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Protocol - Valves

Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (TRAC): rationale and design for a prospective, randomized, co-operative trial

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Summary

Antiplatelet agents are used for prevention of thromboembolism in surgical patients and in patients with chronic atrial fibrillation. However, up-to-date results of randomized studies comparing antiplatelet agents and oral anticoagulation have not been reported. The aim of this study is to compare the efficacy and safety profile of triflusal versus acenocoumarol for primary prevention of thromboembolism in the early postoperative period after implantation of a bioprosthesis. This is a prospective, multicentric, randomized, open, pilot trial in which four acute-care teaching hospitals participate. Patients will be randomly assigned to treatment with triflusal or acenocoumarol the day before valve replacement with a bioprosthesis. Primary outcome will be the combined endpoint of the rate of either thromboembolism or hemorrhage and valve-related mortality in each treatment group. Secondary outcomes will include the analysis of each of these rates separately together with permanent valve-related impairment according to the guidelines for reporting morbidity and mortality after cardiac valvular operations. A total of 200 patients will be recruited in a competitive manner (100 patients per arm) over an 18-month period. The study will be completed in 2 years. Treatment assigned will be open to investigators and patients because of the need of blood monitoring and dosage adjustment in oral anticoagulant therapy. In order to minimize the bias, randomization is centrally performed. The study medication will be given for 3 months being discontinued afterwards. Follow-up visits are scheduled at the time of patient's inclusion in the study and at 1, 3, and 6 months thereafter. Homogeneity of groups will be analyzed using the Student's t test, the Mann–Whitney U test, and the chi-square test, when appropriate. Rates of thromboembolism and hemorrhage will be calculated with the hazard function. In conclusion, antiplatelet treatment for patients undergoing valve replacement with a bioprosthesis is clinically relevant because of avoidance of inconveniences of oral anticoagulation (monthly blood testing, dosage adjustment) and decreased risk of bleeding. In case the results favor the use of antiplatelet drugs in these patients, this study will contribute to future development of strategies in the prevention of thromboembolism.

Keywords: Antiplatelet drugs; Acenocoumarol; Triflusal; Bioprosthesis; Thromboembolism

1. Introduction

Valve replacement with a bioprosthesis is usually performed when there is a contraindication for anticoagulant therapy and in elderly patients when expected valve durability matches the patient's life expectancy. Current valve bioprostheses have proven excellent hemodynamic performance as well as being free from structural deterioration for up to 15 years. Their main advantage is low thrombogenicity, with a thromboembolic rate per patient-year of about 1%, avoiding the need for oral anticoagulant therapy [1]. However, during the first 3 months after surgery the risk of thromboembolism is about five times higher [2]. Oral anticoagulation is usually recommended for 3 months being discontinued thereafter unless some risk factors are

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present (e.g. atrial fibrillation). Antiplatelet treatment offers a promising alternative; in contrast to anticoagulation regimens, repeated blood testing for dosage adjustment is not needed and the risk of bleeding during antithrombotic therapy is generally low. Although experience with antiplatelet therapy for primary prevention of thromboembolism is scarce, favorable results after implantation of a bioprosthesis or in patients with chronic atrial fibrillation have been initially reported [1,3].

Triflusal, an antiplatelet agent structurally related to aspirin, exerts its antithrombotic effect by acting on different targets involved in platelet aggregation and vascular inflammatory processes [4]. Although triflusal and aspirin irreversibly inhibit platelet cyclooxygenase [5], triflusal inhibits endothelial cyclooxygenase only slightly, so that prostacyclin formation in endothelial cells is not significantly reduced [6]. Both triflusal and its long-lasting active metabolite, 2-hydroxy-4-trifluoromethylbenzoic acid (HTB), inhibit degradation of platelet and endothelial cell cAMP, thereby increasing cAMP levels and blocking intracellular calcium mobilization and platelet–endothelial cell interactions [4,7]. In addition, triflusal increases nitric oxide synthesis in neutrophils resulting in increased vasodilation potential [8]. As compared with the antithrombotic action of aspirin, triflusal offers a more favorable safety profile due to the lesser degree of platelet cyclooxygenase inhibition resulting in a lower risk of bleeding [9,10].

Therefore, to assess the efficacy and safety profile of triflusal in the primary prevention of thromboembolism in the early postoperative period after implantation of a bioprosthesis in the aortic or mitral valve position, a prospective, randomized, open, co-operative pilot trial was designed in which triflusal is to be compared with acenocoumarol as the active reference drug [11]. The hypotheses established were as follows: higher (null hypothesis) or equal or lower (alternative hypothesis) incidence of either thromboembolism, hemorrhage, or valve-related death in patients treated with triflusal than in patients receiving acenocoumarol. The aim of the present report is to describe the methodology of this ongoing clinical trial.

2. Methods

2.1. Design

This is a prospective, randomized, open, pilot clinical trial in which the departments of cardiovascular or cardiac surgery of four acute-care teaching hospitals from Spain agreed to participate. The purpose is to enroll a total of 200 patients (ideally 50 cases of bioprosthetic valve implants per center) in a period of 18 months. Recruitment is competitive among the participating hospitals in an attempt to ensure prompt enrollment on time. The study is expected to be completed in 2 years.

2.2. Eligibility criteria

Male or female patients older than 18 years of age undergoing mitral or aortic valve replacement with a bioprosthesis are eligible after giving written informed consent. The following exclusion criteria apply: (1) history of allergy to any of the study drugs; (2) scheduled for elective surgery in the next 6 months; (3) life expectancy of less than 1 year for reasons different from that of the heart disease; (4) not able to understand or comply with the study protocol; (5) left atrium larger than 60 mm; (6) use of antiplatelet or anticoagulation for any reason other than valve heart disease; (7) severe renal or liver dysfunction; (8) severe uncontrolled hypertension; (9) history of intracerebral hemorrhage; (10) active peptic ulcer, or coagulation disorder; (11) acquired immunodeficiency syndrome; (12) concomitant treatment with non-steroidal anti-inflammatory drugs; (13) intravenous drug abuse; (14) oral intake not possible; and (15) participation in a clinical study in the previous 3 months. Pregnant women, nursing mothers, or women of childbearing potential not using adequate methods of contraception are also excluded.

2.3. Ethical approval

The study is conducted in accordance with the Republic of South Africa amendment to the Declaration of Helsinki. The study protocol has been approved by the ethical committee or institutional review board at each of the participating hospitals. After institutional approval, the study protocol was approved by the Spanish Drug Agency. Written informed consent will be obtained from all eligible patients.

2.4. Randomization

An independent clinical research organization (Staticon International, Madrid, Spain) will be responsible for randomization and study monitoring. A single random list will be obtained by means a computer program simulating numbered balls extraction that will be correlatively assigned to one of two codes and then, according to a random code, treatment with triflusal or acenocoumarol will be randomly assigned to each code. A single clinical research assistant from Staticon International will be responsible for treatment assignment. At the time of the patient's inclusion in the study just before surgery, the randomization code will be requested by e-mail or telephone call to the clinical research assistant.

2.5. Masking

To prevent bias, all study investigators are blinded to the

randomization schedule. Otherwise, the study is not blind and both the investigator and the patient are going to be aware of which medication will be received. This type of design is due to the need for frequent blood testing for adjusting the oral anticoagulant dose that must be individually titrated. In this respect, performing repeated blood test in patients assigned to the triflusal arm in order to mask the treatment to the patient is ethically unjustifiable. On the other hand, blinding is difficult to maintain since coagulation profile abnormalities induced by acenocoumarol are easily recognized by the investigator.

2.6. Medications

Treatment with the study medication will be started as soon as the patient resumes oral intake after surgery but not later than 48 h postoperatively. Medications administered consisted of 600 mg of triflusal (Disgren®, J. Uriach, Barcelona, Spain) in a single daily dose and 4 mg of acenocoumarol (Sintrom®, Novartis, Barcelona, Spain). In case of gastric intolerance, the dose of triflusal can be divided in 300 mg every 12 h. The dose of acenocoumarol must be titrated individually to keep international normalized ratio (INR) between 2 and 3. A full record of all INR measurements will be obtained in order to control the quality of oral anticoagulation. Study medication will be supplied, packed, and labeled by J. Uriach in accordance with current good manufacturing practices and good clinical practices. For each patient enough medication to ensure 3 months of treatment will be provided.

2.7. Clinical procedures

All patients will take the assigned medication for 3 months. After this period, study medications will be interrupted and packages returned to the investigator to assess compliance. At 3 months, however, patients will continue to receive oral anticoagulants, antiplatelet agents, or no medication at all according to criteria of his/her surgeon, cardiologist, or referring physician. The length of the follow-up period is 6 months. Four visits are scheduled as follows: (a) baseline visit (day 0) at the time of the patient's inclusion in the study in which the investigator will check eligibility criteria and had informed consent signed; at the same time demographic features and clinical data of the pre- and perioperative period will be recorded; (b) visit 1 (day 30); (c) visit 2 (day 90); and (d) visit 3 (day 180). In all these outpatient visits, clinical data will be recorded and electrocardiograms (EKG) will be obtained. An echocardiogram and laboratory tests will be performed between visits 1 and 2. For patients assigned to oral anticoagulation, all INR values will be registered. Patients with values lower than 2 repeatedly reported after the first week will be considered as not properly anticoagulated. This will be checked at the end of the study as a quality control of oral anticoagulation. As for the triflusal group, the number of capsules taken will be counted. If a 10% deviation from the theoretical count is registered, the patient will be excluded from the study. EKGs are performed in order to monitor closely the cardiac rhythm. The echocardiogram will help to assess the presence of thrombus or 'smoke-like' low flow turbulence in the left atrium as a quality control of the antithrombotic treatment.

2.8. Tolerability

Information on adverse events will be obtained through spontaneous reports by the patients and by non-suggestive questioning at each assessment. Patients will be asked the time of onset, duration, and intensity of the adverse event. The intensity will be determined by subjective evaluation of the patient and classified as mild (it does not interfere with the subject's normal functional capacity), moderate (it interferes to a certain extent with the subject's normal functional capacity) and severe (it significantly interferes with the subject's normal functional capacity). The investigator will determine the relationship between the study medication and adverse event (not related, unlikely, possible, probable), will initiate appropriate treatment and will decide whether to withdraw the patients from the study.

2.9. Statistical analysis

The paucity of previous studies concerning the use of antiplatelet treatment after implantation of a bioprosthesis makes it difficult to calculate the adequate sample size. Furthermore, the incidence of thromboembolism in the first 3 months after implant is suspected to be as high as 10%, but the true incidence is unknown. For sample-size calculation purposes, we estimated a fivefold improvement with a rate of 2% incidence for the alternative treatment [3], thus, a sample of two groups of 100 patients can be considered large enough to show significant differences between the two treatment arms and will allow to obtain information for further studies.

Homogeneity of groups will be analyzed using the Student's t test, the Mann–Whitney U test, and the chi-square (χ^2) test, when appropriate. Clinical variables are defined according to guidelines for reporting morbidity and mortality after cardiac valvular operations [12] (Table 1). Primary and secondary endpoints of the study are given in detail in Table 2. The main variable is the incidence of the combined endpoint of either thromboembolism, hemorrhage, or valve-related death. Traditionally, this is expressed as a linear rate. This is adequate when there is a constant time-course in the risk for events, but when analyzing short follow-up periods, as in case of the present study, linearity exaggerates the risk and is an unreliable statistical measure. We assume that the overall risk is higher in the first days after surgery and declines slowly thereafter until reaching a constant risk after 3 months of surgery. Therefore, the hazard function will be used to compare the efficacy among

Table 1
Definitions for reporting morbidity and mortality after cardiac valvular operations[a]

Embolism	Any embolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed)
Valve thrombosis	Any thrombus, in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or that interferes with function of the valve
Bleeding event (formerly anticoagulant hemorrhage)	Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or requires transfusion
Structural valvular deterioration	Operated valve dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy, or clinical investigation
Non-structural dysfunction	Non-structural problems that result in dysfunction of an operated valve exclusive of thrombosis and infection diagnosed by reoperation, autopsy, or clinical investigation
Operated valvular endocarditis	Any infection involving an operated valve; morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, is included under this category and is not included in other categories of morbidity

[a] Edmunds et al. [12].

the two groups of treatment. The same analysis will be performed to assess other secondary variables. However, some sort of analysis that considers time-related events must be applied, i.e. Cox multivariate analysis. This study is in some way exploratory and different rates can be obtained that could force to reconsider the population size.

Treatment tolerance will be exhaustively assessed. Any adverse event, severe or not, valve-related or not, will be reported for further analysis. Incidence of adverse events in both groups will be analyzed by means of the χ^2 test or the Fisher's exact probability test.

Statistical analyses will be performed for intention-to-treat population (all randomized patients regardless of whether or not they received the study medication) and the per-protocol population (all randomized patients who adhered to all protocol conditions).

3. Discussion

The role of antiplatelet drugs in preventing thromboembolism is not yet clearly defined. Several studies have reported promising good results in some selected groups of patients after valve replacement with bioprosthesis [1,3].

Table 2
Primary and secondary endpoints of the trial

Primary endpoint
First episode of either
• Thromboembolism, or
• Treatment-related hemorrhage, or
• Valve-related mortality
Secondary endpoints
• Thromboembolism
• Treatment-related hemorrhage
• Valve-related mortality
• Permanent valve-related impairment

Usually patients treated with antiplatelet agents are those with lower risk of thromboembolism, i.e. bioprosthetic aortic valve recipients in sinus rhythm, leaving mitral valve patients or those in atrial fibrillation for oral anticoagulation treatment. Therefore, a bias in patient selection is almost always present in these studies. In fact, many surgeons believe that aortic valve patients in sinus rhythm can be treated safely without oral anticoagulation from the beginning of the postoperative period.

However, till date there is no conclusive evidence supporting the use of antiplatelet treatment in preventing thromboembolism of cardiac origin, but it has proven its efficacy in preventing ischemic episodes in carotid artery disease, after coronary stent implantation, and vascular arterial grafts [13–15]. After a bioprosthesis implantation, the main phenomena that occur predisposing to thrombosis are fibrin deposits and platelet aggregation on foreign surfaces, such as Dacron suture rings or endothelium devoid valve leaflets, until 'healing' occurs around 3 months after surgery. Therefore, there is a place for trying antiplatelet agents. Only those situations in which blood stasis is the main event leading to thrombosis, such as giant left atrium with turbulent flow would not benefit from this treatment and would require permanent anticoagulation. A properly conducted randomized trial can give some light on this matter. The safety profile of antiplatelet agents and the evidence on their efficacy in preventing thromboembolism would result in a significant improvement in the patient's quality of life thanks to the avoidance of monthly blood test, dosage adjustments, and a decreased risk of bleeding. Recently, the Cochrane Library [16] called upon for trials to participate in a review comparing anticoagulants and antiplatelet therapy for prevention of thromboembolism in adults with chronic atrial fibrillation. It has been assumed that only one-third of these patients receive coumadin for prevention of thromboembolism because of concerns on the benefit and risk ratio of such intervention. If the alternative

treatment proves to be equivalent in terms of efficacy, then the cost-effectiveness of the alternative treatment would be highly relevant.

In summary, the scope of the present ongoing clinical trial is limited to a small population of postoperative patients, but evidence in favor of the non-inferiority of antiplatelet drugs in comparison with anticoagulants may be the first step for expanding the use of antiplatelet therapy to other indications, such as chronic atrial fibrillation.

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