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Warfarin prevents venous obstruction after cardiac devices implantation in high-risk patients: partial analysis

Varfarina previne obstruções venosas pós-implante de dispositivos cardíacos em pacientes de alto risco: análise parcial

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Abstract

Introduction: **The incidence of venous thrombosis after cardiac devices implantation is high. Ventricular dysfunction and previous transvenous temporary leads ipsilaterally to the permanent implantation are independent risk factors. The effect of prophylactic strategies to prevent these complications remains controversial.**

Objectives: **To evaluate the efficacy of prophylactic use of warfarin in patients with high risk of lead-associated thrombosis.**

Method: **Clinical, prospective, randomized and blinded study, in patients submitted to first transvenous leads implantation with LVEF < 0.40 and/or previous ipsilateral temporary pacing. After device implantation, patients were randomly assigned to placebo or warfarin. Periodical clinical and laboratorial evaluations were performed to anticoagulant management. After a six-month period, every patient was submitted to a digital subtraction venography.**

Results: **From Feb/2004 to Nov/2006, 101 patients underwent randomization. Baseline characteristics were similar in both groups (*P*=NS). Venographic analysis showed 31.4% of venous obstructions in patients assigned to warfarin as compared with 57.1% in patients assigned to placebo (RR= 0.57 [95% CI, 0.33 to 0.98]; *P*=0.015). In the warfarin group, 72% of the PT/INR tests were in therapeutic INR range. Only one patient required warfarin discontinuation and cross-over to placebo group due to gastrointestinal bleeding.**

Conclusions: **These preliminary results showed that anticoagulation therapy has been safe and reduced the frequency of venous thrombosis after transvenous cardiac devices implantation in high risk patients.**

Descriptors: **Cardiac Pacing, artificial. Postoperative complications. Venous thrombosis. Anticoagulants. Clinical trial.**

Resumo

Objetivos: **Avaliar a utilidade da varfarina na prevenção dessas complicações nos pacientes de alto risco.**

Métodos: **Estudo clínico prospectivo, randomizado, cego, em pacientes submetidos ao primeiro implante transvenoso de DCEI, com FEVE<0,40 e/ou MPT ipsilateral ao implante definitivo. Após o procedimento, os pacientes foram**

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randomizados para o uso diário de placebo ou varfarina. Avaliações clínicas e laboratoriais foram realizadas periodicamente. A pesquisa de obstruções venosas foi feita pela venografia por subtração digital, seis meses após o implante. De fevereiro de 2004 a novembro de 2006, foram selecionados 101 pacientes, havendo homogeneidade das características clínicas e operatórias de ambos os grupos (*P*=NS).

***Resultados:* No grupo Varfarina, 31,4% dos pacientes apresentaram obstruções venosas em comparação a 57,1% do grupo Placebo (RR= 0,57; IC 95%= 0,33 a 0,98; *P*= 0,015). No grupo Varfarina, 72% dos exames de INR realizados encontraram-se em nível terapêutico. Houve um caso de sangramento gastrintestinal, que justificou a interrupção do uso da varfarina e mudança para o grupo Placebo.**

***Conclusão:* Os resultados preliminares mostraram que o uso profilático da anticoagulação mostrou-se seguro e reduziu significativamente a incidência de obstruções venosas pós-implante de DCEI nos pacientes de alto risco.**

***Descritores:* Estimulação cardíaca artificial. Complicações pós-operatórias. Trombose venosa. Anticoagulantes. Ensaio Clínico.**

INTRODUCTION

Venous obstructions after transvenous implantation of electronic cardiac devices have been described as the commonest complication related to this approach [1-12], with ventricular dysfunction and the presence of temporary pacemakers ipsilateral to the implantation side being risk factors for its occurrence [6].

With the high risk of venous lesions, 3% to 10% of patients present with clinical manifestations, of which, deep venous thrombosis of the arms is the commonest complication [1-12]. Severe complications, such as pulmonary embolism and superior vena cava syndrome, with rates that vary between 0.6% and 5%, have been rarely described in the literature, [13-17]. Usually, these obstructions develop within one to three months after implant with a gradual reduction in their incidence six months after the implantation of the device [1-4,9,10].

Prevention of these complications is important both because of their high incidence and clinical manifestations and the difficulties of reoperations to substitute or implant additional electrode leads and to perform other diagnostic or therapeutic interventions that depend on this venous access [1-18]. The lack of contusion-related evidence that justifies the use of prophylactic strategies thus demonstrating their efficacy and safety impedes the routine application of this stratagem.

The aim of this study was to evaluate the role of oral anticoagulation compared with a placebo over the first six months, in the prevention of thromboembolic complications after the transvenous implantation of cardiac devices in high-risk patients, analyzing the influence of prophylactic anticoagulation therapy on the incidence of venous obstructions, its safety, efficacy and complications.

METHODS

Population

In the period from February to November 2006, 101 adult patients submitted to the first transvenous implantation of implantable cardioconverter-defibrillators or cardiac resynchronizers and who suffered from ventricular dysfunction with a left ventricular ejection fraction < 0.40 and/or had been submitted to the implant of a temporary transvenous pacemaker ipsilateral to the implantation site of a definitive device were studied.

Patients with a progressive history of venous thromboembolism, atrial fibrillation, coagulation disease or thrombophilias, malignant neoplasias, digestive tract hemorrhages or active gastroduodenal ulcers within the previous six months, those with alterations in the prothrombin time (PT)/activated partial thromboplastin time (APTT) greater than 40% or presenting with the INR (International Normalized Ratio) ≥ 1.5 and patients taking anticoagulants were not included in the study.

All patients gave written consent to participate in the study. The research project was approved by the Ethics committee of the institution (protocol number 468/03) and the work was carried out in the Heart Institute (InCor) of Hospital das Clinicas, Medicine School of the University of Sao Paulo (HCFMUSP).

Study design

This is a simple-blind, controlled, randomized, prospective clinical study. The dynamics of the study is summarized in Figure 1.

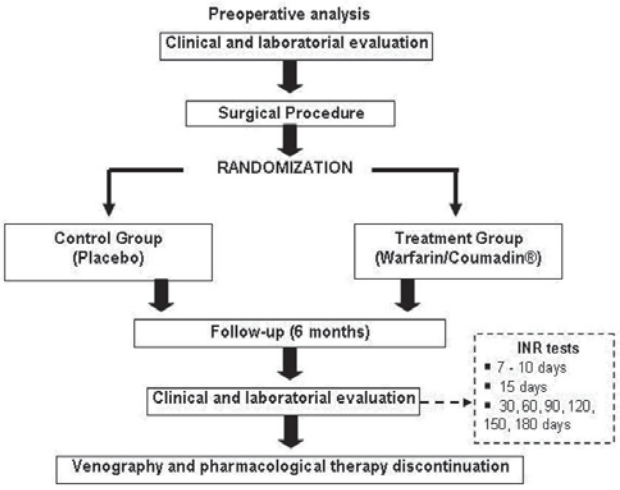

Fig. 1 – Flow chart of the study

The preoperative analysis of the patients enrolled included: physical examination (age, gender, risk factors for thrombosis, prior disease, medications taken, heart failure functional class according to the criteria of the New York Heart Association – NYHA; laboratorial examinations (complete blood test, platelets and coagulogram); and imaging examinations (thoracic radiography and transthoracic echocardiogram).

Surgical implantation procedure of the devices

The implantation procedures were always performed by transvenous access. General or local anesthesia under sedation was used depending on the clinical conditions of the patient. Antibiotic prophylaxis was achieved with a single dose of cephazolin (1g). Venous access for the implantation of the electrode leads was obtained by dissection of the cephalic vein or puncture of the subclavian vein on the right or the left, depending on the preference of the surgeon. Similarly, the site where the electrodes were implanted was a decision of the medical team dependent on the necessity of the patient and on the indicated pacing mode. The pacers were implanted in the submuscular or subcutaneous tissue, again at the discretion of the surgical team, with the main parameter being the size of the pacemaker. Before closure, a dose of gentamicin (80 mg) was injected at the site of the pacer. Closure was always performed by layers using 3-0 absorbable sutures for the subcutaneous tissue and single-filament nylon with individual sutures for the skin.

Definition of the groups and the start of medicinal therapy

After the surgical procedure and return to the hospital ward, the patients were allocated to two groups by random distribution using a computer generated list. The Control Group was composed of patients who received an inert placebo medication; the Treatment Group consisted of patients who received crystalline sodium warfarin (Coumadin®) adjusted depending on the laboratorial control of the PT/INR, with the aim of maintaining this ratio within the range of 2 to 3.5 times the normal value. Anticoagulation therapy was initiated on the first day after implantation of the device.

Clinical follow up of the patients

Clinical and laboratorial evaluations were performed periodically at the following intervals: 7 to 10, 15, 30, 90 120, 150 and 180 days after the surgical procedure.

The clinical evaluation aimed at identifying pain or edema of the arm, dyspnea, thoracic pain and determination of the functional class using the criteria of the NYHA. Complications related to the anticoagulation therapy were actively studied, particularly in respect to clinical signs of bruising, radiological signs of hemithorax and hemipericardium and history of bleeding (gingival, nasal, gastrointestinal or genitourinal). The periodic laboratorial examinations aimed at adjusting the intensity of anticoagulation (determined by the PT/INR) and early detection of complications related to anticoagulation therapy (measurement of hemoglobin and hematocrit).

Standardization of oral anticoagulation therapy

Control of the intensity of anticoagulation was achieved following the recommendations of the international consensus on antithrombotic therapy [19,20], which established a standardization by adjusting the weekly dose according to the INR. With the exception of the professional responsible for the adjustment of the anticoagulation therapy, the other professionals involved in the research project (surgeons, physicians responsible for the follow up of patients, radiologists that performed and evaluated the venographs) did not know to which group the patients were allocated. After the six-month study period, the medications were suspended and the patients were submitted to digital subtraction venography ipsilateral to the implantation site.

Digital subtraction venography

Images by digital subtraction were achieved using a Philips ® DVI apparatus with a 1024 x 1024 matrix and arch for multiple views. The continuous infusion of contrast was achieved utilizing an Angiomat 6000 injection pump with controlled volume and velocity. Digital subtraction imaging was obtained sequentially, allowing analysis of the axillary, cephalic, subclavian, innominate and superior cava veins. The images were classified as normal or with venous stenosis. All the examinations were evaluated by two physicians of the Interventionalist Vascular Radiology Service and the definition of the radiological findings was by consensus between the examiners.

Variables studied and statistical analysis

The frequency of venous obstructions identified by digital subtraction venography and the clinical and epidemiological characteristics of the patients according to the random distribution were analyzed employing the Student t, chi-squared or Fisher's exact tests. Analysis of variance for repeated measures was employed to establish the trend of the findings of laboratorial examinations over the study.

The data were analyzed following the "intention-to-treat" principle, utilizing the Statistical Package for Social Sciences (SPSS) version 15.0 software with p-values < 0.05 considered significant.

RESULTS

Analysis of the demographic, clinical and operative characteristics of the patients

Of the sample selected for this study, 49 patients were allocated to the Warfarin Group and 52 to the Placebo Group. There were no statistically significant differences between the basal characteristics of the patients of the two groups (Table 1).

Incidence of post-implantation venous obstructions

Digital subtraction venographies were performed ipsilateral to the implantation site of the definitive device in 70 patients. The analysis of the venographs identified a total of 31 cases of varying degrees of stenotic venous lesions, involving the territory of the subclavian (74.2%) and innominate (16.1%) veins and the transitions of the subclavian vein with the innominate vein (6.5%) and innominate vein with the superior vena cava (3.2%) – Figure 2.

Of the patients allocated to the Warfarin Group, 31.4% presented with venous obstructions compared to 57.1% of the Placebo Group, giving a reduction of 23.5% of absolute risk (Relative Risk = 0.57; 95% confidence interval = 0.33 to 0.98) – Table 2.

Analysis of pharmacological therapy

The mean value of the INR of patients in the Placebo Group during the six-month period following implantation was 1.1 ± 0.4, while in the Warfarin Group the mean value of INR was 2.6 ± 1.2, with this difference being maintained over the entire follow up period (Figure 3).

In the Warfarin Group, of the 220 examinations of PT/INR, 72% had adequate levels of anticoagulation with the INR ranging from 2 to 3.5. Insufficient coagulation, with an INR < 2.0 was observed in 17% of the examinations and excessive with an INR > 3.5 was seen in 9.7% of the evaluations.

During the follow-up period, the mean values of hemoglobin and hematocrit were similar in both groups; 14.0 ± 1.4g/dL and 41.9 ± 3.7%, respectively for the Warfarin Group and 13.9 ± 1.6g/dL and 41.2 ± 4.6% for the Placebo Group. One patient in the Warfarin Group was transfused with blood derivatives. Analysis of variance for repeated measurements demonstrated that the groups did not present with significant differences in the trends over the evaluation period and also did not present with significant differences in either of the measurements.

Deaths and complications

During the follow-up period five patients died, three directly related to progress of the underlying heart disease and two sudden deaths. Of the total deaths, three patients were in the Warfarin Group and two in the Placebo Group.

Table 1 - Patients baseline characteristics, according to randomization

Variables	Warfarin (n=49)	Placebo (n=52)	*P*
Age (mean ± SD)	59.9 ± 11.6	62.0 ± 11.8	0.379
Women	65.3%	50.0%	0.120
Inclusion criteria			
Ventricular dysfunction	59.2%	51.9%	
Temporary pacemaker	38.8%	44.2%	0.655
Both	2.0%	3.8%	
HF FC (NYHA)			
I - II	55.1%	51.9%	
III - IV	44.9%	48.1%	0.749
Diagnosis at admittance			
complete or advanced heart block	30.6%	32.7%	
Ischemic myocardiopathy	26.5%	15.4%	0.372
Non-ischemic myocardiopathy	42.9%	51.9%	
Personal history			
Systemic hypertension	79.6%	86.5%	0.351
Diabetes mellitus	24.5%	17.3%	0.374
Acute myocardial infarction	32.7%	17.3%	0.074
Heart failure	55.1%	42.3%	0.199
Chagas Disease	16.3%	21.2%	0.535
Smoking (current)	6.1%	5.8%	1.00
Use of antiplatelet agents	38.8%	42.3%	0.718
LVEF (mean ± SD)	0.39 ± 0.17	0.43 ± 0.21	0.248
Type of procedure			
conventional pacemaker	44.9%	48.1%	
Multisite pacemaker	38.8%	28.8%	
conventional ICD	6.1%	13.5%	0.376
Multisite ICD	10.2%	9.6%	
Access route			
subclavian vein puncture	98.0%	92.3%	0.363
Dissection of cephalic vein	31.3%	31.3%	0.846
Both	28.6%	22.4%	0.388
Side of access			
Right	40.8%	46.2%	0.589
Left	59.2%	53.8%	
Material lining of the electrodes			
Silicon	51.0%	61.5%	
Polyurethane	32.7%	17.3%	0.201
Both	16.3%	21.2%	
nº de transvenous electrodes			
One	-	9.6%	
Two	59.2%	55.8%	0.098
Three	40.8%	34.6%	

SD = Standard deviation; HF FC NYHA = Heart failure functional class according to the criteria of the NYHA; LVEF = Left ventricular ejection fraction; Conventional = ventricular or atrioventricular pacing; ICD = Implantable cardioverter-defibrillator

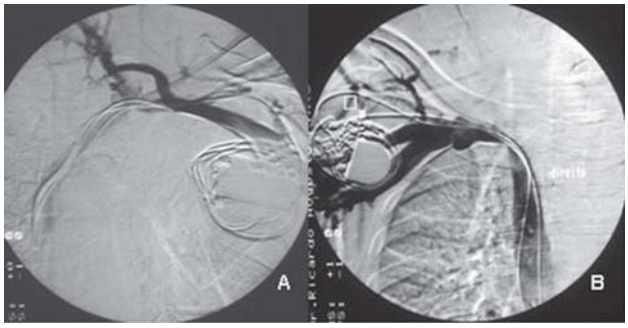

Fig. 2 - venous obstructions observed by digital subtraction venography: A. Occlusion of the left subclavian vein; B. Moderate stenosis at the junction of the right subclavian vein with the internal jugular vein

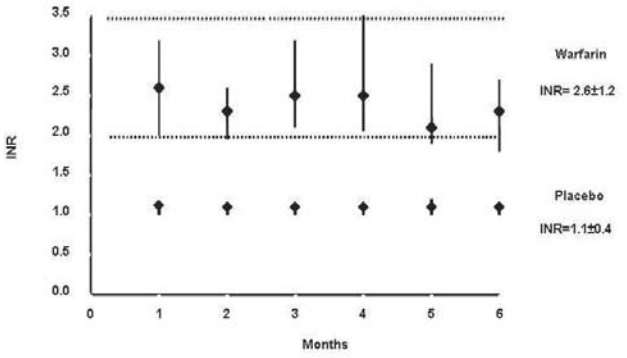

Fig. 3 – Distribution of the mean INR over the six-month follow-up period according to the randomization

Table 2. Incidence of venous obstructions after the transvenous implantation of artificial heart pacing devices according to the randomization

Venous obstructions	Warfarin Group	Placebo Group	*P*	RR	RAR
Present	11 (31.4%)	20 (57.1%)			
			0.015	0.57	23.5%
Absent	24 (68.6%)	15 (42.9%)			

RR = relative risk; RAR = reduction of absolute risk

There were no cases of site bruising. One patient of the Warfarin Group presented with gastrointestinal bleeding thereby justifying cessation of the anticoagulation agent and transference to the Placebo Group. One patient of the Placebo Group presented with early clinical manifestations of venous thrombosis of the arm ipsilateral to the device implantation site, with evidence of reduced blood flow detected by Doppler ultrasound, thus justifying anticoagulation treatment and transfer to the Warfarin Group.

DISCUSSION

Prevention of the development of venous obstructions related to implantable electronic cardiac devices has become an important issue for professionals working in the area of artificial heart pacing [1-18]. Until now, however, the efficacy of prophylactic strategies for these complications remains unknown.

Considering the physiopathologic mechanisms related to the occurrence of obstructions, the aspects inherent to the operative technique, such as the access route, the number of electrodes, the material lining the electrodes, and the lesion caused to the endothelium by the electrodes will be difficult to change, as these factors depend exclusively on the characteristics of the patient, the type of device implanted and the experience of the surgical team.

On the other hand, it has been demonstrated that patients can present with a hypercoagulation state with a significant elevation of coagulation activation markers and of the inhibition of fibrinolysis after transvenous implantation of electrode leads [21,22], thus supporting the hypothesis that anticoagulation therapy may play a role in minimizing these physiopathologic mechanisms.

Among the studies that report on predicting factors, Costa et al. [6] in 2002, confirmed that patients with ventricular dysfunction and/or temporary electrode leads ipsilateral to the definitive implantation site presented with a higher risk of venous obstructions, factors that defined the inclusion criteria of the current study. Recently, other risk factors have been described such as infection [7], lack of anticoagulation therapy [9,12], female hormones [9], previous history of thrombosis [9], multiple electrodes [9], atrial fibrillation [11], multisite pacemakers [11], previous implantation of a definitive pacemaker [8] and implantable cardioverter-defibrillator electrode lead with a double coil [8].

Incidence of post-implant venous lesions

Although the incidence of post-implant venous obstructions was high, the preliminary results of this randomized clinical study demonstrate that the use of oral anticoagulant therapy significantly reduced the incidence of venous obstructions in patients considered high risk.

We can presume that the main reason for this high incidence is related to the fact that patients in the current study constitute a high-risk population, whether due to the presence of severe left ventricular dysfunction or by the prior use of temporary electrode leads.

The great variation of venous lesion rates after the transvenous implantation of electrode leads observed in different publications may be due to differences in the definitions and in the diagnostic criteria used. Digital subtraction venography, as utilized in most recent studies, has allowed a more precise evaluation of the venous territory, increasing the diagnostic precision, which was previously restricted to severe or total obstructions. With this methodology, the estimated incidence of lesions ranges from 14 to 64% of total implantations [1-12]. The incidence of venous lesions of 57.1%, observed in the Placebo Group of the current study, is in agreement with the results reported by most of these studies [1-12].

Some studies that evaluated the use of anticoagulation or antiplatelet therapy did not establish the real value of these therapeutic modalities, as the designs were inappropriate [3,9,12,17]. The first study, performed by Seeger et al. [17] in 1986, demonstrated that the use of low doses of heparin after the implantation of pacemakers significantly reduced the occurrence of pulmonary thromboembolism. Due to the small sample size of this study, however, it is impossible to safely and definitively establish the role of this prophylaxis.

The preventative effect of oral anticoagulation therapy or platelet anti-aggregation was initially evaluated by Goto et al. [3] in patients with pacemakers who were already taking these medications for other clinical indications. The lack of standardization of the therapy however, made consistent conclusions on the dose, type of pharmacological agent and time of use impossible. Using a similar methodology, two recent studies [9,12] showed that patients that utilized oral anticoagulation and/or platelet anti-aggregation therapy presented with lower risks of venous thrombosis after transvenous implantation of implantable converter-defibrillators. Similar to the study described previously [3], the patients used these medications for other clinical indications and thus there was a lack of standardization of the therapy.

Analysis of oral anticoagulation therapy

The medication chosen for this study was Warfarin, a cumarinic agent that acts as an vitamin K antagonist, due to its low cost, effectiveness and safety as proved by several clinical trials [19,20]. However, its main disadvantage is the difficulty to adjust the intensity of anticoagulation that may oscillate between the risk of hemorrhagic complications and the occurrence of thromboembolic events, obliging the institution to provide rigorous therapeutic control. Large experiments, mainly with patients with atrial fibrillation or heart valve prostheses, have confirmed the effectiveness and safety of oral anticoagulation in primary prophylaxis of thromboembolic events [19,20,23-25].

Maintenance of the effectiveness and safety of the dose of Warfarin is dependent on the laboratorial control of INR, which should be within the therapeutic range for each clinical indication. Therapeutic values between 2.0 and 3.0 have been recommended for most situations, except for mechanical circulatory assistance, metallic valve prostheses substituting the mitral valve and in antiphospholipid syndrome, when levels between 2.5 and 3.5 are recommended [19,20]. There is no consensus in respect to the level of anticoagulation recommended for patients with implanted electronic cardiac devices.

Although it is a prosthesis implanted in the deep venous system and endocardium, suggesting a level of anticoagulation of up to 3.5, this is offset by the fact that this system is related to the right chambers. Hence, the current study aimed at maintaining the patients with an INR between 2.0 and 3.0, with values up to 3.5 being considered acceptable.

The quality of oral anticoagulation therapy was evaluated by Ansell et al. [25], in a multicenter study. Of a total of 18,148 examinations of INR performed for 1234 patients, the percentage of tests with adequate levels of anticoagulation varied from 50.8% (United States) to 60% (Italy). In this study, the percentage of patients of the Warfarin Group maintained within the therapeutic range was higher than these aforementioned values, demonstrating that oral anticoagulation, under adequate therapeutic control, is a reliable and safe strategy in the prevention of thromboembolic complications in patients submitted to the transvenous implantation of electronic cardiac devices. The low index of hemorrhagic complications observed supports this statement.

Comprehension and limitations

The preliminary results of our study suggest a beneficial effect of anticoagulation therapy as prophylaxis of venous obstructions after the transvenous implantation of cardiac devices in high-risk patients. The impact of these measures in low-risk patients remains unknown, as does the usefulness of an association with platelet anti-aggregation agents.

The difficulty to follow-up patients on anticoagulation therapy, due to the cost of laboratorial examinations and the necessity of frequent medical check ups, as well as in respect to the risk of hemorrhagic complications inherent to this treatment, are the main unfavorable factors to the use of this preventative measure. We believe that the long-term clinical follow up of patients in this study, focusing on the active investigation of clinical complications is

fundamental to understand the long-term prognosis of venous obstructions and for the implantation of routine prophylactic therapy.

CONCLUSION

The preliminary results of this study show that the prophylactic use of oral anticoagulation therapy is safe and significantly reduces the incidence of venous obstructions in high-risk patients as observed by digital subtraction venography.

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