Adenosine-induced Transient Asystole for Intracranial Aneurysm Surgery

A Retrospective Review

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Brief Summary: We describe the use of adenosine-induced cardiac arrest to facilitate intracranial aneurysm clip ligation.

Background: Cerebral aneurysms are highly variable which may result in difficult surgical exposure for clip ligation in select cases. Secure clip placement is often not feasible without temporarily decompressing the aneurysm. This can be accomplished with temporary clip ligation of proximal vessels, or with deep hypothermic circulatory arrest on cardiopulmonary bypass, although these methods have their own inherent risks. Here we describe an alternate method of decompressing the aneurysm via adenosine-induced transient asystole.

Methods: We examined the records of 27 patients who underwent craniotomy for cerebral aneurysm clipping in which adenosine was used to induce transient asystole to facilitate clip ligation. Duration of adenosine-induced bradycardia (heart rate < 40) and hypotension (SBP < 60) recorded on the electronic anesthesia record and outcome data including incidence of successful clipping, intraoperative and postoperative complications, and mortality were recorded.

Results: Satisfactory aneurysm decompression was achieved in all cases, and all aneurysms were clipped successfully. The median dose of intravenous adenosine resulting in bradycardia greater than 30 seconds was 30 mg. The median dose of adenosine resulting in hypotension greater than 30 seconds was 15 mg, and greater than 60 seconds was 30 mg. One case of prolonged hypotension after rapid redosing of adenosine required brief closed chest compressions before circulation was spontaneously restored. No other adverse events were observed.

Conclusions: Adenosine cardiac arrest is a relatively novel method for decompression of intracranial aneurysms to facilitate clip application. With appropriate safety precautions, it is a reasonable alternative method when temporary clipping of proximal vessels is not desirable or not possible.

Key Words: neuroanesthesia, cerebral aneurysm, subarachnoid hemorrhage, adenosine arrest, asystole

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Treatment of intracranial aneurysms currently involves endovascular therapy (ie, coil embolization) or craniotomy with clip ligation. Clip ligation can be difficult, particularly in larger aneurysms, as one has to visualize the aneurysm circumferentially. This includes visualization of the surrounding structures, the parent vessel, branches, and important perforators. The larger size in small working surgical corridors can make clip ligation challenging. To provide adequate visualization and access to the neck of large or technically challenging aneurysms, decompression of the aneurysm sac is often necessary. Traditionally this has been accomplished through occlusion of proximal vessels with temporary surgical clips. However, temporary clipping may be injurious to the vessel, resulting in stroke, dissection, or even rupture.[1,2] Furthermore, the surgical approach and exposure may preclude temporary clip placement. When the surgical corridor is narrow, such as with large aneurysms or deep aneurysms that are close to the skull base, the temporary clip makes the available space for dissection and visualization even smaller.[2,3] Deep hypothermic circulatory arrest with cardiopulmonary bypass has also been used to facilitate collapse of the aneurysm sac and improve visualization, however, this is highly invasive and complications related to the prolonged hypotension and hypothermia can be significant.[4]

Adenosine, with its rapid onset and short half-life, provides a transient asystole that allows for decompression of the aneurysm sac and improved visualization, without the effects of prolonged hypotension.[5] It is particularly useful when the surgical space is limited, preventing the use of a temporary clip, such as in paraclinoid basilar apex and some anterior and posterior communicating artery aneurysms that are in close proximity to the skull base.[3,5] Adenosine has been used

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intraoperatively to facilitate certain vascular procedures, such as endovascular thoracic and abdominal aortic aneurysm stenting[6,7] and embolization of cerebral arteriovenous malformations.[8] However, there is very little literature on the use of adenosine-induced asystole to facilitate cerebral aneurysm clip ligation surgery. Until recently there were only 3 single patient case reports,[5,9,10] and one case series of 16 patients using adenosine during intraoperative cerebral aneurysm rupture.[11] In May 2010, Bebawy et al[12] reported the use of adenosine-induced asystole for intracranial aneurysm surgery in 24 patients.

We conducted a retrospective chart review of 27 patients in which we electively used adenosine to induce transient asystole and circulatory arrest to facilitate intracranial aneurysm clipping. Here we describe anesthetic management, complications, and patient outcomes. We also provide a suggested adenosine dose range for transient asystole to facilitate cerebral aneurysm surgery.

METHODS

With Duke University School of Medicine Institutional Review Board approval and waiver of written informed consent, case records were reviewed for all patients undergoing craniotomy for clip ligation of intracranial aneurysms by 2 neurosurgeons (G.W.B. and A.R.Z.) over a 2-years period (January 2008 to December 2009) at Duke University Medical Center. Out of 128 intracranial aneurysm clip ligation surgeries, 27 patients were identified as having received intraoperative adenosine to facilitate aneurysm clip ligation. Demographic data including sex, race, age, height, and weight were obtained, as well as relevant comorbidities, such as prior cardiac history, coronary artery disease, conduction abnormalities, and reactive airway disease. Cases were noted to be elective or emergent after recent subarachnoid hemorrhage. Size and location of aneurysms were recorded. Individual and total doses of adenosine were calculated. The electronic intraoperative records (Innovian Anesthesia Information Management System, Draeger Medical Inc, Telford, PA) collect data continuously but only store data points for heart rate and blood pressure averaged over 30 second epochs. For each adenosine dose, we determined the number of 30 second epochs of bradycardia (defined as heart rate < 40/min by electrocardiography) and hypotension (defined as systolic blood pressure < 60 mm Hg by arterial line). Intraoperative and postoperative complications, length of hospital stay, and modified Rankin scale on discharge were noted.

The general anesthetic management was as follows: intravenous midazolam premedication was titrated to anxiolysis. Induction was accomplished with intravenous lidocaine (1 mg/kg), propofol (1 to 2 mg/kg), fentanyl (2 to 3 μg/kg), and vecuronium (0.1 mg/kg) or rocuronium (0.5 to 0.7 mg/kg) with careful avoidance of hypertension. An arterial line was placed. After endotracheal intubation, a jugular or subclavian central venous line was placed and a bladder catheter. Transcutaneous cardiac pacing pads were placed as a precautionary measure in preparation for adenosine cardiac arrest. Most patients received lumbar drain placement. Maintenance anesthesia was accomplished with inhaled isoflurane or sevoflurane and intravenous remifentanil infusion. Intravenous nicardipine infusion was used for control of hypertension not remedied with anesthetic agents. No active cooling was performed. Mannitol 1 gm/kg (20% wt/vol) was used to control brain bulk. Patients were kept normocapneic ($PaCO_2$ < 40 mm Hg) or hypocapneic ($PaCO_2$ 25 to 30 mm Hg) as needed to provide further brain relaxation. All patients were monitored with a BIS (Aspect Medical Systems, Norwood, MA) depth of anesthesia monitor. If burst suppression was desired, propofol was administered and titrated to a flat line electroencephalogram, or burst suppression ratio of approximately 1:10. Mean arterial pressure was maintained with phenylephrine infusion.

Adenosine Cardiac Arrest

The neurosurgical team decided that adenosine cardiac arrest was necessary when temporary clip application did not seem feasible based on the surgical approach. This was due to large aneurysms and deep aneurysms where the surgical corridor was small and a temporary clip would have further limited available space for visualization and dissection. When it was determined that adenosine cardiac arrest was needed to facilitate aneurysm clipping, the anesthesiologist performed a dose-titration exercise. Adenosine was given as a rapid intravenous bolus in escalating doses starting with 6 mg (typically 6-12 to 18-24 mg) and plotted against the duration of asystole after each bolus to determine the approximate dose necessary to achieve 30 seconds of asystole. Full recovery between each bolus was allowed before further dose escalation. All adenosine boluses were followed by a saline flush and were given through the central line. When requested by the surgeon, the estimated dose of adenosine required for definitive clipping of the aneurysm was administered. Thereafter, that defined adenosine dose was given as many times as necessary throughout the procedure to facilitate dissection around the aneurysm, identification of perforating vessels, visualization of surrounding structures, or clip placement/adjustment.

RESULTS

Twenty-seven patients were identified as having received adenosine during intraoperative cerebral aneur-

TABLE 1. Demographic Characteristic: Presented as Number of Patients (% Total) or Mean ± SD

Sex (male/female)	7 (25.9%)/ 20 (74.1%)
Race (White/African-American)	23 (85.2%)/ 4 (14.8%)
SAH/elective surgery	7 (25.9%)/ 20 (74.1%)
Age (y)	56.9 ± 12.4
Height (cm)	167.6 ± 7.2
Weight (kg)	74.2 ± 12.6
Body mass index	25.5 ± 6.4

SAH indicates subarachnoid hemorrhage.

TABLE 2. Location of the Aneurysms

Internal carotid artery	4 (14.8)
Middle cerebral artery	1 (3.7)
Ophthalmic artery	1 (3.7)
Anterior communicating artery	10 (37.0)
Posterior communicating artery	6 (22.2)
Pericallosal artery	1 (3.7)
Basilar artery	4 (14.8)

ysm clipping (Table 1). About one-quarter of the patients had recent (within 2 wk) subarachnoid hemorrhage, whereas the majority of cases were elective. Twelve patients were smokers, 18 had previously diagnosed hypertension, 2 had cardiac disease, and 3 had pulmonary disease. Four of the aneurysms (15%) were in the posterior circulation and 23 (85%) were in the anterior circulation (Table 2).

The individual adenosine dose range was 3 to 60 mg (median 15 mg) and the total dose range was 3 to 285 mg (median 70 mg). Patients received as few as one dose or as many as 8 individual doses, including the dose escalating exercise to determine dose response. Redosing for clip adjustment or further dissection was carried out in 15 patients. For many doses, the duration of bradycardia (defined as heart rate <40) was <30 seconds and not able to be captured by the electronic medical record (Fig. 1). The median dose of adenosine that provided < 30 seconds of bradycardia was 12 mg (or 0.16 mg/kg). The remainder of the doses resulted in a duration of bradycardia between 30 and 60 seconds (or one epoch), with a median dose of 30 mg (or 0.42 mg/kg).

The median dose of adenosine that resulted in < 30 seconds of hypotension was 12 mg (0.15 mg/kg), the dose that resulted in 30 to 60 seconds of hypotension (1 epoch) was 15 mg (0.24 mg/kg), and the median dose that resulted in 60 to 90 seconds of hypotension (2 epochs) was 30 mg (0.53 mg/kg) (Fig. 2). There was one case of rapid redosing of adenosine that resulted in prolonged hypotension (11 epochs or greater than 5.5 min) in which closed chest compressions had to be initiated; this data point was excluded from the figure.

In this case, there was intraoperative rupture of the aneurysm during manipulations after a dose of adenosine. Owing to the emergent need for further hypotension to facilitate control of the aneurysm, adenosine was redosed at half the initial dose before full recovery of a normal hemodynamic profile. At the same time there was approximately 500 mL cumulative acute blood loss into the surgical field from the uncontrolled vessel that may have contributed to the protracted hypotension to some degree. The patient maintained a cardiac rhythm (sinus tachycardia or normal sinus rhythm) throughout this period of hypotension. Closed chest compressions were initiated owing to the extreme hypotension (essentially pulseless electric activity) and boluses of phenylephrine and low dose epinephrine were given. After approximately 3 minutes, there was spontaneous restoration of circulation and chest compressions were stopped. The remainder of the case was without incident. The aneurysm was successfully clipped and the patient was extubated in the operating room at the end of the case.

Intravenous nicardipine infusion was used intraoperatively for control of hypertension not remedied with anesthetic agents in 14 patients. However, nicardipine was not used in conjunction with adenosine. Nicardipine was most often used at the end of the case to control hypertension associated with lightened anesthesia and emergence, but was also occasionally used for a brief period of time after endotracheal intubation or intermittently throughout the case. There was no report of bronchospasm in any patients in the anesthetic records. ST-segment depression was noted intraoperatively for one patient, but this was before dosing of adenosine, was self-limited, and subsequent cardiac enzymes were all normal. There was one case of intraoperative rupture during dissection before dosing of adenosine (distinct from the case discussed above), but for all other cases

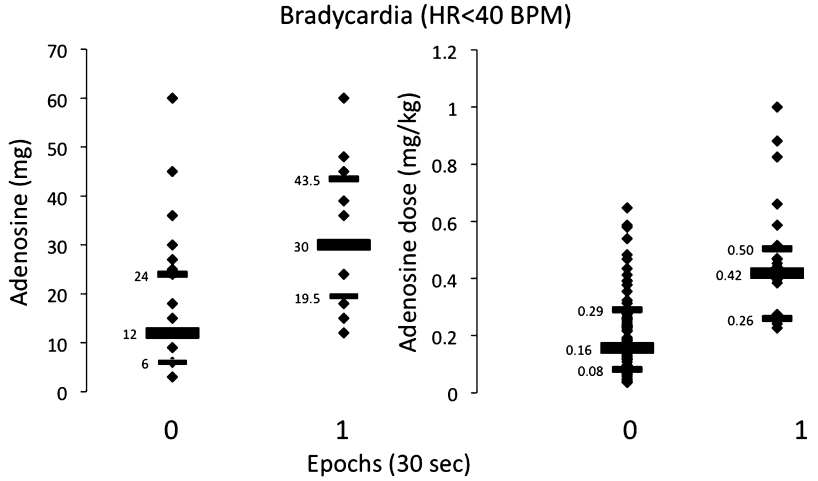

FIGURE 1. Dose of adenosine and resulting duration of bradycardia in mg and mg/kg. The number on the x-axis refers to number of 30 second epochs of bradycardia (0 epochs = <30 s, 1 epoch = 30 to 60 s). Horizontal bars refer to median and interquartile range.

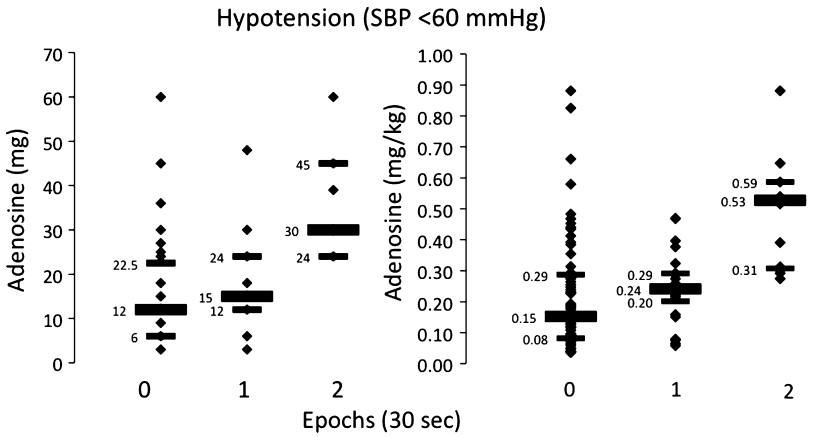

FIGURE 2. Dose of adenosine and resulting duration of hypotension in mg and mg/kg. The number on the x-axis refers to number of 30 second epochs of hypotension (0 epochs = < 30 s, 1 epoch = 30 to 60 s, 2 epochs = 60 to 90 s). Horizontal bars refer to median and interquartile range.

adenosine was administered electively to improve surgical visualization. Temporary clipping was attempted before dosing of adenosine in 5 of the cases, but did not provide adequate exposure, and thus adenosine arrest was employed to improve visualization.

Postoperatively, there was 1 death attributed to vasospasm in a patient with subarachnoid hemorrhage, 1 wound infection, and 2 hematomas that required surgical evacuation. Adenosine therapy resulted in satisfactory operative exposure in every case. All aneurysms were able to be clipped successfully and condition on discharge was generally good as recorded by the modified Rankin Scale (Table 3).

DISCUSSION

Adenosine is an endogenously occurring nucleoside analog that decreases heart rate and prolongs conductance through the sinoatrial and atrioventricular nodes.[13] Adenosine acts on cardiac A1 receptors to reduce cyclic adenosine monophosphate activity, thereby decreasing inward calcium conductance and diminishing pacemaker current.[13] It has a short half-life (<10 s) secondary to rapid reuptake by erythrocytes and vascular endothelial cells and enzymatic breakdown. Adenosine is the drug of choice in treatment of supraventricular tachycardia.[14] The resultant asystole is usually self-limited.

This is only the third case series to our knowledge describing the use of adenosine to facilitate intracranial aneurysm repair. The first series included 16 patients, all with intraoperative aneurysm rupture. In that case series, Luostarien et al[11] reported that 5 of their 16 patients underwent surgery for basilar artery aneurysms. Likewise, 2 of the 3 preexisting single patient case reports describing adenosine for cerebral aneurysm clipping[5,9] were for patients with basilar artery aneurysms, and Luostarien et al[11] believed this may be related to the technically challenging location of these aneurysms. In addition to basilar artery aneurysms, our surgical colleagues feel that paraclinoid, ophthalmic, and some anterior and posterior communicating artery aneurysms close to the skull base have limited surgical corridors that prevent application of a temporary clip.[3] Thus the majority of the aneurysms in our study were in the anterior circulation.

The second case series using adenosine to facilitate intracranial aneurysm surgery included 24 patients.[12] In this report by Bebawy et al,[12] a large number of the aneurysms were intracranial internal carotid artery aneurysms, which they felt also provided a difficult anatomy for temporary clip application based on the close proximity of the carotid bifurcation into the middle and anterior cerebral arteries.

Although all patients experienced some degree of asystole or bradycardia, the hypotension resulting from adenosine administration outlasted the circulatory arrest as the cardiac conductance and rhythm recovered to baseline values. The circulatory arrest softens the aneurysm and allows for better visualization of the neck, particularly in large aneurysms, and dissection of the dome away from surrounding structures. It is both the duration of the hypotension and the relative asystole that is necessary for clip application, with the former being of greatest importance. Although we were limited in our data resolution of bradycardia and hypotension secondary to the restrictions of our electronic medical record, our data suggests a general dose range of 0.24 to 0.42 mg/kg of adenosine to provide about 30 to 60 seconds of hypotension and bradycardia, which generally

TABLE 3. Outcome Data: Presented as Number of Patients or Median With Interquartile Range

Successful clipping (yes/no)	27/0
Died (yes/no)	1 (3.7%)/ 26 (96.3%)
Length of hospital stay (d)	7 (4-15)
Modified Rankin scale on discharge	2 (1.5-3)

correlates with the time necessary for clip application. Similarly, Bebawy et al[12] reported a dose range of 0.29 to 0.44 mg/kg (median 0.34 mg/kg) to provide 26 to 105 seconds (median 57 s) of hypotension.

A large case series (n = 98) describing adenosine-induced asystole for endovascular aortic aneurysm repair reported a 2% incidence of self-limited ST-segment depression on electrocardiography and a 4% incidence of temporary heart block requiring < 30 second of pacing.[7] In our smaller series of intracranial aneurysm patients, no temporary pacing was required. However, we routinely apply pacing pads after induction of anesthesia to be prepared for this potential complication. Cardiac dysrhythmias have been reported after adenosine administration (after the asystolic period)[13] and Bebawy et al[12] reported 2 patients out of 24 who experienced transient and hemodynamically stable atrial fibrillation upon recovery from adenosine. In our series of 27 patients, we did not witness this complication.

Adenosine is used in cardiac stress testing to induce steal.[15] Adenosine vasodilates healthy coronary arteries, but not atherosclerotic vessels. It thereby augments perfusion to healthy vascular beds. As a result, patients with known coronary artery disease have at least a relative contraindication to adenosine therapy. We had one patient with coronary disease and one patient with valvular disease and history of atrial fibrillation in our study. The patient with coronary disease had prolonged hypotension requiring cardiopulmonary resuscitation. Postoperative cardiac enzymes were found to be normal. Bebawy et al[12] reported 2 out of 24 patients with mildly elevated troponin levels postoperatively without clinical or transthoracic echocardiographic evidence of cardiac dysfunction. In our study, one patient had transient ST-segment depression that was self-limited and temporally unrelated to administration of adenosine. Cardiac enzymes were subsequently measured and found to be normal in this patient. However, we did not routinely measure postoperative levels of cardiac enzymes.

Adenosine is a potent systemic vasodilator secondary to its action on the A2 receptor, causing relaxation of both endothelium and vascular smooth muscle.[15] The major complication that we encountered was severe persistent hypotension in one patient after emergent redosing of adenosine at half the initial bolus dose. The patient's rhythm returned, but severe systemic hypotension persisted, requiring chest compressions and vasopressor boluses (phenylephrine and epinephrine). The cumulative acute surgical blood loss was approximately 500 mL at this time and may have had a contributory effect. This leads us to recommend that adenosine redosing does not occur until the patient has returned to preadenosine hemodynamic stability. Furthermore, we advocate preparation for this potential serious complication with application of pacing pads and availability of vasopressors.

Adenosine can cause bronchoconstriction.[13] Therefore, patients with significant reactive airway disease (asthma or chronic obstructive pulmonary disease) have a relative contraindication to adenosine. We did not witness any bronchospasm or adenosine-related obstructive pulmonary physiology intraoperatively or postoperatively despite having 3 patients in our study with asthma and/or chronic obstructive pulmonary disease.

One patient in our study died. This was an emergent case for a patient presenting with high-grade subarachnoid hemorrhage and consequently at high risk for cerebral vasospasm. The intraoperative course was without complication. However in the postoperative period the patient developed persistent vasospasm and stroke, and the family elected to withdraw care.

The one significant complication directly related to adenosine administration was persistent severe hypotension after redosing of adenosine to manage aneurysmal rupture. It would require a large randomized clinical trial to prove benefit versus harm from adenosine compared with temporary clipping. For now, we can only advise careful patient selection in regard to cardiac history including coronary artery disease, valvular disease, dysrhythmias, or conduction abnormalities. Patients with reactive airway disease have a relative contraindication to adenosine therapy owing to risk of bronchoconstriction. Finally, precautions must be undertaken to prepare for potential complications (pacing pads, bronchodilators, vasopressors, etc).

Our study is limited by the use of retrospective data and relatively small sample size. However, in combination with other reports[11,12] we can construct reasonable parameters for the use of this therapy in cerebral aneurysm surgery. With the knowledge of associated complications and appropriate precautionary measures, adenosine cardiac arrest can be effectively used to decompress intracranial aneurysms, facilitating surgical exposure and aneurysm clip ligation in cases where temporary clipping of proximal vessels is undesirable or impossible.

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