reasons, but who had been given 10 mg initial warfarin doses for the first 2 days of treatment, reducing to 5 mg on the third day and adjusting the dose thereafter on the basis of INR (target range: 2 to 3). It should be pointed out that both sets of patients were followed-up at our Anticoagulation Clinic using the same criteria. When there was a clinical suspicion of recurrence, diagnosis was confirmed using duplex scanning for suspected VTE, or by clinical examination for ATE. In all cases, parenteral anticoagulant treatment was started with an initial intravenous UFH bolus of 5,000 UI, for deep vein thrombosis (DVT) cases or during surgery for arterial thromboembolectomy, or 10,000 UI (in cases of pulmonary thromboembolism [TEP] or TVP), followed by maintenance doses via an infusion pump sufficient to maintain aPTT between 1.5 and 2.5 times the reference values. These patients were followed-up for varying periods (10 to 28 days), recording data from the first day of admission, through discharge, up to their first return appointments at the Anticoagulation Clinic.

The research project was approved by the Research Ethics Committee and all patients in the prospective cohort signed free and informed consent forms.

The following cases were excluded from the study: expectant mothers; patients less than 18 years old; patients with indications for vena cava filters; patients with contraindications to anticoagulation, such as active hemorrhage, postoperative recovery after major surgery, neurosurgery, hemorrhagic cerebral vascular accident, liver or kidney failure, and being administered antiplatelet or anti-inflammatory drugs.

Demographic data, efficacy outcomes (recurrence of thromboembolism) and safety outcomes (bleeding, side effects) were all analyzed. Additionally, the following were also analyzed: duration of hospital stay, time taken to reach the therapeutic range, warfarin dose at discharge, INR at discharge and INR at first return appointment. The period analyzed extended from hospital admission to the first consultation after hospital discharge.

The chi-square test or Fisher's exact test were used for statistical analysis of categorical variables. Quantitative variables were subjected to analysis of variance, with calculation of the F statistic, and means were compared using the Tukey test. The significance level was set at 5%.

None of the authors have any conflicts of interests related to this study.

RESULTS

Table 1 lists the patients' demographic data and comorbidities. Table 2 lists the main outcome results and Table 3 lists complications broken down by study group (5 mg vs. 10 mg).

The follow-up period for these patients was brief, on average lasting less than 30 days (Table 2).

In general, mean time taken to enter the therapeutic range, warfarin dose at discharge and INR at first return consultation were significantly higher in the group given the 5 mg initial dose than in the 10 mg group (Table 2).

There was no difference in terms of the number of bleeding episodes between the 5 mg and 10 mg groups, because bleeding events were very infrequent in this series [5/220 (2.3%)] and were all minor cases, such as epistaxis and gingivorrhagia (Table 3). Furthermore, just one of these patients had an INR outside of the target range (INR=7.59). All bleeding event patients were female, aged from 24 to 79 years (mean age 59.6 years). Two hemorrhage patients had been given the higher initial warfarin dosage (10 mg) and three patients had been given the lower dosage (5 mg). Two of these patients had ATE and three had VTE. These five patients had initial INR ranging from 1 to 1.18 (mean of 1.05) and took from 4 to 7 days (mean of 5.86 days) to attain the therapeutic range. They were discharged with INRs of 2.2 to 3.17 (mean of 2.5) and on doses of 3.75 to 10 mg of warfarin (mean of 6.5 mg). They returned to the Anticoagulation Clinic from 3 to 11 days (mean of 5 days) after discharge, at which time they exhibited INRs at first return of 2.4 to 13.2 (mean of 5.86) (Table 2). Four of these patients (80%) had

Table 1. Demographic data.

Data	5 mg		10 mg		p
	Arterial G1	Venous G2	Arterial G3	Venous G4	
Male patients/total patients	36/55	20/55/	30/55	23/55	P<0.02
Age (mean)	58.3		57.1		p>0.20
Length of hospital stay (mean)	14.1	7.7	17.1	8.5	A>V (P<0.0001) 5 mg = 10 mg
Smoking	52.7%	20.0%	58.2%	27.3%	A>V (p<0.001) 5 mg = 10 mg
Hypertension	70.9%	20.0%	52.7%	9.1%	A>V (p<0.001) 5 mg = 10 mg
Diabetes mellitus	16.4%	10.9%	16.4%	5.5%	p>0.10
Heart disease	45.5%	7.3%	38.2%	10.9%	A>V (p<0.001) 5 mg = 10 mg
Initial INR	1.19	1.21	1.15	1.15	

Table 2. Outcomes.

Data	5 mg		10 mg		p
	Arterial G1	Venous G2	Arterial G3	Venous G4	
Length of hospital stay in days (mean)	14.1	7.7	17.1	8.5	A>V (P<0.0001) 5 mg = 10 mg
Initial INR	1.19	1.21	1.15	1.15	
Mean time to therapeutic INR range (days)	4.5	4.4	5.7	5.9	5mg> 10mg P< 0.0001
Mean INR at discharge	2.61	2.52	2.53	2.56	
Mean warfarin dose at discharge (mg)	4.3	5.3	5.2	7.3*	A>V (p<0.001) 5mg> 10 mg P< 0.001 *P< 0.01
Interval between discharge and first return consultation (days)	6.4	4.0	6.9	3.8	A>V (p<0.001)
INR at first return consultation	3.26	2.90	3.55	4.06*	*p<0.05 5mg > 10 mg P<0.0001

Table 3. Complications.

Data	5 mg		10 mg		p
	Arterial G1	Venous G2	Arterial G3	Venous G4	
Recurrence between discharge and first return consultation	0	0		0	
Bleeding on admission	0	0	0	0	
Bleeding between discharge and first return consultation	3/110		2/110		p>0.05

not complied with the medical advice they had been given on discharge

None of the patients suffered further clinically diagnosed thrombotic complications during follow-up (relapse of TVP or TEP, occlusion of arterial grafts or arterial rethrombosis). Comparison between venous and arterial patients showed that the venous subset were on significantly higher warfarin dosages at discharge and returned to the clinic after significantly earlier discharge. The 10 mg venous subset had higher warfarin doses at discharge and higher INR at first return consultation (Table 2).

DISCUSSION

The study design employed here, using a historical series as control, does not offer the highest level of evidence, which can only be provided by randomized clinical trials. Notwithstanding, the study does provide interesting information related to the characteristics of Brazilian services. Amián et al.[7] studied warfarin and acenocoumarol, and also used control historical controls, whereas other studies have not used any type of control[8].

The number of patients in each group was considered large enough to evaluate the variables chosen for study, and both groups contained the same number of patients, helping to minimize error during the statistical analysis. Other studies have used similar numbers of patients per group[4,9].

The mean age of patients was 57.7 years, which is in line with data found in the literature on these diseases. Anticoagulant treatment may lead to a risk of bleeding in patients of advanced age[2,10]. In this sample, there were 48 patients over the age of 70 years and 15 older than 80, but there was no greater predisposition to hemorrhagic complications in these subsets.

The subsets of patients with VTE were predominantly female, which is in line with other published data on these conditions. Some authors believe that the predominance of VTE in women is partly the result of contraceptives, hormone replacement therapy, pregnancy and puerperium, among other conditions[11].

The higher initial dose of warfarin (10 mg) is used to attain adequate anticoagulation levels more quickly, but involves the potential risks of an abrupt fall in serum C and S protein levels, and of causing a transitory initial hypercoagulable state that can provoke necrosis[4,12]. In the present study there was a direct influence on the time taken to reach the recommended therapeutic range, but without increasing the risk of recurrence. Monkman et al. observed adequate warfarin levels by the fifth day, using 10 mg initial doses[13]. These results were similar to the findings of other studies[6,9,14,15]. However, two studies analyzed in a systematic review of 11 studies employed two INR assessments instead of one, without detecting a difference in this aspect between the two initial dosages[6]. The conclusions of that review show that there is still great uncertainty with regard to the optimum posology of initial warfarin dosages[6]. Crowther et al.[4] and Quiroz et al.[16] concluded that it would be unlikely that the 10 mg initial dose would be better in this respect. Other authors have observed lower risk of complications with the 5 mg initial dose, but also found that the time taken to reach the therapeutic INR range varied from 6 to 10 days[8]. Some authors take a compromise position, recommending an initial dose of 7.5 mg[17]. On the basis of the body of articles available on the subject,[5] the American College of Chest Physicians' most recent consensus[18] chose the 10 mg dose as the ideal. However, for patients with nutritional deficiencies, liver diseases, heart failure or risk of bleeding, in particular among the elderly[19], the consensus recommends a 5 mg initial dose[20].

With regard to INR levels at discharge, we observed similarities between groups, even though dose adjustments were not made on the basis of a warfarin normogram, but were decided on by the physicians on the basis of experience. Harrison et al.[9] and Crowther et al.[4] state that using specific normograms for the different therapeutic regimens can reduce differences in dose adjustments that are caused by subjectivity, standardizing conduct. Notwithstanding, there is still a need for more

controlled clinical studies to compare the efficacy of the two dose adjustment methods.

Patients with thromboembolic disease given the lower loading dose needed higher doses of warfarin at hospital discharge, when compared with the group of patients given the higher loading doses. In general, these patients' dosages were adjusted from the fourth day onwards and they took longer to enter the therapeutic range and required a larger number of dose adjustments. These adjustments may the primary reason why these patients were discharged on higher doses and returned to the clinic with higher INRs.

Patients with ATE spent longer in hospital than patients with VTE. It is probable that this is because of a combination of several factors, including the fact that the majority of patients with ATE (85.5%) had surgical treatment and in general required longer recovery times, when compared with patients with VTE who were exclusively treated clinically. The same was true of patients who underwent endovascular treatment (arterial) and were prescribed anticoagulation, since they required longer periods for stabilization than patients with VTE, probably as a result of complications related to the procedure. However, warfarin loading dosage did not have an effect on length of hospital stay in any of the treatment groups. We were unable to find data in the literature analyzed related to the relationship between 'initial warfarin dose and length of hospital stay' in treatment for thromboembolic disease.

Oral anticoagulant treatment was prescribed for patients with ATE because of reconstructive arterial surgery with poor prognosis. In these cases, warfarin was the long-term adjuvant therapy of choice, since they involve an elevated risk of thrombotic complications related to reduced arterial blood flow, caused by the vessel's insufficient diameter and by poor distal arterial flow, and also by clinical comorbidities (thrombophilia and atrial fibrillation) or other related conditions, such as extensive endothelial injury. Another reason for choosing oral anticoagulant as adjuvant treatment, was postoperative recovery in patients with acute arterial occlusion caused by embolism, generally of cardiac origin. There were no differences between patients who underwent arterial surgery, when divided by initial warfarin dose for treatment of thromboembolic disease. Patients with VTE were only given clinical treatment, since there was no need for surgical intervention. Four patients were given thrombolytic treatment using streptokinase for late acute arterial occlusion and another two patients received the same treatment after angioplasty of the popliteal artery, because they suffered distal occlusion during or soon after the procedure. Two patients did not respond well to this technique and required open surgical intervention. None of the patients with VTE were given thrombolytic treatment. Patients who had had prior thrombolytic treatment did not differ in terms of initial warfarin dose (5 or 10 mg).

There were no episodes of major or minor bleeding while in hospital, possibly because of the rigid schedule of daily laboratory tests, conducted in order to avoid large variations in aPTT or INR levels. The overall rate of severe hemorrhagic complications (hematuria and hematemesis) in patients on warfarin at this service is 2.2%[21].

There were no clinical recurrences during follow-up (whether arterial or venous), which is a casual observation, with no scientific or clinical relevance, in view of the short follow-up period, especially for venous patients.

CONCLUSIONS

Initial therapeutic warfarin doses of 5 mg or 10 mg are equally effective and safe for in-patient anticoagulant treatment of thromboembolic disease, irrespective of underlying disease.

In this study, patients who were treated with the lower initial warfarin dose entered the therapeutic range later, were discharged from hospital on higher doses of warfarin and returned to the Anticoagulation Clinic with higher INRs, indicating a potentially higher risk of suffering hemorrhagic complications, when compared with patients given the higher initial warfarin dose.

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