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Anticoagulation Therapy Following Embolic or Hemorrhagic Stroke in the Patient with a Mechanical Heart Valve

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Abstract

Background: An estimated 95,000 heart valve replacements are performed annually in the United States. Prosthetic valves may be either mechanical or bioprosthetic in composition. Mechanical valves offer added durability but commit the patient to taking lifelong anticoagulant therapy. Maintaining therapeutic levels of anticoagulation may be challenging, and inadequate anticoagulation can lead to thromboembolic or hemorrhagic complications. When a patient with a mechanical valve suffers a stroke, management of anticoagulation becomes more controversial and complicated. This article reviews the available evidence and guidelines for management of systemic anticoagulation following stroke in patients with mechanical heart valves.

Methods: A review of the PubMed database for pertinent articles, using the keywords "mechanical heart valve", "anticoagulation", "cerebrovascular accident", and "stroke". The clinical guidelines offered by the American College of Cardiology, American Heart Association, and American Stroke Association were also reviewed.

Results: There are no definitive guidelines for the management of patients with mechanical heart valves who suffer a stroke. Most of the data is from small case series and retrospective reviews.

Conclusion: Based on the available data, anticoagulation should be resumed rapidly following thromboembolic stroke in patients with a mechanical heart valve, once the risk of hemorrhagic transformation has declined. In the setting of a hemorrhagic stroke, it also appears safe to resume anticoagulation relatively rapidly (after approximately one week), although the risks of further bleeding must be considered. In either case, holding anticoagulation after a stroke for a few days does not expose the patient to significantly increased risk of acute thrombosis.

Keywords: Mechanical heart valve; Stroke; Cerebrovascular accident; Anticoagulation; Warfarin

An estimated 95,000 cardiac valve surgeries are performed each year in the United States [1], the majority of which are for mitral or aortic valve disease. In most cases the choice of prosthetic valve is between the mechanical or bioprosthetic types. While a number of factors must be considered in choosing the type of valve to place, the need for anticoagulation with mechanical valves weighs heavily on this decision. Mechanical valves provide durability while necessitating life long anticoagulation, while bioprosthetic valves are more subject to structural deterioration [2], but spare the need for blood thinning drugs.

Warfarin is the mainstay for anticoagulation in patients with a mechanical heart valve. While warfarin is effective in reducing the risk of valve thrombosis and thromboembolism, it requires frequent blood tests for monitoring and strict patient compliance to be effective. Warfarin therapy is monitored and titrated based on the patient's prothrombin time (PT) and international normalized ratio (INR).

According to the American College of Cardiology and American Heart Association 2008 Update to the 2006 Guidelines for the Management of Patients with Valvular Heart Disease [3], the target INR varies depending on the position of the mechanical valve and individual patient risk factors for stroke. In the aortic position the target INR for a mechanical valve ranges between 2.0 and 3.5 depending on the exact specifications of the valve, while mechanical mitral valves are at greater risk for thrombosis and all require a higher target INR in the 2.5- 3.5 range.

The risk associated with inadequate (either under or over anticoagulation) warfarin therapy is significant. Numerous studies have evaluated the risk of stroke or hemorrhage in patients taking warfarin for AF. In a recent prospective study evaluating warfarin for primary prevention in over 3000 patients with AF, the rates of bleeding and thrombotic events during follow-up were 1.24 and 0.76 per 100 patients-yrs, respectively [4]. Studies evaluating mechanical valve thrombosis have identified inadequate anticoagulation, valve endocarditis, and the type of valve employed as risk factors. Prosthetic valve occlusion has been estimated to occur in 1- 13 percent of cases [5]. In a retrospective review over 23 years, evaluating 6700 patients with prosthetic valves (5610 mechanical and 1090 bioprosthetic valves), the mean time interval between valve placement and thrombosis was 8.4 years [6].

Cerebrovascular accidents (CVA) in patients with prosthetic valves may be hemorrhagic or athroembolic in nature, and may be unrelated to the valve entirely. In a prospective study of 89 patients presenting with CVA more than 90 days following mechanical valve placement, 77.5 percent of patients experienced cerebral hemorrhage, 17 percent embolic stroke, and eight percent were non-embolic lacunar infarcts [7]. In a retrospective study of patients with mechanical heart valves

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between 1970 and 1992, Cannegieter and colleagues observed an incidence of major embolism in 4 per 100 patient- years in those not receiving anticoagulation therapy [8]. Antiplatelet therapy and warfarin reduced this risk to 2.2 per 100 patient- years and 1 per 100 patient-years, respectively. The incidence of major bleeding complications in patients on warfarin was 1.4 per 100 patient-years, and this risk was further increased by the combined use of warfarin and antiplatelet therapy. In a retrospective review of patients with mechanical heart valves visiting an anticoagulation clinic for warfarin dose management, Torn and colleagues observed an incidence of untoward event (defined as major thromboembolism or hemorrhage) as 4.3 percent for patients with mechanical heart valves [9]. They concluded that the optimal level of anticoagulation for this patient population was an INR of 2.5 – 2.9.

Mechanical valves are more commonly placed in younger patients who do not want to have to undergo a second valve replacement later in life due to structural degeneration of a tissue valve over time. In exchange for this added valvular durability, anticoagulation is almost always prescribed with mechanical valves. The data suggests an incidence of major embolism of 4 per 100 patient- years in those not taking anticoagulation therapy [8]. While warfarin may reduce this risk substantially, it increases the risk of hemorrhage. Both embolic and hemorrhagic strokes may be serious complications for any patient, but may be particularly devastating to a young patient in the prime of their working years. Following placement of a mechanical valve, anticoagulation represents the standard of care. However, if a patient with a preexisting mechanical valve suffers a stroke, management of anticoagulation may become particularly complicated. In this case, the decision for future anticoagulation must carefully weigh the risks and benefits from both the points of view of a mechanical valve and a cerebral infarction. What may be good for the heart may not be tolerable for the brain, and vice versa.

Prosthetic valve thrombosis leading to an embolic, ischemic CVA may be managed according to the guidelines presented by the American Heart Association and American Stroke Association [10]. These guidelines call for the use of recombinant intravenous tissue plasminogen activator (rtPA) in patients presenting within three hours of stroke, and intra-arterial thrombolytics in those presenting within six hours of stroke within the middle cerebral artery and who are not otherwise candidates for intravenous rtPA. Heparin is not indicated within the first 24 hours after stroke, while aspirin is recommended after 24- 48 hours [10].

Judicious implementation of these guidelines is important in the immediate postoperative period. While the risk of thromboembolism is elevated in the first six months following valve placement [11], acute thrombosis in the days following surgery is uncommon. The period of time following cardiac surgery after which the use of thrombolytics is safe is not clearly defined, and careful consideration of the risks of bleeding at the surgical site is important. In the setting of an acute stroke in the immediate postoperative period, the benefits of intravenous or intra-arterial rtPA may outweigh the risk of bleeding in the chest. Tamponade or bleeding at a suture line can usually be treated surgically, while the effects of an ischemic stroke are largely permanent. The cerebral risks of thrombolytics must also be considered, with a hemorrhagic transformation rate between 10- 30 percent when acute ischemic strokes are treated with rtPA [12]. The risk of hemorrhagic transformation is highest in the days following stroke onset.

There are no clear guidelines as to when to reinitiate anticoagulation in the patient with a mechanical valve who experiences an ischemic stroke. In general, particularly for a mechanical valve in the mitral position, anticoagulation should be restarted as soon as the risk of cerebral bleeding has declined to an acceptable level. This will depend on the size and distribution of the stroke, and consultation with a neurologist is recommended.

In patients who suffer a stroke while taking warfarin to reduce the risk of thromboembolism from a mechanical valve, the majority of these are hemorrhagic in nature [6]. As described above, difficulty maintaining therapeutic levels of warfarin may be challenging for a large number of patients. In the case of a hemorrhagic stroke, determining when to reintroduce anticoagulation may be particularly challenging. There are numerous case reports of patients with mechanical valves on anticoagulation who subsequently experience cerebral hemorrhage. In a series of 35 patients with oral anticoagulant related intracerebral or intraspinal hemorrhage (16 patients were taking anticoagulants for a prosthetic heart valve), Butler and colleagues did not observe the development of any valve thrombosis when anticoagulant was held and the INR fell below 2 (some of these patients were treated with heparin but this rarely reached therapeutic levels) [13]. Based on estimates of the annual incidence, the risk of thromboembolism in a patient with a mechanical heart valve off anticoagulation for seven days is between 1/240 and 1/1300 [13].

In a patient with a life threatening hemorrhage related to anticoagulation, the immediate concern is controlling the bleeding. As noted above, the literature supports temporarily discontinuing anticoagulation with minimal risk of acute thromboembolism related to a mechanical heart valve. Ultimately, the decision as to whether to resume anticoagulation must be addressed. The longer the period without anticoagulation in a patient with a mechanical valve, the greater the risk of thrombus development. However, reinitiating anticoagulation exposes the risk of further bleeding or hematoma expansion.

Babikian and colleagues reported a series of six patients with prosthetic heart valves who all experienced intracranial bleeding while on anticoagulation [14]. Anticoagulation was resumed an average of 19 days after the initial bleeding diagnosis. No thrombotic complications were observed during the time off anticoagulation, and no further bleeding episodes were noted over the subsequent six month observation period. Based on their experience treating patients with cerebral hemorrhage and mechanical heart valves, Lau and

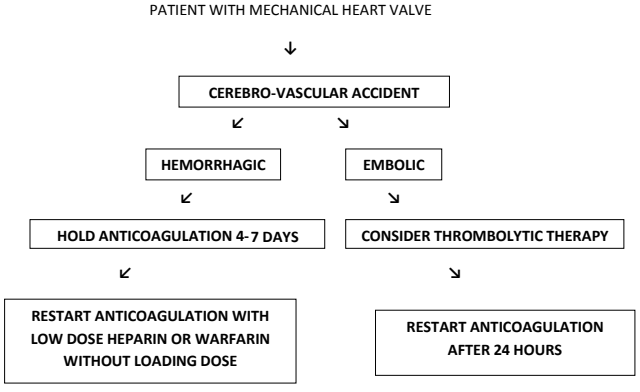

Figure 1: Management algorithm for the patient with a mechanical heart valve who experiences a cerebro-vascular accident.

colleagues recommend reinstituting anticoagulation within 4-7 days after hemorrhage, as long as the patient is clinically and radiologically stable [15]. They recommend initially considering heparin or warfarin without a loading dose to decrease the likelihood of further bleeding. In a review of six observational cohort studies of patients with intracranial hemorrhage and mechanical heart valves (all of which were low quality according to the authors), Romualdi and colleagues concluded that both holding anticoagulation for a few days (7-14) and subsequently restarting it are safe [16].

Mechanical heart valves have the benefit of durability compared to bioprosthetic valves, but have the disadvantage of requiring life long anticoagulation. The difficulty of maintaining a therapeutic level of warfarin (the most common anticoagulant used for patients with mechanical valves), may lead to complications of both excessive and under anticoagulation. The literature clearly demonstrates that hemorrhagic complications are more common than thrombotic ones. When a patient with a mechanical valve suffers a cerebral infarction, either thromboembolic or hemorrhagic in origin, the management of anticoagulation for the valve becomes particularly challenging.

While there is a dearth of quality studies specifically addressing anticoagulation for mechanical valves following stroke, the available data seems to suggest that following intracerebral hemorrhage, there is minimal risk associated with holding anticoagulation for several days (up to two weeks), and subsequently restarting warfarin. In the case of thromboembolic stroke, the risk of hemorrhagic transformation is highest in the first few days following the event and decreases there after. In these cases, once the patient is out of the high risk window for hemorrhagic conversion, it may be prudent to take a more aggressive approach to anticoagulation to ensure there are no further thrombotic events (Figure 1).

While further research to identify blood thinners that are easy to titrate and, perhaps, have the ability to maintain a higher therapeutic concentration around the mechanical valve would be useful, even better would be the development of a mechanical valve that was not thrombogenic and did not require anticoagulation. While efforts to create such a valve have thus far failed, such a technological advance has the potential to revolutionize the postoperative management of patients with mechanical valves.

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