

LESSON OF THE MONTH

Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves

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Abstract

Mechanical heart valves are associated with a risk of thromboembolism and anticoagulation is generally recommended. However, this is inevitably associated with a risk of intracranial bleeding. The case of a patient who sustained an intracranial bleed while taking warfarin for a prosthetic aortic valve and a further two intracranial bleeds while on heparin as an inpatient is discussed and the literature on the management of intracranial haemorrhage in patients on warfarin with prosthetic valves is reviewed.

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Case report

A 70 year old man presented with a sudden onset of right sided weakness and difficulty in speaking. He had had a St Jude prosthetic aortic valve inserted 7 months earlier for severe aortic stenosis and was anticoagulated with warfarin (target international normalised ratio (INR) 3–4). His INR had been between 2–3.6 for 6 months before presentation. On examination he was in sinus rhythm and was normotensive. He was fully alert but had a mild fluctuating expressive dysphasia. He had a right upper motor neuron VII nerve lesion and a mild right sided pyramidal weakness. His INR was 3.6. Cranial CT disclosed a left sided intracerebral haematoma. It was initially decided to reduce his INR to about 2, but not to reverse the coagulopathy fully because of the presumed risk of valve thrombosis. This management plan was altered after discussion with the regional neurosurgical team and cardiothoracic team and he was converted to intravenous heparin with a plan to remain on this for 6 weeks and to then restart warfarin. On day 38 of the admission a sudden worsening of his expressive dysphasia was noted. His activated partial thromboplastin time (APPT) was 105 (50–75) and platelet count was 230 (150–400). Cranial CT showed two new intracranial haematomas. After a neurological opinion, anticoagulation was reversed with fresh frozen plasma and he remained without anticoagula-

Relative thrombogenicity of different types of prosthetic heart valves

Mechanical valves		Thrombogenicity
Caged ball Single tilting disc	Starr-Edwards	++++
	Bjork-Shirley	
	Medtronic Hall	+++
Bileaflet tilting disc	Omnicarbon	
	St. Jude Medical	
	Carbomedics	+++
Bioprosthetic valves:		
	Heterograft	
	Carpenter-Edwards	
	Hancock	+ to ++
	Ionescu-Shiley	
Homograft		+

Adapted from Vongpatanasin *et al.*¹²

tion for a further 6 weeks. Warfarin was reintroduced on day 80. He had no further vascular events and was discharged on day 90. By discharge he was fully mobile with minimal expressive dysphasia and dyspraxia.

Discussion

There are two main groups of prosthetic heart valves: mechanical and bioprosthetic (table). Mechanical valves are more thrombogenic and anticoagulation is recommended (target INR 3–4). In the absence of atrial fibrillation anticoagulation is not recommended for bioprosthetic valves.¹ There are two main thrombotic complications: thrombus of the valve leading to valve failure and embolisation to the brain and other organs. A meta-analysis published in 1994 suggested that the incidence of prosthetic valve thrombosis in patients not anticoagulated or taking antiplatelet drugs is 1.8% per patient-year (95% CI 0.9–3.0%).² In those with mechanical valves, the risk of thrombosis is similar (though not identical) for all three designs (table). The incidence of mechanical valve embolism resulting in death, stroke, or peripheral ischaemia requiring surgery is 4% per patient-year (95% CI 2.9–5.2%). This is reduced to 2.2% by antiplatelet drugs and 1.0% per patient-year with warfarin. The risk of embolisation is increased with mitral valve prostheses, caged ball valves, and multiple prosthetic valves.² Both valve thrombosis and embolisation occur at a similar rate in

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patients with bioprosthetic valves and in those with mechanical valves who are adequately anticoagulated.³

Various studies have suggested that anticoagulation increases the risk of intracranial haemorrhage by 7–10 fold, to an absolute risk of 0.3–1% per year. The mortality associated with oral anticoagulant related intracranial haemorrhage is about 60%.⁴ As in the case of this patient, there is often confusion over whether the risk of valve thromboembolism from reversing anticoagulation outweighs the benefit of arresting any continuing bleeding. It has been suggested that intracranial haemorrhage occurring while on warfarin may continue to evolve over 24 hours in 50% of patients. This is by contrast with non-anticoagulated patients in whom only 10% of haemorrhages continue to enlarge in the first 24 hours.^{4,5} Thus if treatment is given to reverse the coagulopathy it should be given as rapidly as possible.

Anticoagulation with warfarin can be reversed with vitamin K, fresh frozen plasma, or factor concentrates. Warfarin reduces the availability of vitamin K and thereby reduces the concentration of the vitamin K dependent clotting factors (II, VII, IX, and X). Vitamin K is always required to achieve more than a temporary reversal of anticoagulation, but takes 4–6 hours to work.¹ A dose of 5–10 mg is recommended for life threatening haemorrhages such as intracranial bleeding.¹ There is often reluctance to use vitamin K because it can result in warfarin resistance and difficulty in reanticoagulating the patient. Vitamin K does not affect subsequent use of heparin.

As synthesis of clotting factors after vitamin K takes several hours, coagulation factors should also be replaced directly. Fresh frozen plasma is the standard treatment used; the alternatives are individual factor concentrates. Current guidelines on the reversal of warfarin anticoagulation in the event of intracranial haemorrhage⁶ are not based on prospective randomised trials: none have been done. Two retrospective studies suggest that individual factor concentrates may provide faster and more complete reversal of the warfarin effect than fresh frozen plasma.^{7–8} In the first study, 17 patients with anticoagulant related intracerebral haemorrhage were treated either with fresh frozen plasma (8 ml/kg (seven patients)) or with prothrombin complex concentrate containing factor II, IX, and X (25.8 iu/kg, based on the factor IX content).⁷ The decision to use fresh frozen plasma or prothrombin complex concentrate was made by the physician in charge of the patient in conjunction with a haematologist. All received vitamin K (10–20 mg intravenously). The mean INR pretreatment was similar in both groups (2.83 in the prothrombin complex concentrate group and 2.97 in the fresh frozen plasma group). After treatment the INR was significantly lower in the group treated with prothrombin complex concentrate (1.22 *v* 1.74, *p*<0.05). This was probably because the dose of prothrombin complex concentrate was equivalent to three times that of fresh frozen plasma. Giving an

equivalent volume of fresh frozen plasma would have required a 2 litre infusion, which may have resulted in volume overload. Another advantage was the shorter infusion time required for prothrombin complex concentrate, resulting in a more rapid reversal of the INR in this group of patients.

The second study included 41 patients on warfarin with either life threatening haemorrhage or a dangerously high INR.⁸ All were given vitamin K (1–5 mg intravenously). Twelve received fresh frozen plasma (800 ml) and 29 received prothrombin complex concentrate or prothrombex T (factors II, VII, IX, and X) 25–50 units/kg, based on the factor IX content. It is not stated how treatment was allocated. INR was measured before treatment and 15 minutes after the infusion ended and assays for factors II, VII, IX, and X were performed in 11 of the patients treated with fresh frozen plasma and 14 of the patients treated with coagulation factors. Unfortunately the groups were not well matched for pretreatment INR or concentration of individual clotting factors, but in no patient did fresh frozen plasma completely reverse the INR, whereas it was reversed in 28 of the 29 patients treated with coagulation factors. The concentrations of individual clotting factors did not correct as well after fresh frozen plasma as after the coagulation factors. This was most marked for factor IX. Different batches of fresh frozen plasma had a threefold variation in the concentration of individual clotting factors. The authors concluded that in life threatening emergencies (such as intracranial haemorrhage) individual clotting factors should be used in preference to fresh frozen plasma.

Having reversed anticoagulation, it is uncertain when to recommence it. There are no prospective studies. However, if the risk of embolism from prosthetic heart valves resulting in major stroke or death is 4% a year and the risk of valve thrombosis is 1.8% a year,² the daily risk can be estimated to be 0.016%. Thus stopping anticoagulation for 6 weeks is associated with a risk of major stroke or death of 0.67%. The decision to reintroduce anticoagulation should be based on the balance between a patient's thromboembolic risk and their bleeding risk.

The prolonged use of intravenous heparin (unfractionated heparin), as in this patient, cannot be recommended. Heparin was used because it can be reversed rapidly (half life about 1 hour) in the event of further intracranial bleeding. However, the use of intravenous heparin is associated with both altered platelet function and with thrombocytopenia in about 1% of patients.^{9–10} The risk of thrombocytopenia is particularly high early in treatment (days 2–3), when it is generally asymptomatic. Delayed onset thrombocytopenia, occurring a week after starting heparin is more serious and related to an antibody that causes platelet aggregation in the presence of heparin. This antibody can persist for at least 6 weeks after heparin has been stopped. Paradoxically, thrombocytopenia is associated with intravascular thrombosis. Low molecular weight

heparin is rarely associated with thrombocytopenia and is generally considered safer than long term unfractionated heparin.

In conclusion, the management of intracranial bleeding (or any life threatening bleeding) in a patient receiving warfarin for a prosthetic heart valve is to initially reverse the coagulopathy with vitamin K (5 mg by slow intravenous infusion) and individual coagulation factors.¹ A prothrombin complex concentrate containing factor VII as well as II, IX, and X and including protein C, antithrombin, and a minimal dose of heparin (to forestall risks of thrombosis and disseminated intravascular coagulation) which has undergone standard antiviral processing (for example, Beriplex P/N, Centeon Pharma GmbH) should be stocked at all hospitals where patients on warfarin may present with intracranial bleeds, with hub and spoke rotation between centres to prevent wastage if appropriate. Warfarin should be stopped on clinical suspicion of intracranial haemorrhage and 50 u factor IX/kg of prothrombin complex concentrate infused as soon as the diagnosis is confirmed; this fixed dose is superior to titration against the INR, which is insensitive to factor IX. An ongoing study is evaluating the efficacy of 30 u factor IX/kg, but until it is formally reported the higher dose should be used. The use of vitamin K should avoid further infusions of prothrombin complex concentrate. Timely issue of the expensive multidonor prothrombin complex concentrate and coagulation assays to prove adequate correction, require the involvement of a haematologist as soon as a likely intracranial bleed presents in a patient on warfarin. If prothrombin factor concentrate is not available FFP (15 ml/kg) should be given.

The decision to recommence anticoagulation should take into account the risk of a

thromboembolic complication while not receiving warfarin (0.016%/day) versus the risk of further intracranial bleeding. Full correction of haemostasis until the bleed has resolved should not be held back in fear of rebound thrombosis, as such events are rare.¹¹ We think that a period of 4–6 weeks should elapse before anticoagulation is restarted. A repeat CT before recommencing anticoagulation is probably advisable to confirm that the bleed is resolving. Whenever anticoagulation is recommenced, either oral warfarin or low molecular weight heparin may be safer than intravenous unfractionated heparin.

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