The management of patients with mechanical heart valves and intracerebral haemorrhage

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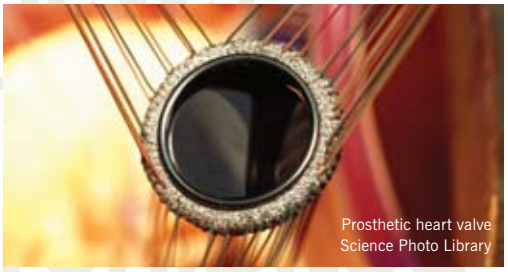
Patients with mechanical prosthetic heart valves require oral anticoagulation to reduce the risk of thromboembolic events, but this can be complicated by anticoagulant-associated intracerebral haemorrhage (ICH). In order to make appropriate decisions about the resumption of anticoagulation in patients with mechanical heart valves and ICH, the risks of further bleeding must be weighed against those of thromboembolic events. There is limited evidence available to guide clinical decision-making in this situation and each case must be assessed individually, ideally with a multi-disciplinary team approach.

Introduction

Patients with a mechanical heart valve prosthesis require oral anticoagulation to reduce the risk of thromboembolic events. However, this can be complicated by anticoagulant-associated intracerebral haemorrhage (ICH). This presents a therapeutic dilemma as regards future anticoagulation. Here we present a case report, and discuss the available evidence used to guide subsequent management.

Case report

A 63-year-old, retired carpet-fitter, presented with headache and visual disturbance. There was no history of head injury or trauma. He had undergone a CarboMedics© mechanical mitral valve replacement following endocarditis five months earlier. Postoperatively an echocardiogram had demonstrated normal left ventricular function with a mildly dilated left atrium. He was anticoagulated with warfarin and his international normalised ratio (INR) had been well controlled since discharge with an INR on admission of 3.3 (target INR 3.0–4.0). On examination, he was in controlled atrial fibrillation and was found to have a left homonymous hemianopia. His blood pressure on arrival was 142/76 mmHg. A computed



Prosthetic heart valve
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tomography (CT) scan demonstrated a 5 cm right occipital ICH with significant mass effect (**figure 1**).

After discussion with the haematologists, his anticoagulation was reversed using vitamin K and fresh frozen plasma. The CT images were reviewed by the neurosurgeons who recommended a conservative approach and advised that warfarin was withheld for two weeks. Two days later he was treated with intravenous heparin, aiming for an activated partial thromboplastin time ratio (APTTR) between 1.5 and 2, with 12 hourly activated partial thromboplastin time (APTT) measurements. His visual fields improved and a repeat CT scan two weeks after presentation demonstrated significant resolution of the haematoma (**figure 2**). He was then recommenced on warfarin with a slightly lower target INR (2.0–3.0) and discharged home well.

Background

The absolute risk of anticoagulation-related ICH is between 0.3 and 1% a year,[1] compared with a spontaneous rate of 0.15% per year. Anticoagulation-related ICH is associated with a mortality of approximately 50% within the first 30 days.[2] The mortality rate varies according to the neurological status of the patient at the time of admission. Patients who are unconscious on arrival have a 96% mortality rate, while those that receive anticoagulant antagonists when still conscious have a mortality rate of 28%.[3]

Acute management

Active bleeding into the brain occurs mostly within the first 24 hours after symptom onset.[3] In view of this, it

Figure 1. Initial computed tomography (CT) brain scan demonstrating a 5 cm right occipital intracerebral haemorrhage with significant mass effect

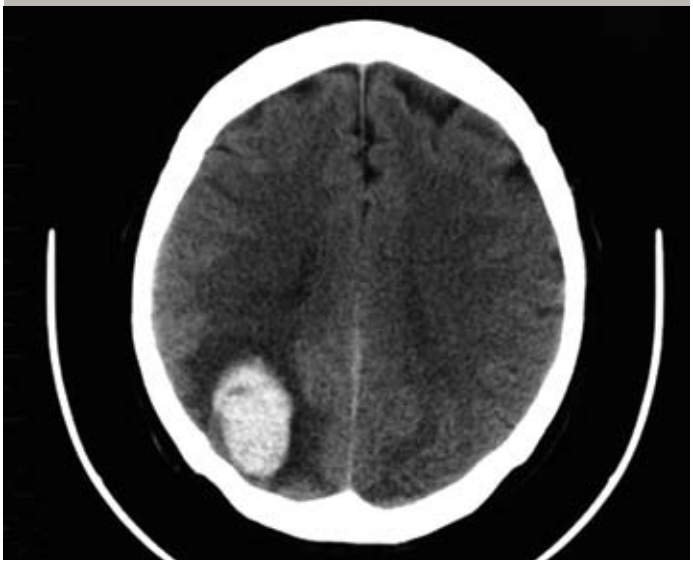
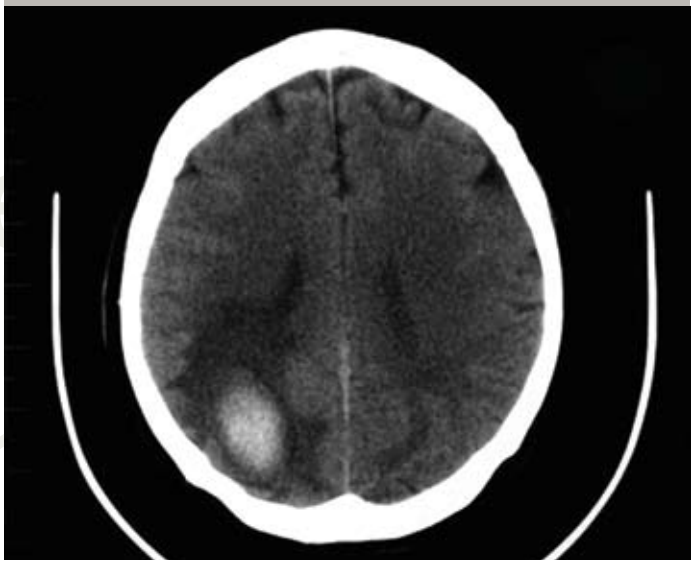


Figure 2. Repeat CT scan two weeks after presentation demonstrating significant resolution of the haematoma



is imperative to confirm the diagnosis with urgent CT imaging and reverse the anticoagulation defect promptly. This can be achieved with vitamin K, fresh frozen plasma or prothrombin complex concentrates. The latter are more expensive, but provide more rapid reversal with less volume than fresh frozen plasma.

Long-term management

In order to make appropriate decisions regarding the resumption of anticoagulation in patients with mechanical heart valves and ICH, we need to balance the risks of recurrent bleeding against those of thromboembolic events.

Risks of recurrent bleeding

There is very limited information available regarding the rate of recurrent bleeding in patients with anticoagulant-associated ICH. Our management was influenced by data from patients who have primary/spontaneous ICH. These patients' risk of recurrent bleeding is 2–3% per year without antiplatelet or anticoagulant therapy.[4,5] This corresponds to an increase in relative risk over the general population of approximately 10-fold.[4,5] The site of the initial haemorrhage is also important, as lobar haemorrhage involving the cerebral cortex appears to carry a higher risk of recurrence than deep hemispheric haemorrhage.[4,5]

There are no data regarding the risks of aspirin or warfarin on recurrent bleeding in patients with warfarin-associated ICH. The risk of spontaneous ICH is increased by about 40% with aspirin,[6] and threefold with warfarin.[4] It is impossible to know whether the relative risk of a primary event can be extrapolated to a secondary event. The risk of major bleeding with warfarin therapy is ~1.4% per year in patients without a previous bleed.[7]

Risks of thromboembolism

A meta-analysis by Cannegieter *et al.* looked at the risks of thromboembolism in patients with mechanical heart valves.[7] This study included 13,088 patients studied for 53,647 patient-years. The incidence of valve thrombosis was 1.7% per year (in the absence of anticoagulation) and the incidence of major embolism (death, residual neurological deficit or peripheral ischaemia requiring surgery) was 4% per year. These risks are influenced by the position and type of mechanical valves. Mitral valves have a fivefold increase in the risk of valve thrombosis and 1.5-fold increase in the risk of major embolism when compared with aortic valves. Ball and cage valves (e.g. Starr-Edwards©) have approximately twice the risk of embolism as compared to bileaflet valves (e.g. CarboMedics©).

Aspirin reduces the risk of valve thrombosis from 1.7% to 1.0%. Anticoagulation reduces it further to 0.2%. Use of aspirin reduces the risk of major embolism from 4% to 2.2% per year, while warfarin reduces it to 1% per year.[7] In one case-series of 1,608 anticoagulated patients followed during 6,475 patient-years in The Netherlands, the overall frequency of thromboembolic events was 0.5% per year with mechanical aortic valves, 0.9% per year with mechanical mitral valves, and 1.2% per year with both mitral and aortic valves.[8] The overall frequency of thromboemboli was 0.5% per year with bileaflet valves, 0.7% per year with tilting disk valves (e.g. Medtronic Hall©) and 2.5% per year with caged ball and caged disk valves.

In a patient with prior ICH, the risk of an ischaemic stroke is 1–1.5% per year, approximately twice that of an age-matched population. The risk of thromboembolism is also affected by a number of well-known variables, including hypertension, atrial fibrillation, age, left atrial size, left ventricular systolic function and diabetes mellitus. There are several algorithms, which can be used to estimate the overall thromboembolic risk, e.g. CHADS 2.[9]

Balancing the risk

Eckman *et al.* used a decision-analysis model to give a more objective assessment of the bleeding and thromboembolic risks.[10] The authors recommended anticoagulation with warfarin, only in patients with deep hemispheric ICH, with high thromboembolic risk – in excess of 10% a year.

When to restart anticoagulation?

The appropriate time to reintroduce warfarin requires an understanding of the natural history of ICH and the risks of all thromboembolic events, including deep venous thrombosis and pulmonary embolus, in the acute stage. The greatest risk of further bleeding is within the first 24 hours following ICH. Following this period, the risk of further bleeding is ~2% between 24 hours and two weeks after ICH.[3]

Estimates for the risk of deep venous thrombosis and pulmonary embolism in the acute stage of an ICH are derived from studies in pooled stroke patients, the majority of whom had ischaemic strokes. The risk of clinically evident deep venous thrombosis is between 2% and 10% without prophylaxis and these tend to occur after the first week.[11] The risk of pulmonary embolism occurs in 1% to 3% of patients, and is fatal in approximately half of these.[12] Pulmonary emboli tend to occur two to four weeks after a stroke.

The annual risk of prosthetic valve thrombosis in pooled patients is 1.7% and the risk of a major embolic event is 4%.[7] Hence, in patients with mechanical heart valves, without any form of anticoagulation, the combined annual risk of a major thromboembolic event is ~5.7%. Thus, the daily risk can be calculated to be 0.016% (5.7% per 365 days). This figure will be an underestimate in patients whose anticoagulation has been acutely reversed with prothrombin complex concentrates.[13] Clearly, this will also be dependent on the type of valve, the valve position and any other risk factors (see above).

It is evidently difficult to decide at which stage to reintroduce anticoagulation and there is no consensus of opinion. The risks and benefits have to be weighed up on an individual basis. Consequently, there are a number of different recommendations including withholding warfarin for four to six weeks,[14] withholding warfarin for one to two weeks,[15,16] and the administration of full-dose intravenous heparin immediately after correction of the INR.[13]

Conclusion

Our patient had a deep hemispheric haemorrhage, which has a lower risk of recurrent bleeding than lobar haemorrhage. He was over 50 years old, had a mechanical valve in the mitral position and was in atrial fibrillation, putting him in a high-risk group for thromboembolism.[17] After discussion with the haematologists and acute reversal of his anticoagulation, we elected to commence intravenous unfractionated heparin after 48 hours. We felt that this would be outside the highest risk period for further bleeding, but early enough to significantly reduce the risk of thromboembolism. Our patient had improved clinically over the first 48 hours and there was no evidence of progression of his haemorrhage. The use of intravenous heparin also gave us the option of withdrawing anticoagulation acutely if there had been any concerns regarding further bleeding (half-life between 30 and 150 minutes). The heparin control was monitored closely with APTT measurements every 12 hours aiming for a relatively low APTTR between 1.5 and 2.0. There is a small risk of thrombocytopenia with the use of intravenous heparin (~1%) and platelet levels were therefore monitored closely. Low molecular weight heparin is rarely associated with thrombocytopenia, but this was not considered an appropriate option due to the lack of any robust data in patients with mechanical valves and the lack of effective monitoring.

Following discussion with the neurosurgical team we repeated his CT brain scan after two weeks, which demonstrated resolution of the haematoma. Together with his symptomatic improvement, we therefore recommenced warfarin with a target INR of 2 to 3. The lower range was chosen after discussion with the cardiothoracic surgeons who agreed that, in the clinical situation described, this would be a reasonable target INR for his CarboMedics© valve. These newer types of valves have lower reported rates of thromboembolism than some older types of mechanical valves.[8] We did not feel that antiplatelet therapy with aspirin, dipyridamole or clopidogrel would provide adequate prophylaxis against thromboembolism on their own. One option would have been to add low-dose aspirin and aim for a lower target INR,[8,18] but we felt that the risks of bleeding would be too great with combined therapy.

In view of the lack of data regarding patients with mechanical heart valves and ICH, each case must be assessed on an individual basis. We would recommend a multi-disciplinary team approach involving haematologists, neurosurgeons, neurologists, cardiothoracic surgeons and cardiologists. The risks of further haemorrhage need to be weighed against those of thromboembolism. Large-scale randomised-controlled trials are probably impossible in these patients due to the small numbers involved and the numerous variables in each case. However, a prospective national or international registry would be one useful way to assess outcome and help us manage our patients in the future

Conflict of interest
None declared.

Key messages

- Patients with mechanical heart valve prosthesis require oral anticoagulation to reduce the risk of thromboembolic events, but this can be complicated by anticoagulant-associated intracerebral haemorrhage (ICH)
- Active bleeding into the brain occurs mostly within the first 24 hours after symptom onset. It is therefore imperative to confirm the diagnosis with urgent imaging and reverse the anticoagulation defect promptly
- In order to make appropriate decisions regarding the resumption of anticoagulation in patients with mechanical heart valves and ICH, the risks of recurrent bleeding must be balanced against those of thromboembolic events
- The absolute risk of anticoagulation-related ICH is between 0.3 and 1% a year. There is very limited information available regarding the rate of recurrent bleeding in patients with anticoagulant-associated ICH
- In the absence of anticoagulation, the estimated annual risk of prosthetic valve thrombosis is ~1.7% and the risk of a major embolic event is ~4% in pooled patients. Mitral valves have a fivefold increase in the risk of valve thrombosis and 1.5-fold increase in the risk of major embolism when compared to aortic valves

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