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ADENOSINE-INDUCED TRANSIENT ASYSTOLE

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Abstract

Cerebral aneurysms are an important health issue in the United States, and the mortality rate following aneurysm rupture, or SAH, remains high. The treatment of these aneurysms uses endovascular options which include coil placement, stent assistant coiling and, recently, flow diversion. However, microsurgical clipping remains an option in those aneurysms not suited for endovascular therapy. These are often the more complicated aneurysms such as in large, giant aneurysms or deep-seated aneurysms. Circumferential visualization of the aneurysm, parent vessels, branches, perforators, and other neurovascular structures is important to prevent residual aneurysms or strokes from vessel or perforator occlusion. Decompression of the aneurysm sac is often required and we believe that adenosine-induced transient asystole should be an important option for clipping of complex cerebral aneurysms.

Introduction

Cerebral aneurysms are an important health issue in the United States, and it is estimated that approximately 5% to 15% of all stroke cases are due to ruptured saccular aneurysms.[1] Although cerebral aneurysms can present with other symptoms related to their mass effect, such as cranial nerve palsies, the most significant sequelae are related to subarachnoid (SAH) secondary to aneurysm rupture. The mortality rate following aneurysm rupture, or SAH, remains at 20% to 40%, and up to 50% of those who survive are left disabled.[2-4] Poor outcome is largely related to the effects of the hemorrhage; therefore, preventing rehemorrhage in ruptured aneurysms and initial hemorrhage in unruptured aneurysms is the primary strategy for lowering mortality. This can only be achieved by successfully excluding the aneurysm from the circulation, which can be accomplished with either open microsurgical or endovascular treatment strategies.

This review explores the benefits and risks of endovascular versus surgical treatment of aneurysms, with a specific focus on microsurgical clipping using adenosine-induced flow arrest as a viable option for patients who are not candidates for endovascular therapy.

Comparison of Endovascular Occlusion and Microsurgical Exclusion

Endovascular occlusion of cerebral aneurysms is appealing for its lower approach-associated morbidity; it also has shown to be safer than clipping. However, the primary goal of treatment is to exclude the aneurysm from the circulation and prevent hemorrhage or rehemorrhage in unruptured and ruptured aneurysms, respectively. When comparing endovascular treatment with surgical occlusion for complete obliteration of aneurysms, the efficacy of endovascular aneurysm occlusion appears less optimal.

Aneurysm treatment using endovascular occlusion compared to microsurgical exclusion is quite different, and this difference may have significant implications for residual aneurysms after treatment. In the clipped aneurysm residua, the walls are closely apposed and the remaining aneurysm is completely excluded from the circulation. With endovascular techniques, however, coils keep the remnant's walls apart. Moreover, although experimental models of coiled aneurysms demonstrate that the aneurysm neck becomes entirely occluded by organized thrombus and that the free luminal surface is covered by endothelium, endothelialization is not observed in coiled aneurysms immediately after treatment and has been absent in some cases obtained at autopsy or when viewed later at the time of surgery.[5] These factors mean that any intra-aneurysmal thrombus or coil is exposed to circulating blood, which may allow compaction of the coils or flow around the coil's periphery into the aneurysm sac. This "efficacy" has been an important factor in favor of microsurgical clipping, since clipping results in more durable outcomes in both the short- and long-term.

Most series report a 92% to 96% exclusion rate of the aneurysm from the circulation with microsurgical clipping, as confirmed by postoperative angiography.[6-8] This efficacy is preserved with a 0.5% rate of recurrence per year in completely clipped aneurysms.[6] Most importantly, microsurgical clipping significantly changes the natural history of the disease. Over a 4.4-year follow-up period of patients with ruptured aneurysms, David and colleagues reported a 0% incidence of rebleeding in 147 aneurysms that had been completely clipped.[6] Twelve (8.2%) of the 147 aneurysms had a residual neck, and these were divided into two groups: *dog ear* residua and *broad-based* residua. Patients with the dog-ear type had a 1.9% annual risk of recurrent hemorrhage, and patients with the broad-based type had no recurrent hemorrhage although they had significant regrowth. Combined, these residuals had a recurrent bleeding rate of 1.5% per year in the 8.2% of aneurysms with residual necks after clipping.[6] The impact of microsurgical clipping in altering the natural history has also been found in unruptured intracranial aneurysms (UIAs).

With respect to endovascular coiling, most series report 40% to 55% complete exclusion, 35.4% to 52% near-complete exclusion,

and 3.5% to 8% incomplete exclusion of the aneurysms from the circulation.[9,10] The Cerebral Aneurysm Re-rupture After Treatment (CARAT) study found a rate of rupture after treatment to be 1.8%, which is comparable to the 1.7% rerupture rate reported earlier in the International Subarachnoid Aneurysm Treatment study.[11] Recently, their subtotal occlusion cohort study of 1,010 patients treated with coil embolization or surgical clipping found that degree of occlusion was associated with a lower risk of rerupture. Cumulative risk over a 9-year period was 1.1% for complete occlusion, 2.9% for 91% to 99% occlusion, 59% for 70% to 90% occlusion, and 17.6% for < 70% occlusion, with a higher rate of subtotal occlusion occurring in coiled aneurysms. Risk of rerupture was greater in those aneurysms that were coiled versus clipped in univariate analysis (cumulative hazard 3.4% versus 1.3%; $P <$ 0.09). However, the difference did not persist after adjusting for degree of aneurysm occlusion and other potential confounders (HR 1.09; 95% CI, 0.32 to 3.69; $P < 0.89$). The only characteristic that independently predicted rerupture was peripheral vascular disease ($P < 0.034$).

The long-term durability of endovascular coiling is concerning, with rates of recanalization reported to range from 0.6% to 28%.[10-12] This recanalization, however, was found to be associated with larger aneurysms and those with a poor dome-to-neck ratio.[10] Despite the fact that microsurgical clipping provides a far superior anatomic cure compared to endovascular coiling, coiling has been shown to be effective in changing the natural history of unruptured and ruptured aneurysms as well. Therefore, complete anatomic cure is not required to change the natural history of cerebral aneurysms. In the report by Kuether et al. on 74 patients with 77 aneurysms, including both ruptured and unruptured aneurysms, the authors had no reported hemorrhage over a follow-up period of 1.9 years in those aneurysms that demonstrated complete exclusion.[9] In those with near-complete occlusion, a hemorrhage rate of 1.4% per year was found in the same follow-up period.[9] In a meta-analyses on the treatment of UIAs in 1,379 patients, Lanterna et al. found a total of 13 nonprocedural bleeding events occurring in 703 eligible patients during an average follow-up time of 0.5 to 3.8 years.[13] The overall annual bleeding rate was 0.9% per year, and, importantly, only partially occluded UIAs of 10 mm or more hemorrhaged. Specifically, the bleeding rate of the UIAs larger than 10 mm was 3.5% per year.[13] Therefore, although endovascular treatment does change the natural history of a cerebral aneurysm, it can be considered inferior to clipping with regard to complete occlusion.

Therefore, despite the fact that intracranial aneurysm treatment has evolved over the last 10 years and despite advances in endovascular techniques, microsurgical clipping remains an important treatment option for those patients who are not ideal candidates for endovascular therapy. This is particularly true for wide-necked, blister-like, large and giant, and complex cerebral aneurysms.

Challenges of Microsurgical Clipping

Microsurgery and clip ligation can be challenging in large, giant aneurysms or deep-seated aneurysms as circumferential visualization of the aneurysm, parent vessels, branches, perforators, and other neurovascular structures is important to prevent residual aneurysms or strokes from vessel or perforator occlusion. Decompression of the aneurysm sac is often required for large aneurysms and can be accomplished with several techniques, including temporary parent vessel occlusion, intraoperative adenosine-induced transient asystole,[14,15] deep hypothermia with circulatory arrest,[16-18] and rapid ventricular pacing for flow arrest.[19] Temporary parent vessel occlusion can potentially injure the vessel and cause dissection or stroke from ischemia. Furthermore, it is not feasible in deep areas or areas in close proximity to the skull base, where paraclinoid, basilar apex, and certain anterior and posterior communicating aneurysms would cause additional space limitations. Deep hypothermia with circulatory arrest, which is ideal for providing cerebral protection during surgery, is associated with significant complications such as coagulopathy, and overall complication rates are in the range of 40% to 80%.[18] Rapid ventricular pacing for flow arrest is another good option, albeit more complicated, and perforation of the atrium has been reported. We believe that adenosine-induced transient asystole should be the first option for clipping of complex cerebral aneurysms.

Adenosine-Induced Transient Asystole

Adenosine-induced asystole for cerebral aneurysms surgery was first described by Groff et al.[14] in 1999 in posterior circulation aneurysms. Adenosine is an endogenous nucleoside analog that alters electrical conduction at the atrioventricular (AV) node and has a negative chronotropic effect on the sinoatrial node. Adenosine acts on cardiac A1 receptors to reduce cyclic adenosine monophosphate activity, which decreases inward calcium conductance and diminishes pacemaker current, resulting in bradycardia, AV nodal blockade, and sinus pauses. It has a very short half-life time (less than 10 seconds) and is rapidly taken up by the vascular endothelium and erythrocytes. The effect on heart rate is seen within 10 to 20 seconds after administration, with the duration of asystole reaching a plateau between 40 to 60 seconds at 1 mg/kg. There is a relative hypotension period of 1 minute after asystole.

Multiple doses are usually required for very large and complex aneurysms to obtain repeated episodes of asystole; however, there is limited data to assist in the selection of an appropriate initial dose. Hashimoto et al. presented dose-response data for patients undergoing embolization of arteriovenous malformations.[20] They recommended establishing an individual dose-response relationship for each patient by injecting escalating doses of adenosine separated by an interval of 3 to 10 minutes. Bebawy et al. recommended an initial dose of between 0.3 and 0.4 mg/kg ideal body weight (IBW) as the starting dose to achieve approximately 45 seconds of profound systemic hypotension.[21] Powers et al. gave between 2 and 5 escalating doses during aneurysm clipping, repeating the dose as often as every 1 to 2 minutes.[22] The standard initial dose of 6 mg was used on all patients and escalated to 6 mg more than the previous dose (e.g., 6 mg, 12 mg, 18 mg, 24 mg) until 30 to 40 seconds of asystole was reached.

Very few case series have described the use of adenosine in intracranial aneurysm surgery. Luostarien et al. reported the first series of 16 patients demonstrating its safety and efficacy during surgery for ruptured intracranial aneurysm.[23] Of these 16 patients, 12 received a single adenosine bolus and 4 received repeated boluses. The median dose for a single bolus was 12 (6-18) mg, whereas the median total dose for multiple boluses was 27 (18-89) mg. Ten minutes after adenosine administration, all patients were hemodynamically stable, and 13 patients required vasoactive drugs during the procedure. Bebawy et al. reported the second series of 24 patients using adenosine to facilitate surgery for intracranial aneurysms, a large number of which were internal carotid artery aneurysms with difficult anatomy for temporary

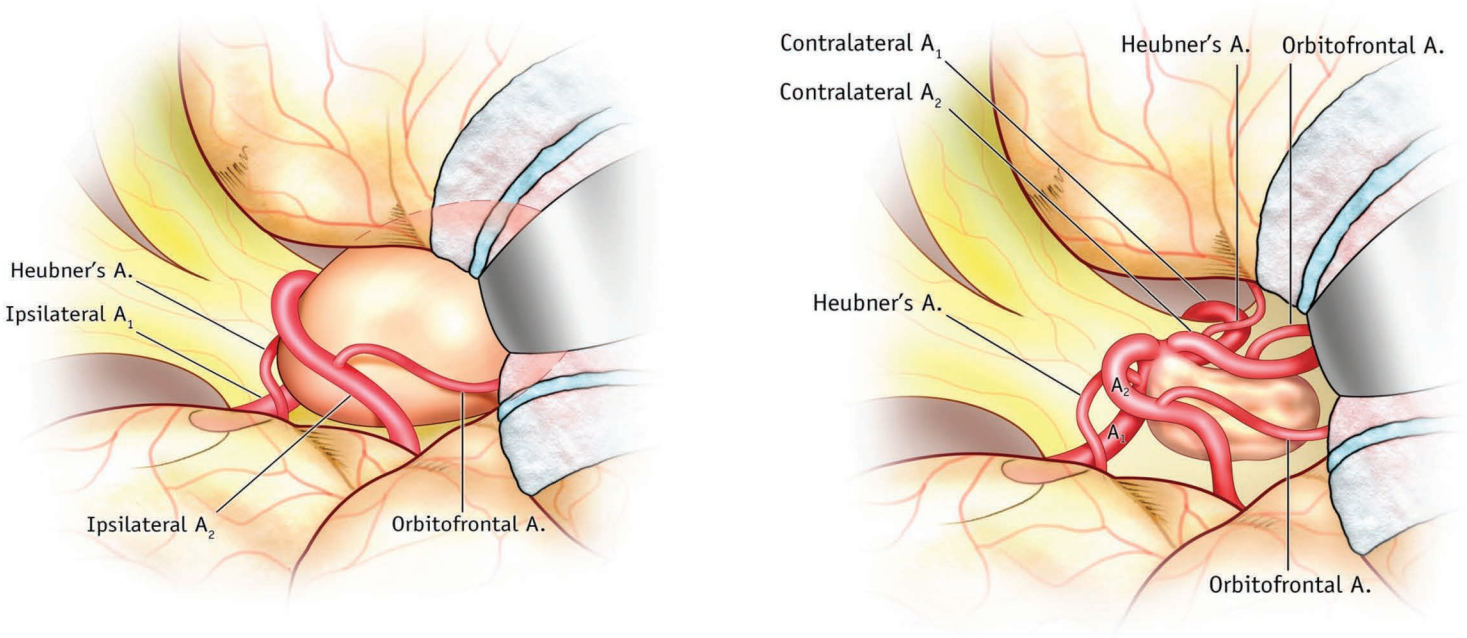

Figure 1. Schematic representation of an anterior communicating artery aneurysm. On the left (pre-adenosine), the large mass does not allow circumferential visualization of the aneurysm, branches, and perforators. On the right (post-adenosine), the aneurysm is now collapsed and the surgeon can identify all the major and important branches and perforators.

clip.[21] Only two patients developed transient but hemodynamically stable atrial fibrillation on recovery from adenosine; one converted to sinus rhythm spontaneously and the other required treatment with amiodarone. No patient had any pulmonary side effects. The third case series, reported by Guinn et al.,[15] included 27 patients whose aneurysms were primarily in the anterior circulation and whose surgeries where primarily elective. The individual adenosine dose range was 3 to 60 mg, and the total dose range was 3 to 285 mg. They demonstrated adenosine's effectiveness in decompressing intracranial aneurysms, thereby facilitating exposure and clip ligation in cases when temporary clipping is not feasible. Of the 27 patients, one had prolonged extreme hypotension after rapid redosing due to intraoperative aneurysm rupture, requiring closed chest compression and pressors; spontaneous restoration of circulation occurred after 3 minutes.

Advantages of Adenosine-induced Transient Asystole

Adenosine-induced flow arrest briefly reduces cerebral perfusion pressure and reduces the turgor of the aneurysm, thereby facilitating the clip ligation (Figure 1). Periods of flow arrest have to be carefully coordinated with the surgeon such that necessary working time is available for aneurysm dissection and clip placement. Adenosine-induced transient asystole is safe and efficacious when administered at an average of 0.3 to 0.4 mg/kg IBW in combination with remifentanil/low-dose volatile anesthetic with propofol. The adenosine dose will achieve approximately 45 seconds of controlled systemic hypotension and a bloodless surgical field. Adenosine offers the advantage of easy applicability in different situations without advanced preparation or complex logistical coordination with anesthesiology and cardiovascular surgery. This technique also allows the surgeon to have the maximum amount of space available to manipulate the aneurysm and place the clips, as no temporary clips are in the field of view. Also, temporary clips only decrease flow from the clipped inflow, whereas adenosine produces a more global hypotension and therefore often a better collapse of the aneurysm.

Disadvantages, Complications, and Contraindications of Adenosine-Induced Transient Asystole

Adenosine vasodilates healthy coronary arteries but not atherosclerotic vessels, therefore patients with coronary artery disease may have a relative contraindication to adenosine therapy. Post-adenosine arrhythmias and troponin 1 elevation have been reported with an incidence of less than 1%. Adenosine is also a potent systematic vasodilator, and the major complications encountered have been persistent hypotension, sometimes requiring chest compression and vasopressor boluses. External defibrillator pads are recommended for all patients who receive adenosine to provide external pacing if prolonged bradycardia or asystole were to develop or cardioversion in case of hemodynamically unstable atrial fibrillation. In addition, adenosine can cause bronchoconstriction and therefore may be contraindicated for patients with asthma or chronic obstructive pulmonary disease.[14,15,20-23]

Conclusion

Despite the fact that an open craniotomy and clipping of a cerebral aneurysm is now the second line of therapy, clipping remains a viable option in certain aneurysms. Adenosine-induced flow arrest reduces cerebral perfusion pressure briefly and reduces the turgor of the aneurysm, which facilitates circumferential exposure of the aneurysm and therefore a safer and more effective clip ligation. This technique therefore should be part of the armamentarium of the microvascular neurosurgeon.

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