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Research Article

ROLE OF LOW DOSE ASPRIN WITH ANTICOAGULANTS IN PATIENTS WITH MECHANICAL VALVE PROSTHESIS

Praveen Dhaulta* and Vikas Panwar

Department of Cardio-thoracic and Vascular Surgery, IGMC, SHIMLA, HP, India

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Oral anticoagulation alone, or the addition of antiplatelet drugs, has been used to minimise this risk.

ABSTRACT

Background: Patients with prosthetic heart valves are at increased risk for valve thrombosis and arterial thromboembolism. Oral anticoagulation alone, or the addition of antiplatelet drugs, has been used to minimise this risk. An important issue is the effectiveness and safety of adding single antiplatelet.

Objectives: To further assess the safety and efficacy of combined oral anticoagulant and antiplatelet therapy versus oral anticoagulant monotherapy in patients with prosthetic heart valves regarding prosthetic valve thrombosis.

Method: In last 10 years around 870 patients underwent mitral and aortic valve replacement on monotherapy. In last 3 year data around 60 patients presented with prosthetic valve thrombosis who were on anticoagulation alone. Most of patients were those who underwent mitral valve replacement out of which 90 % were female patients. From last one year onward 60 patients were put on low dose antiplatelets75 mg plus anticoagulant, out of which till now no patient presented with valve thrombosis.

Results: Adding low daily dose of aspirin 75mg reduce the incidence of prosthetic valve thrombosis and thromboembolism as is already proven in many studies. Similar results were observed in our study. But its too early to conclude, as duration is only one year, so it need further evaluation to reach end point.

Conclusion: Adding antiplatelet therapy, either dipyridamole or low-dose aspirin, to oral anticoagulation decreases the risk of systemic embolism or death among patients with prosthetic heart valves. The risk of major bleeding is decreased with antiplatelet therapy by having lower target INR value (2.5). These results apply to patients with mechanical prosthetic valves or those with biological valves and indicators of high risk such as atrial fibrillation or prior thromboembolic events. The effectiveness and safety of low-dose aspirin (75 mg daily) appears to be similar to higher-dose aspirin and dipyridamole. So consideration should be given to it for patient benefit.

INTRODUCTION

Patients with prosthetic heart valves are at increased risk for both valve thrombosis and arterial thromboembolic events, including stroke (1,2). Consequently, anticoagulation therapy is used to lessen the thromboembolic risk, albeit at the expense of increased anticoagulation-associated hemorrhage. Recently, several systematic reviews have attempted to clarify the current best evidence for prosthetic valve management (3,4). As such, current recommendations tend to be very specific and are tailored to several clinical features, including prosthetic valve location and type, presence of atrial fibrillation and prior history of thromboembolism (4,5). Unfortunately, the literature supporting these recommendations is often difficult to interpret due to small numbers of patients, lack of consistent control groups and older studies with anticoagulation monitoring that predates the International Normalized Ratio (INR). As a means of improving the efficacy of antithrombotic therapy after cardiac valve implantation, anticoagulation has been augmented with an antiplatelet agent. Although the results of some of the trials have been encouraging, showing Improved effectiveness with no substantial increase in bleeding risk, the results are far from consistent (6–17). Previous meta-analyses addressing the efficacy and safety of combined antiplatelet and oral anticoagulant for prosthetic valve management were potentially limited, having reviewed either English language trials, published data (18,19) or trials using dipyridamole (20) only. The goal of this study was to assess the safety and efficacy of combined oral anticoagulant and antiplatelet therapy

Corresponding author:* **Praveen Dhaulta
Department of Cardio-thoracic and Vascular Surgery, IGMC, SHIMLA, HP, India

versus anticoagulant monotherapy in patients with prosthetic heart valves.

METHOD

In last 10 years around 870 patients underwent mitral and aortic valve replacement on monotherapy. In last 3 year data around 60 patients presented with prosthetic valve thrombosis who were on anticoagulation alone. Most of patients were those who underwent mitral valve replacement out of which 90 % were female patients. Target INR was around 2.5 to 3.5 , but most patients was not adhering to target value and drug intake. From last one year onward 60 patients were put on low dose antiplatelets75 mg plus anticoagulant, out of which till now no patient presented with valve thrombosis.

RESULTS

Adding low daily dose of aspirin 75mg reduce the incidence of prosthetic valve thrombosis and thromboembolism as is already proven in many studies. Similar results were observed in our study. Moreover with the increasing incidence of redo surgeries which carry higher rates of morbidity and mortality antiplatelet therapy is further advocated. But its too early to conclude, as duration is only one year, so it need further evaluation to reach end point.

DISCUSSION

The conclusion of various meta-analysis is that the addition of an antiplatelet agent, either aspirin or dipyridamole, to warfarin in patients with prosthetic heart valves reduces the risk of death and systemic thromboembolic events.Other analysis showed that dipyridamole and aspirin reduced the risks of death and thromboembolism similarly.The risk of major bleeding is increased with both dipyridamole and aspirin. Although the point estimate of bleeding risk seemed to favour aspirin over dipyridamole and for trials performed after 1990 rather than before, there was no evidence of statistical heterogeneity. Lower-dose (100 mg or less) aspirin may have the lowest bleeding risk.

Chesebro and colleagues (1) performed a randomised trial comparing warfarin and dipyridamole (400 mg daily) to warfarin and aspirin (500 mg daily) in patients with a prosthetic heart valve replacement (Chesebro 1983). The risk of a thromboembolic event was slightly lower, but not statistically significant, among those allocated dipyridamole compared with aspirin (0.5 versus 1.8 per100 patient-years). Bleeding rates were higher among those receiving concomitant aspirin as compared to dipyridamole (6.6 versus 1.6 per100patient-years,P<0.001). 500 mg in the Chesebro study (Chesebro 1983) as compared to the lower risk of bleeding when doses of aspirin of 100 mg daily (Turpie 1993) are used.

The Antiplatelet Trialists' Collaboration found that aspirin or other antiplatelet drugs were protective against vascular events in high-risk patients. Furthermore, they felt that the available evidence supports the use of low-dose aspirin (75 to 150 mg daily) as an effective antiplatelet regimen for long-term use (Antiplatelet 2002). In our meta-analysis the relative effectiveness and safety of aspirin may reflect patient selection, the target intensity of anticoagulation (target international normalised ratio (INR)), or the dose of aspirin used. Among the six aspirin trials there was some evidence of statistical heterogeneity for total mortality (P = 0.09) but not risk of thromboembolism (P = 0.48) or major bleeding (P = 0.15). One possible explanation is the dose of aspirin used: 100 mg daily in one trial (Turpie 1993) compared to 200 to 1000 mg daily in the other aspirin trials (Altman 1976; Dale 1977; Laffort 2000). The risk of death was lower in the low-dose aspirin trial (Turpie 1993) (odds ratio (OR) 0.37, 95% confidence interval (CI) 0.17 to 0.84; P = 0.014) compared with the higher-dose aspirin trials (OR 1.15, 95% CI 0.53 to 2.49; P = 0.72) and the test of interaction for the differences between these subgroups was conventionally statistically significant (P=0.05). For the low-dose aspirin trial (Turpie 1993)(14) the risk of major bleeding (OR 1.29, 95% CI 0.68 to 2.44) was not increased compared with warfarin alone. Although the risk of major bleeding was increased for the higher-dose aspirin trials (OR 2.58) and statistically significantly greater than OAC alone (P = 0.002), there was no statistical evidence of interaction based on dose of aspirin (P = 0.13). It must be stressed that these subgroup analyses, although pre-defined, are based on a limited number of events in each subgroup and, as such, are potentially unstable. They should be considered hypothesis generating.

Turpie 1993 (14) had the highest methodology score (Characteristics of included studies). It was a double-blind, randomised controlled trial where 186 patients were assigned to aspirin (100 mg/day sustained release) plus warfarin and 184 to placebo plus warfarin(Turpie 1993).

Patients were included if they had a mechanical prosthetic valve or were those with tissue valves and atrial fibrillation or a history of thromboembolism. The target INR was 3.0 to 4.5. The primary endpoint (major embolism or death) was reduced among those assigned to aspirin (1.9% versus 8.5% per year; P < 0.001). The stroke rate (1.3% versus 4.2% per year;P=0.027)and overall mortality(2.8%versus7.4%;P=0.01) was reduced with aspirin. Furthermore, a composite outcome that could reflect net clinical benefit (major systemic embolism, nonfatal intracranial haemorrhage, death due to haemorrhage, and vascular deaths) was also reduced with aspirin (3.9% versus 9.9% per year; P = 0.005). Although the risk of bleeding was increased with aspirin this was primarily due to minor bleeding including bruising, epistaxis, and haematuria. Importantly, the risk of major haemorrhagic events did not differ significantly between groups (8.5% aspirin versus 6.6% placebo; P = 0.43).

In the Meschengieser 1997 (15) trial patients were randomized to either a high target INR(3.5to4.5;mean achieved 3.98) or a lower target INR (2.5 to 3.5; mean achieved 3.11) plus aspirin 100 mg daily. The primary outcome events were rates of thromboembolism and bleeding. The rates of thromboembolism were similar at 2.8% and 2.7%, respectively.The risk of major bleeding (4.5%warfarin alone versus 2.3% warfarin plus aspirin) and minor bleeding(17% warfarin alone versus 14% warfarin plus aspirin) did not differ between groups but tended to favour the combination of low-dose aspirin and lower target level of anticoagulation. Three intracranial haemorrhages occurred in the warfarin alone arm; none were seen in the combination arm. Therefore, the addition of low-dose aspirin with a lower level of anticoagulation was as effective, and possibly safer, when compared with a higher level of anticoagulation. Similar results were seen in the LIWACAP 2007 trial in which patients were randomised to

standard-intensity OAC(INR between 3.0 and 4.5, target 3.7) versus low-intensity OAC (INR between 2.0 and 3.0, target 2.5) and 100 mg aspirin. Follow up was only for six months and there were few events in this pilot study. There were no differences in thromboembolic or major bleeding events although the trial was severely underpowered.

These results are consistent with the randomised trial by Altman 1991 (17) who compared the effect of a low (INR 2.0 to 3.0) or high (INR 3.0 to 4.3) degree of anticoagulation in combination with dipyridamole (150 mg/day) and aspirin (660 mg/day) in patients with heart valve replacement.The rates of thromboembolic events were similar between the low and high INR groups (1.92 versus 4.94 per 100 patient-years, respectively),although there were very few events overall.The risk of bleeding, however,was less with the lower targetINR(3.8versus24.7 per100 patient-years,P<0.02). They concluded that a lower INR (2.0 to 3.0) used conjointly with platelet inhibitors was effective and safer than a higher target INR (Altman 1991).

The most recent trial(Dong2011) (21)` included young patients (mean age of 35 years) with primarily rheumatic heart disease who underwent mechanical valve replacement.The risk of major bleeding was only 0.4%. In addition, they used low-dose aspirin (75 to100 mg daily) and a target INR of 1.8 to 2.5. In this study the rate of reliable anticoagulation was only 33% to 36%. Thromboembolism rates favoured the combination of OAC and low-dose aspirin at 2.1% versus 3.6% with OAC alone (OR 0.59, 95% CI 0.32 to 1.09).

CONCLUSION

Adding antiplatelet therapy, either dipyridamole or low-dose aspirin, to oral anticoagulation decreases the risk of systemic embolism or death among patients with prosthetic heart valves. The risk of major bleeding can be decreased by keeping target INR value around 2.5.These results apply to patients with mechanical prosthetic valves or those with biological valves and indicators of high risk such as atrial fibrillation or prior thromboembolic events. The effectiveness and safety of low-dose aspirin (75 mg daily) appears to be similar to higher-dose aspirin and dipyridamole . So adding antiplatelets therapy is benecificial and cost effective and should be considered.

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