Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (trac): prospective, randomized, co-operative trial

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Abstract

Objective: Antiplatelet agents are used for prevention of thromboembolism in surgical patients and in patients with chronic atrial fibrillation. Up to date, however, results of randomized studies comparing antiplatelet agents and oral anticoagulation have not been reported. The aim of this study was to compare the efficacy and safety of triflusal (an antiplatelet agent) versus acenocoumarol for primary prevention of thromboembolism in the early postoperative period after implantation of a bioprosthesis.

Methods: In this prospective, multicentric, randomized, open pilot trial, patients were assigned to treatment with triflusal (600 mg/d) or acenocoumarol (target INR 2.0–3.0). Study medication was started 24–48 h after valve replacement with a bioprosthesis, and continued for 3 months. Four follow-up visits were scheduled: baseline, and at 1, 3 and 6 months thereafter. The primary end-point was a composite of the rate of thromboembolism, severe hemorrhage and valve-related mortality.

Results: A total of 193 patients were included (97 received triflusal and 96 acenocoumarol), with a mean age of 72.5 years. Half were men. Aortic valve replacement was performed in 181 patients (93.8%), mitral valve replacement in 10 patients (5.2%) and double valve replacement in 2 (1.0%). Hospital mortality was 11 (5.7%). Primary outcome was recorded in 9 patients with triflusal (9.4%) and in 10 patients with acenocoumarol (11%). There were nine episodes (4.7%) of thromboembolism, six in the triflusal group and three in the acenocoumarol group, and three episodes of permanent neurological deficits, one in the triflusal group and two in the acenocoumarol group. Severe hemorrhage: nine episodes, six in the acenocoumarol group and three in the triflusal group. None of the observed differences in efficacy were statistically significant. Regarding safety, three patients in triflusal group reported at least one hemorrhage, compared to 10 in acenocoumarol group (P = 0.048).

Conclusions: There were no significant differences in efficacy between both groups, however, triflusal showed a significantly lower incidence of bleeding episodes.

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1. Introduction and background

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 the 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 present (e.g. atrial fibrillation (AF)). 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 AF 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 vasodilatation 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, we designed this prospective, randomized, open, co-operative pilot trial, in which triflusal was to be compared with acenocoumarol as the active reference drug [11].

2. Methods

2.1. Participants

TRAC (Triflusal vs Anticoagulant in Bioprosthetic valve replacement) was a prospective randomized, multicentre, open, pilot trial that took place from May, 2000, to July, 2003, which involved four acute-care teaching hospitals in Spain.

The design and methodology of the protocol has been published elsewhere [12], and these were its main features. Patients aged 18 years or older were eligible if they had undergone mitral or aortic valve replacement with a bioprosthesis and had given written informed consent.

The following exclusion criteria applied: (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 anticoagulant or any other 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 nonsteroidal antiinflammatory 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 were also excluded.

The study was run according to the Declaration of Helsinki and the European Good Clinical Practice guidelines. Study approval by local research ethics committees was obtained. Written informed consent was obtained from all eligible patients.

2.2. Randomization and coding

An independent and masked contract research organization (CRO) was responsible for randomization. At the time of the patient’s inclusion in the study just 24 h before surgery, the randomization code was requested by e-mail or telephone call to the clinical research assistant. The same CRO was responsible for coding the information on adverse events as recorded by the investigators according to the World Health Organization adverse reaction terminology. All reported primary and secondary end-points were validated by all four investigators, who reached an agreement after reviewing all information available, without unblinding the treatment assigned.

2.3. Medications

Study medication was started as soon as the patient resumed oral intake after surgery but not later than 48 h postoperatively. Medications administered consisted of triflusal 600 mg (Disgren®, J. Uriach, Barcelona, Spain) in a single daily dose and acenocoumarol 4 mg (Sintrom®, Novartis, Barcelona, Spain). In case of gastric intolerance, the dose of triflusal could be divided in 300 mg every 12 h. The dose of acenocoumarol had to be titrated individually to keep international normalized ratio (INR) between 2 and 3.

Treatment with any nonsteroidal antiinflammatory drug, or anticoagulant or antiplatelet agent other than the study drug was not allowed during the study.

2.4. Clinical procedures

All patients had to take the assigned medication for 3 months, and after that, patients continued 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 was 6 months in this protocol although the patients are later followed once a year on a routine basis. Four visits were scheduled as follows: (a) baseline visit (day 0) at the time of the patient’s inclusion in the study in which the investigator checked eligibility criteria and had informed consent signed; at the same time demographic features and clinical data of the pre- and perioperative period were recorded; (b) visit 1 (day 30); (c) visit 2 (day 90); and (d) visit 3 (day 180). In all these outpatient visits, clinical data were recorded and electrocardiograms were obtained. An echocardiogram and laboratory tests were performed between visits 1 and 2. For patients assigned to oral anticoagulation, all INR values were registered. Patients with values lower than two repeatedly reported after the first week were considered as not properly anticoagulated. EKG’s were performed in order to monitor closely the cardiac rhythm. The echocardiogram helped to assess the presence of thrombus or ‘smoke-like’ low flow turbulence in the left atrium as a quality control of the antithrombotic treatment.

Information on adverse events was obtained through spontaneous reports by the patients and by nonsuggestive
questioning at each assessment. Patients were asked for time of onset, duration, and intensity of the adverse event. The intensity was determined by subjective evaluation of the patient and classified as mild (it did not interfere with the subject’s normal functional capacity), moderate (it interfered to a certain extent with the subject’s normal functional capacity) and severe (it significantly interfered with the subject’s normal functional capacity). The investigator determined the relationship between the study medication and adverse event (not related, unlikely, possible, probable), initiated appropriate treatment and decided whether to withdraw the patients from the study.

2.5. Statistical analysis

Homogeneity of groups was analyzed using the Student’s t-test, the Mann-Whitney U-test, and the chi-square ($\chi^2$) test when appropriate. Clinical variables were defined according to guidelines for reporting morbidity and mortality after cardiac valvular operations [13]. The main variable was the incidence of the combined end-point of either thromboembolism, hemorrhage, or valve-related death, and a survival analysis was also performed. Incidence of adverse events in both groups was analysed by means of the $\chi^2$ test or the Fisher’s exact probability test.

Statistical analyses were performed for intention-to-treat population (all randomised patients who received at least one dose of study medication, and had at least one efficacy assessment).

2.6. Outcome events

Primary outcome events included the first occurrence of either thromboembolism, hemorrhage (any episode of major internal or external bleeding that causes death, hospitalization or permanent injury, or requires transfusion), or valve-related death. Secondary end-points were the occurrence of each of these events separately as well as permanent valve-related impairment.

3. Results


Trial profile is shown in Fig. 1. Of the 228 patients screened, 200 were randomized, 100 were assigned to treatment with triflusal and 100 to acenocoumarol. Seven patients (three in triflusal group and four in acenocoumarol group) who did not take any dose of the study medication were excluded from the study. Two additional patients were excluded from the ITT population because there was not any treatment with triflusal and acenocoumarol. Seven patients (three in triflusal group and four in acenocoumarol group), who did not take any dose of the study medication and adverse event (not related, unlikely, possible, probable), initiated appropriate treatment and decided whether to withdraw the patients from the study.

A total of 109 patients reported at least one adverse event (57 [59%] in the triflusal group and 52 [54%] in the acenocoumarol group), which reported a total of 192 adverse events (103 and 89, respectively). The difference was not significant ($P=0.52$).

As shown in Table 3, the most frequent related or unrelated adverse events were included in heart rate and rhythm disorders (29 vs. 20% in the triflusal and acenocoumarol groups, respectively), being AF the first in incidence. No significant differences were detected between groups. New onset of AF occurred in 15 patients, of them six in the triflusal group and nine in the acenocoumarol one. One single episode of thromboembolism happened while the patient was in AF either chronic or new onset (1/33; 3%) not different from the rate of TE while in sinus rhythm (8/160; 5%). The same happened when comparing mitral valve
replacement vs. aortic valve replacement. There was one episode of thromboembolism in one mitral patient (1/12; 8%) vs. 8 in the aortic patients (8/181; 4%), P = ns.

Forty-nine patients experienced 65 serious adverse events (related or unrelated). The most frequent serious adverse event was ‘respiratory insufficiency’, with five episodes in 5 patients.

A total of 10 (10%) patients assigned to acenocoumarol group reported at least one hemorrhagic adverse event as compared with three (3.1%) in the triflusal group (P = 0.048; Table 4).

We performed an additional analysis with all data on INR values recorded during the follow-up of patients on acenocoumarol. The exhaustive monitorization is one of the main difficulties in managing therapy with anticoagulants, and a number of adverse events can arise from a bad control.

Table 5 summarizes all records on INR values from all patients assigned to acenocoumarol, collected after first week of therapy.

There were 147 instances where INR values were over three. However, risk increases dramatically when INR values are out of range for a long time.

Fig. 3 summarizes frequencies of INR values according to the number of days: values within range represent most of the sample, although there is a relevant number of values over three, precisely in the longest range of days. The mean period when the patients were out of target INR range was $11.8 \pm 7$ days.

Table 1

Summary of baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Triflusal (N=97)</th>
<th>Aacenocoumarol (N=96)</th>
<th>Total (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years ± SD)</td>
<td>73.4 ± 6.8</td>
<td>71.5 ± 9.5</td>
<td>72.5 ± 8.3</td>
</tr>
<tr>
<td>Men</td>
<td>48 (50%)</td>
<td>48 (50%)</td>
<td>96 (50%)</td>
</tr>
<tr>
<td>Weight (kg ± SD)</td>
<td>68.3 ± 12.9</td>
<td>72.1 ± 12.5</td>
<td>70.2 ± 12.8</td>
</tr>
<tr>
<td>Height (cm ± SD)</td>
<td>158.6 ± 8.7</td>
<td>160.1 ± 8.1</td>
<td>159.3 ± 8.4</td>
</tr>
<tr>
<td>Cardiac rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>88 (90.7%)</td>
<td>87 (90.6%)</td>
<td>175 (90.7%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (9.3%)</td>
<td>9 (9.4%)</td>
<td>18 (9.3%)</td>
</tr>
<tr>
<td>AV block</td>
<td>3 (3.1%)</td>
<td>5 (5.1%)</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>82 (85%)</td>
<td>89 (92.7%)</td>
<td>171 (87%)</td>
</tr>
<tr>
<td>Ischemia or necrosis</td>
<td>4 (4.1%)</td>
<td>8 (8.3%)</td>
<td>12 (6.2%)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1 (1.0%)</td>
<td>-</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54 (56%)</td>
<td>51 (53%)</td>
<td>105 (54%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (17%)</td>
<td>20 (21%)</td>
<td>36 (19%)</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>6 (6.2%)</td>
<td>6 (6.3%)</td>
<td>12 (6.2%)</td>
</tr>
<tr>
<td>Noninsulin dependent</td>
<td>11 (11%)</td>
<td>14 (15%)</td>
<td>25 (13%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>81 (84%)</td>
<td>79 (82%)</td>
<td>160 (83%)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>34 (35%)</td>
<td>27 (28%)</td>
<td>61 (32%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>44 (45%)</td>
<td>49 (51%)</td>
<td>93 (48%)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>3 (3.1%)</td>
<td>4 (4.2%)</td>
<td>7 (3.6%)</td>
</tr>
<tr>
<td>Replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve</td>
<td>92 (94.8%)</td>
<td>89 (92.7%)</td>
<td>181 (93.8%)</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>4 (4.1%)</td>
<td>6 (6.3%)</td>
<td>10 (5.2%)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (1.0%)</td>
<td>1 (1.0%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Valve lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic mitral</td>
<td>3 (3.1%)</td>
<td>5 (5.2%)</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>Rheumatic aortic</td>
<td>9 (9.3%)</td>
<td>4 (4.2%)</td>
<td>13 (6.7%)</td>
</tr>
</tbody>
</table>

Fig. 2. Survival analysis of primary end-point (embolism, treatment-related hemorrhage, valve-related death).
Echocardiogram was performed in all survivors between visits 1 and 2 (before third month). Not a single instance of thrombus or 'smoke-like' turbulence could be detected in the left atrium, suggesting adequate antithrombotic protection (Table in Supplementary material). Therefore, the treatment was not interrupted in any case at the light of the Echo data.

4. 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]. 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 AF 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. In a recent survey run by the CTSnet 60% of surgeons believed that antiplatelet treatment was superior to oral anticoagulation after aortic tissue valve replacement without major co morbidities (Anticoagulation therapy after aortic tissue valve replacement [webpage]; http://www.ctsnet.org/file/AnticoagulationSurveyFinalResultsSlidesPDF.pdf [Accessed 31 Aug 2004]).

To our best knowledge, this is the first randomized trial dealing with the role of antiplatelet treatment in preventing thromboembolism after a bioprosthetic implantation. The present study has some limitations. First, the incidence of thromboembolism in the first months after surgery is unknown. Previous studies seem to estimate the incidence in about 10%, but they are not case controlled trials and it is probably an overestimation of the real incidence. At the light of the present study the real incidence in a well-controlled population is much lower, being about 5%, which seems to correspond with current practice [14–16]. The lack of previous randomized trials makes difficult to estimate the sample size. We could not demonstrate any superiority in efficacy in both groups. In the triflusal group most thromboembolic events were minor (going from dizziness to transient ischemic attack) and only two major thromboembolism events were recorded, the same as in the acenocoumarol group. Therefore, triflusal is useful in preventing
tissue valve replacement. Both treatments were useful in anticoagulation during the critical first 3 months after surgery. A bioprosthetic 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. In this situation the use of antiplatelet therapy seems a more rational approach. Recently, Gherli [18] published the results of a prospective study comparing aspirin vs. oral anticoagulation after aortic tissue valve replacement in sinus rhythm. They found no difference in efficacy or safety between both groups, thromboembolism rate being less than 5%. The fact that the study was not randomized produced some biases reflected in the fact that the aspirin group is younger and with a minor Euroscore.

We included patients in AF or with mitral valve replacement excluding only those situation where blood stasis was a predominant factor for thrombosis in giant left atrium (>60 mm). Triflusal was useful in preventing thromboembolism in this cohort of patients also. It is a noteworthy fact that new onset of AF in the first postoperative month had no impact on thromboembolism. Being the most frequent adverse event it would have provoked an excessive rate of abandon of the protocol, had we considered AF a cause of interruption. The fact that no thrombus or smoke-like turbulence was detected in the postoperative Echo supports the quality of this approach.

Regarding safety we demonstrated a statistically significant difference in bleeding adverse events favoring triflusal. Acenocoumarol requires in the first month multiple dosage adjustments and blood tests. Our data show that 25% of the patients fell into the range of INR above five and the mean stay over the therapeutic range was 11 days. It seems obvious that if both treatments are equally useful in preventing thromboembolism the safety profile of antiplatelets and the avoidance of repeated blood tests and dosage adjustments may result in better quality of life for the patients and better treatment compliance.

In conclusion, this study is the first reported randomized trial comparing antiplatelet treatment and oral anticoagulation during the critical first 3 months after tissue valve replacement. Both treatments were useful in preventing thromboembolism but triflusal showed a safer profile with a significant lower incidence of bleeding adverse events. At the light of the present study, the AHA/ACC guidelines for antithrombotic treatment after tissue valve replacement should be revised. The use of oral anticoagulation after aortic valve replacement in patients without co morbidities seems no longer justified.

Appendix. Supplementary material


Acknowledgements

This study was supported by grants from J Uriach y Co mpañía, manufacturer of Triflusal.

References


Appendix A. Conference discussion

Dr R. Dion (Leiden, Netherlands): Could you tell me what is the exact difference between aspirin and triflusal?

Dr Aramendi: Triflusal is a derivative from aspirin that inhibits cyclooxygenase but not completely, therefore it has a safer profile for the gastrointestinal tract, better tolerance, and lesser incidence of hemorrhage.

Dr J. Revuelta (Santander, Spain): Looking at your data, you include most of the patients with aortic, 93.8%, and you only included 10 patients with a mitral, 5.2%, and double valve replacement, 1%. I think that this study is quite valid, very interesting with this data in the aortic position. You can get the same conclusion for only 10 patients in the mitral and particularly for double valve replacement. So these patients should be excluded to get a real valid analysis.

Dr Aramendi: We can perform the analysis only focused on the aortic valve patients. The results are pretty similar. In fact, this study wants to be a reflection of what we are doing today with the older population. We are doing more and more aortic valve replacements, and mitral valve replacement incidence is diminishing in our population. We wanted to demonstrate whether the fact of including mitral valve patients could determine an excessive rate of thromboembolism, which was not the case, but again, the main conclusion should be drawn from the aortic population, which is the biggest.