CONTEMPORARY NEUROSURGERY
A BIWEEKLY PUBLICATION FOR CLINICAL NEUROSURGICAL CONTINUING MEDICAL EDUCATION
VOLUME 44 • NUMBER 16
November 15, 2022

Adenosine-Assisted Clipping of Intracranial Aneurysms

Megan M. J. Bauman, MS, Jhon E. Bocanegra-Becerra, MD, Evelyn Turcotte, BS, Devi P. Patra, MD, Ali Turkmani, MD, Chandan Krishna, MD, Patrick B. Bolton, MD, Antoun H. Koht, MD, H. Hunt Batjer, MD, and Bernard R. Bendok, MD, MSCI

Learning Objectives: *After participating in this CME activity, the neurosurgeon should be better able to:*

1. *Describe the indications for adenosine in intracranial aneurysms clipping.*
2. *Explain the pharmacology and dosing for adenosine.*
3. *Identify contraindications and potential complications of adenosine.*

Microsurgical clipping of intracranial aneurysms is a technically demanding procedure and requires adaptive skills that greatly vary based on the features of each unique aneurysm. Depending on the location of the aneurysm, a neurosurgeon may be faced with challenges including accessing difficult locations through narrow operative corridors, maneuvering around vital neurologic structures, and manipulating fragile tissues. One of the important challenges and potential complications during aneurysm clipping is intraoperative aneurysm rupture (IAR).[1] This can be daunting especially when it occurs before adequate dissection and exposure of vessel(s) essential for proximal and distal control. Uncontrolled bleeding further obscures the surgical field and hurried maneuvers of an unprepared surgeon increase the risk of neurologic damage. Therefore, it is crucial that a variety of tools and strategies exist for use during intracranial aneurysm clipping to combat any potential challenges that may arise. Although a variety of techniques exist to reduce blood flow to and through the aneurysm during dissection and clipping, temporary arterial occlusion via placement of temporary clips on the parent vessels is the most reliable.[2,3] Placement, however, can be challenging if the rupture occurs early or if the anatomy does not facilitate complete trapping. Prolonged temporary clip placement also increases ischemic risks.[4] Rarely, temporary clips can result in vasospasm of the parent arteries.[3,4]

An alternative to temporary clipping is systemic flow arrest through the IV administration of adenosine. Adenosine administered as a bolus transiently slows sinus rate and atrioventricular (AV) nodal conduction resulting in brief asystole.[5] Spontaneous return of sinus rhythm occurs within seconds as this naturally occurring nucleoside is transported into cells and rapidly deaminated. Significant hypotension from vasodilation often occurs after asystole and return of circulation.

Ms. Bauman and Ms. Turcotte are Medical Students, Mayo Clinic Alix School of Medicine, Mayo Clinic, Rochester, Minnesota; Dr. Bocanegra-Becerra is a Postdoctoral Research Fellow in the Neurosurgery Simulation and Innovation Lab and the Precision Neuro-therapeutics Innovation Lab, Mayo Clinic, Phoenix, Arizona; Dr. Patra is a Neurosurgical Resident and Dr. Turkmani and Dr. Krishna are Neurosurgeons, Department of Neurosurgery, Mayo Clinic, Phoenix, Arizona; Dr. Bolton is Anesthesiologist, Department of Anesthesiology, Mayo Clinic, Phoenix, Arizona; Dr. Koht is Professor Emeritus, Department of Anesthesiology, Northwestern University, Chicago, Illinois; Dr. Batjer is Professor Emeritus, Department of Neurosurgery, UT Southwestern, Dallas, Texas; and Dr. Bendok is Neurosurgeon, Department of Neurosurgery, Mayo Clinic, 5777 E. Mayo Blvd, Phoenix, AZ 85054, E-mail: bendok.bernard@mayo.edu.

All authors, faculty, and staff have no relevant financial relationships with any ineligible organizations regarding this educational activity.

Category: Cerebrovascular

Key Words: Adenosine, Clipping, Intracranial aneurysms

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the newsletter's website (www.contempneurosurg.com).

Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Lippincott Continuing Medical Education Institute, Inc., designates this enduring material for a maximum of 2.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. To earn CME credit, you must read the CME article and complete the quiz and evaluation on the enclosed form, answering at least 70% of the quiz questions correctly. This activity expires on November 14, 2024.

Historical Use of Adenosine in Intracranial Aneurysm Surgery

The first application of adenosine in brain aneurysm surgery dates to 1984 in which Sollevi et al. used adenosine in 10 patients with no known history of cardiopulmonary diseases, including 7 men and 3 women (ages 35-58 years) to provide controlled hypotension during surgery.[6] An adenosine reuptake inhibitor—dipyridamole—was conjointly administered (5 mg/mL at 0.3–0.4 mg/kg) over a 5- to 10-minute period and 20 minutes before the induction of hypotension. During surgery, adenosine (5 mM, 1.34 mg/mL in isotonic saline) was administered by continuous infusion for 12 to 71 minutes at a rate of 0.01 to 0.32 mg · kg/min. The infusion was started at a rate of 0.01 mg · kg/min, which was doubled at 15-second intervals until a desired mean arterial blood pressure of 40 to 50 mm Hg (mean hypotensive period was 32 ± 8 minutes). In this trial study, the total dose did not exceed 1.5 g and electrocardiographic (EKG) changes were recorded in the pre- and postoperative course. Although some patients experienced transient hemodynamic changes such as decreased systemic vascular resistance and QT interval elevations, no clinical repercussions were encountered. Overall, the authors were the first to achieve and demonstrate the utility of adenosine to induce controlled hypotension with reversible without tachyphylaxis upon the termination of infusion.

After the initial characterization of adenosine use in the clipping of intracranial aneurysms, its utility for inducing hypotension was investigated in case reports and small cohorts during the late 1990s and early 2000s. The first report of adenosine-induced cardiac arrest (AiCA) was reported by Groff et al. in 1999 in a 57-year-old woman with a basilar tip aneurysm.[7] Since this report, the investigation and use of adenosine to produce asystole during intracranial aneurysm surgery has markedly expanded. In addition, although AiCA began as a technique to supplement and aid in the placement of temporary clips, more recent studies have suggested that AiCA may allow for the omission of temporary clips in select cases, thereby establishing a central role in neurosurgical practice.

Current Utility in Intracranial Aneurysm Surgery

In contemporary practice, adenosine is typically used in the management of IAR. The incidence of IAR has been documented between 6% and 20% and is more common in preoperative ruptured aneurysms than in unruptured aneurysms.[1,8] As previously described, IAR can be managed through a variety of means, one of which includes the use of a temporary arterial occlusion (ie, a temporary clipping). However, the use of adenosine can lead to better rapid visualization, which may facilitate temporary occlusion and/or direct clipping of the aneurysm, as highlighted in Video 1 (see Supplemental Digital Content 1, published online, http://links.lww.com/CNS/A21). When using adenosine as management for IAR, it is important to recognize that the time window of circulatory arrest is limited to 10 to 30 seconds, so decisive and safe action needs to be executed to control the situation.[9] Our group has reported on the repetitive use of adenosine in select challenging situations.[9] In most cases however, adenosine allows for adequate visualization to either clip the rupture site (pilot clip), definitively clip the aneurysm, or achieve proximal and distal control with temporary clips.

In a series of 16 patients with IAR described by Luostarinen et al., adenosine was used to successfully clip the aneurysm without any hemodynamic instability, adverse events, or worsened patient outcomes.[10] Eleven of these cases used adenosine alongside temporary clip placement, whereas 5 cases used adenosine alone for aid in definitive clip placement. Recently, Nussbaum et al. published a systematic review of 29 patients with IAR (including 6 of their own) that highlighted successful clipping of aneurysms in

The continuing education activity in *Contemporary Neurosurgery* is intended for neurosurgeons, neurologists, neuroradiologists, and neuropathologists.

Contemporary Neurosurgery (ISSN 0163-2108) is published bi-weekly by Wolters Kluwer Health, Inc. at 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742. **Customer Service: Phone (800) 638-3030, Fax (301) 223-2400, or E-mail customerservice@lww.com.** Visit our website at www.lww.com.

Wolters Kluwer

 Priority Postage paid at Hagerstown, MD, and at additional mailing offices. POSTMASTER: Send address changes to Contemporary Neurosurgery, Subscription Dept., Wolters Kluwer, P.O. Box 1610, Hagerstown, MD 21740.

Publisher: Sharon Zinner

Subscription rates: *Individual*: US $891, international $1247. *Institutional*: US $1519, international $1569. *In training:* US $164, international $165. Single copies: $85. GST Registration Number: 895524239. Send bulk pricing requests to Publisher.

all cases using AiCA.[11] Specifically, Nussbaum highlighted 3 individual reports in which adenosine proved particularly useful for controlling intraoperative bleeding. These reports consisted of: (1) a carotid-ophthalmic region aneurysm in which good proximal control could not be gained; (2) an anterior communicating artery aneurysm that presented with copious bleeding from flow related to the contralateral A1 segment despite temporary clipping of the ipsilateral A1 segment; and (3) a vertebrobasilar junction aneurysm that experienced retrograde bleeding from the basilar artery despite temporary clipping of bilateral vertebral arteries. Similarly, Bendok et al. described a case of a ruptured basilar artery-anterior artery aneurysm where placement of a temporary clip on the left vertebral artery was not sufficient to provide a clear field for the safe placement of a permanent clip; thus, adenosine was used to allow for control of the surgical field and definitive clipping of the aneurysm.[9]

Alongside the use of adenosine in IAR management, it has been noted to have additional utility for other aspects of complex aneurysm surgery. For example, multiple case series have documented the benefit of adenosine use to soften large and wide-necked aneurysms before clipping, thus facilitating the safe and precise clip placement.[9,12,13] In a retrospective study, Khan et al. used adenosine in 64 patients (median age 58.8 years) with 66 intracranial aneurysms (median size: 9 mm), of which 49 were located in the anterior circulation (12% in the paraclinoid area) and 17 in the posterior circulation (65% in the vertebrobasilar artery).[14] Similarly, Bendok et al. used adenosine to induce asystole in 40 patients (mean age: 49 years) with 40 aneurysms to aid effective clipping, of which 55% were located in the paraclinoid region or posterior communicating (PCOM) artery and 22.5% in the posterior circulation.[9]

Adenosine has been noted to be especially useful when treating aneurysms in difficult locations.[15-17] Paraclinoid aneurysms often pose a challenge with regard to proximal control. An alternative to proximal flow arrest could be adenosine-induced flow arrest to soften the aneurysm before clipping particularly for wider-necked aneurysms.[9] Aneurysms at the basilar apex aneurysms and others of the posterior circulation require working through very narrow corridors, which may make temporary occlusion challenging.[16,17] Adenosine may also allow better visualization of an outflow branch beyond a large dome [for example, a contralateral A2 associated with a wide-necked large anterior communicating artery (ACOM) aneurysm]. This particular use of adenosine is highlighted in Video 2 (see Supplemental Digital Content 2, published online, http://links.lww.com/CNS/A22).

The presence of complex morphology may also warrant the use of adenosine during aneurysm treatment. Specifically, large aneurysms or those with a broad neck may benefit from the reduced intra-aneurysmal pressure afforded by the reduced blood flow following administration of adenosine.[18] This may allow better circumferential visualization of the anatomy and safer and more precise clip placement of the neck. Other indications of adenosine include adjusting clips, or treatment of aneurysms that are thin-walled, previously coiled, or which have atheroma in the neck of the aneurysm.[9] Additionally, patients with connective tissue disease may benefit from the use of adenosine over temporary clips, given the potential friability of vasculature and concerns for vessel damage or dissection. We previously reported on the use of adenosine for patients with Loeys-Dietz syndrome—a connective tissue disease with highly frail arteries (Table 1).[19]

An example of adenosine use from our institution is presented in a representative case of a 52-year-old woman who was found to have an incidental right PCOM artery aneurysm (Figure 1). Given the recent growth of the aneurysm along with its origin from the PCOM artery proper with fetal configuration, endovascular intervention was deemed to be unsuitable. Therefore, open microsurgical clipping was pursued through a right pterional craniotomy. After exposure of the proximal and distal carotid arteries, the aneurysm was identified (Video 3; see Supplemental Digital Content 3, published online, http://links.lww.com/CNS/A23.) It was noted that the walls of the aneurysm were extremely thin and the neck was essentially transparent with multiple blisters. Given the fragility of the aneurysm and its neck, it was decided to use adenosine. Upon administration of adenosine, an excellent short period of flow arrest was achieved, thereby allowing the successful clipping of the aneurysm neck with a curved clip. An indocyanine green angiogram showed excellent flow in all outflow vessels including the choroidal artery, without any filling of the aneurysm.

Pharmacokinetics, Pharmacodynamics, and Physiological Responses

IV adenosine administration promotes rapid absorption to achieve therapeutic concentrations. The drug distributes rapidly in the cellular, extracellular, and interstitial vascular compartments.[5] However, the catabolism of adenosine is ultrashort with a half-life of 1 to 7 seconds. Uric acid is the predominant metabolite that is later excreted by the kidneys.[5,20] The effects of adenosine rely on the binding to ubiquitous cellular membrane receptors (eg, A1 and A2 receptors), and its effects are predominantly mediated by a secondary messenger system involving the adenylyl cyclase pathway. Intracellularly, metabolization of adenosine occurs through rapid phosphorylation or deamination to nonvasoactive substances such as adenosine monophosphate or inosine, respectively.[20] Upon receptor activation, adenosine produces negative chronotropic, dromotropic, and inotropic effects in the heart via its A1 receptor.[21] On the other hand, binding to the A2 receptors produces peripheral vasodilation. Thus, adenosine causes coronary vasodilation, depression of the sinoatrial node, AV nodal conduction, and ventricular automaticity.[5,20] Due to these

Table 1. Common Indications for Adenosine Use in Brain Aneurysm Surgery

Intraoperative aneurysm rupture
Facilitating or substituting temporary clips
Difficult aneurysm access in narrow corridors
Complex aneurysm morphology (eg, large size, broad neck, or large bulbous dome)

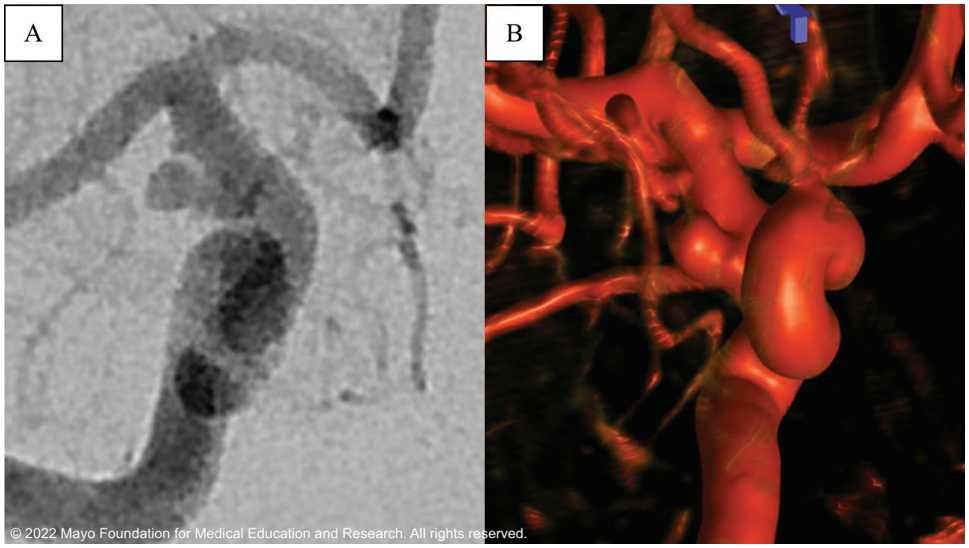

Figure 1. A, Angiography demonstrating a large PCOM aneurysm arising from the supraclinoid right ICA and projecting laterally. Dimensions of the aneurysm measured approximately 4 mm tall × 3.5 mm wide, with a broad 2.84-mm neck. B, Three-dimensional reconstruction beginning at the cavernous ICA and showing the origin of the aneurysm at the PCOM. ICA, internal carotid artery.

properties, adenosine was historically used in emergently or electively treating atrial arrhythmias.[22] Further, the hypotensive and coronary dilating properties are presently exploited for use in nuclear medicine (ie, adenosine/thallium test).

Individual doses usually range from 3 to 60 mg. However, the advanced cardiac life support (ACLS) dosing regimen of 6/6/12 could also provide a dosing reference. As described in the literature, total administered adenosine doses range from 3 to 285 mg,[13,23] though rare reports of more than 700 mg of total adenosine administration exist.[24] Depending on the dose, rapidity of injection, location of the injection (ie, distance from the heart), and individual patient response, administration of adenosine can produce profound hypotension (systolic blood pressure $<$ 60 mm Hg), or asystole/AiCA. The therapeutic effect (asystole) requires the bolus dose of adenosine to reach the heart. Injection through small-gauge, peripheral IV catheters allows for rapid drug elimination during transit through the venous system. If the intraoperative need for adenosine is anticipated, preoperative placement of a central venous catheter or a large-bore external jugular vein cannula increases the likelihood of achieving adequate duration of asystole.

Typically, dose calculations are based on ideal body weight of a patient.[13] In the neurosurgical setting, there are 2 methods to determine the best therapeutic dose: dose estimation and dose escalation.[13] In dose escalation, adenosine is administered as a lower initial dose, often 6 to 12 mg, and subsequently increased through additional doses to achieve the desired effect. Alternatively, dose estimation involves a single, typically larger dose of administered adenosine based on the expected duration of hypotension or asystole. In single doses of adenosine (dose estimation technique), the duration of asystole is positively correlated with the dose administered.[25] This relationship holds especially true for dosages of less than 0.25 mg/kg; however, higher doses of adenosine produce a more variable length of AiCA, in which individual pharmacokinetics and pharmacodynamics become more important. However, in emergent situations in which flow arrest needs to be achieved quickly, it has been found that 0.3 to 0.4 mg/kg of adenosine can be used to achieve 45 seconds of profound hypotension.[23,25] Alternatively, 0.1 to 0.2 mg/kg has been shown to be useful for inducing brief instances of asystole ($<$15 seconds) in nonemergent situations during clip placement.[13] Regardless of the use of adenosine, typically 0.2 to 0.4 mg/kg of adenosine is accepted as a safe and effective range of administration with minimal risks and side effects.[13]

Potential Complications and Contraindications

As a result of prolonged hypotension and/or AiCA, potential side effects of adenosine use are those expected from inadequate organ perfusion. In general, side effects can be grouped based on 2 broad categories: cardiac and noncardiac-related morbidity. Because of coronary vasodilation, known and fixed lesions of the left anterior descending (LAD) artery create the most concern for inducing steal phenomena from the LAD.[26] For this reason, regular monitoring of EKG and troponin levels postoperatively may be required in some patients. However, a subset of patients may experience a temporary, mild elevation in cardiac enzymes after the use of adenosine without any signs of ischemia on EKG or abnormal ventricular wall motion activity on echocardiogram.[9,13,15,25,27] In a retrospective study, Khan et al. compared the 30-day mortality and incidence of perioperative cardiac complications (perioperative myocardial infarction or perioperative cardiac arrhythmias) between 64 and 262 patients who underwent brain aneurysm surgery with and without the use of adenosine, respectively.[14] After adjusting for differences in the incidence of coronary artery disease between the 2 groups, there was no significant difference in the composite outcome (adjusted odds ratio = 2.12; 95% confidence interval 0.76–5.93; $P = 0.15$). Thus, this study suggests adenosine-assisted intracranial aneurysm surgery is not

associated with an increase in perioperative cardiac complications or mortality in patients with low risk of coronary artery disease.

Alternatively, some patients may develop an abnormal electrical rhythm perioperatively. Most commonly, patients may experience transient atrial fibrillation,[13,18,28,29] though reports of sinus tachycardia, sinus bradycardia, and adenosine-induced AV block have been documented.[9] Barring any history of prior arrhythmias, these EKG changes usually spontaneously resolve and do not cause any significant long-term complications or morbidity. Given the possibility of electrical conductance disturbances, it is recommended to have access to external defibrillators pads for external pacing in instances of prolonged bradycardia.[25] In addition, cardioversion may be necessary for patients who develop hemodynamically unstable atrial fibrillation.[25]

Complications after the administration of adenosine also have the potential to affect other organ systems of the body due to reduced blood flow. Given the high metabolic demand of the brain, the central nervous system can be particularly sensitive to flow arrest. For patients receiving adenosine, prolonged periods of asystole may warrant the use of pharmacologic neuroprotection, such as propofol burst suppression.[30] In addition, it is particularly important that postoperative imaging is thoroughly evaluated for any new infarcts, especially along the territory of the parent vessel.[15] However, pharmacological adenosine has not been found to affect evoked potential monitoring; thus, intraoperative neuromonitoring still serves as an effective strategy to avoid neurologic complications during aneurysm clipping.[27] Despite this feared complication, stroke or other neurologic morbidities directly related to adenosine use are very rare.[17] For example, Bebawy et al. evaluated whether the use of adenosine was associated with the presence or absence of a poor neurologic outcome (Rankin scale score >2) 48 hours after surgery in 72 patients (17.4%).[26] Ultimately, 22.2% of the adenosine group compared with 25.8% of the nonadenosine group had a poor neurologic outcome at 48 hours postoperatively ($P = 0.5545$), which reduced to 16.7% in the adenosine group and 18.8% in the nonadenosine group ($P = 0.676$). In another study by Bebawy et al., there were no differences in the incidence of new postoperative deficit when comparing the adenosine group (12.5%) with the nonadenosine group (21.0%) ($P = 0.529$).[25] Further, given the common use of adenosine in IAR, postoperative morbidities may be difficult to attribute to adenosine use versus vasospasm, including any focal deficits or infarct in areas far from the original aneurysm.[11] Therefore, careful monitoring of patient vitals and proper administration of adenosine are of the utmost importance to prevent any systemic morbidities, along with potentially using burst suppression, should long intervals of asystole be anticipated.

Due to the profound impact of adenosine of the heart and circulatory system, patients must be thoroughly evaluated for any history of cardiovascular comorbidities before surgery. Specifically, given the vasodilatory properties of adenosine on vasculature, patients with a known history of coronary artery disease may not be suitable candidates to receive adenosine due to the risk of myocardial ischemia resulting from coronary steal syndrome. Further, the bronchoconstriction properties of adenosine may preclude its use in certain patients with airway disease including chronic obstructive pulmonary disease or asthma.[31] However, given that adenosine has very few side effects and is rapidly eliminated, it overall has a safe profile as long as these contraindications are respected (Table 2).

Table 2. Potential Complications of Adenosine Use

Cardiac-related complications
Myocardial infarction
Cardiac arrhythmias
Noncardiac-related complications
Stroke
Bronchospasm

Current Level of Evidence Regarding the Safety and Feasibility of Adenosine-Assisted Clipping

Numerous studies have included adenosine as an assisting tool in the microsurgical management of brain aneurysms. However, the use of adenosine in these scenarios is an off-label use as the FDA has not listed its indication for brain aneurysm surgery. Nevertheless, adenosine constitutes one of the major options among the documented alternatives for aiding in aneurysm ligation such as rapid ventricular pacing, deep hypothermic circulatory arrest, endovascular balloon occlusion with suction (for giant paraclinoid aneurysms), and temporary clipping.[32-34] Although AiCA has gained popularity as a supplement to temporary clip placement, newer research suggests that there may be a role for adenosine use alone without the need for temporary clip placement in certain patients.[15]

Based on reports in the literature, adenosine offers a great safety profile in select patients without known cardiopulmonary diseases as indicated by evidence from case series, case-control, and cohort studies. In extremely rare circumstances, adenosine may cause neurologic adverse events[15,17]; however, the precise cause of neurologic-associated morbidity and mortality in this subset of patients is difficult to attribute to adenosine itself, especially in the cases of IAR and subarachnoid hemorrhage.[11] Further, high-level evidence from clinical trials is still lacking. Of particular interest, Hishikawa et al. have pioneered in implementing the first trial in Japan to evaluate the safety and feasibility of adenosine for assisting in the clipping of unruptured cerebral aneurysms.[35] As a result of the existing evidence, recommendations for using adenosine are at the discretion of the neurosurgeon based mainly on but not limited to the complex architecture of the aneurysm, the patient's medical history, and the experience of the surgical and anesthetics team.

Conclusions

The use of adenosine in brain aneurysm surgery has evolved over the years and has represented an instrumental tool within the treatment arsenal for aneurysm clipping. Two desired effects have been mainly achieved including

Supplemental videos

Video 1 (http://links.lww.com/CNS/A21). Intraoperative footage demonstrating the use of adenosine to control bleeding after intraoperative rupture, leading to the successful clipping of the ruptured aneurysm.

Video 2 (http://links.lww.com/CNS/A22). Intraoperative footage demonstrating how the administration of adenosine allowed for the aneurysm dome to be pressed, thereby facilitating visualization and temporary clipping of the contralateral A2 in an ACOM aneurysm.

Video 3 (http://links.lww.com/CNS/A23). (0′00″) Diagnostic cerebral angiography with injection of the right internal carotid artery. Angiogram shows aneurysm arising from the PCOM and projecting laterally. (0′05″) Three-dimensional reconstruction that was created using Surgical Theater's segmentation software (Los Angeles, California). Augmented reality of a right pterional craniotomy highlighting the approach to the PCOM aneurysm. (0′14″) Intraoperative footage demonstrating the clipping of a fragile PCOM aneurysm with multiple blisters using adenosine administration to aid in placement of a curved clip over the wide aneurysm neck.

transient asystole and hypotension, which have characterized the utility of adenosine during IAR and clipping facilitation of aneurysms with difficult access and complex characteristics. Although the use of adenosine remains off-label, the current level evidence suggests it is largely safe for most patients without a medical history of cardiac or respiratory comorbidities. Nevertheless, close monitoring of cardiac and neurologic profiles should be accompanied during its administration. Further research including the development of clinical trials is needed.

References

1. Chandler JP, Getch CC, Batjer HH. Intraoperative aneurysm rupture and complication avoidance. *Neurosurg Clin N Am*. 1998;9(4):861-868.
2. Malinova V, Schatlo B, Voit M, et al. The impact of temporary clipping during aneurysm surgery on the incidence of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2018;129(1):84-90.
3. Kumar S, Sahana D, Menon G. Optimal use of temporary clip application during aneurysm surgery—in search of the holy grail. *Asian J Neurosurg*. 2021;16(2):237-242.
4. Woertgen C, Rothoerl RD, Albert R, et al. Effects of temporary clipping during aneurysm surgery. *Neurol Res*. 2008;30(5):542-546.
5. Pelleg A, Porter RS. The pharmacology of adenosine. *Pharmacotherapy*. 1990;10(3):157-174.
6. Sollevi A, Lagerkranser M, Irestedt L, et al. Controlled hypotension with adenosine in cerebral aneurysm surgery. *Anesthesiology*. 1984;61(4):400-405.
7. Groff MW, Adams DC, Kahn RA, et al. Adenosine-induced transient asystole for management of a basilar artery aneurysm. Case report. *J Neurosurg*. 1999;91(4):687-690.
8. Houkin K, Kuroda S, Takahashi A, et al. Intra-operative premature rupture of the cerebral aneurysms. Analysis of the causes and management. *Acta Neurochir (Wien)*. 1999;141(12):1255-1263.
9. Bendok BR, Gupta DK, Rahme RJ, et al. Adenosine for temporary flow arrest during intracranial aneurysm surgery: a single-center retrospective review. *Neurosurgery*. 2011;69(4):815-820.
10. Luostarinen T, Takala RSK, Niemi TT, et al. Adenosine-induced cardiac arrest during intraoperative cerebral aneurysm rupture. *World Neurosurg*. 2010;73(2):79-83.
11. Nussbaum ES, Burke E, Nussbaum LA. Adenosine-induced transient asystole to control intraoperative rupture of intracranial aneurysms: institutional experience and systematic review of the literature. *Br J Neurosurg*. 2021;35(1):98-102.
12. Powers CJ, Wright DR, McDonagh DL, et al. Transient adenosine-induced asystole during the surgical treatment of anterior circulation cerebral aneurysms: technical note. *Neurosurgery*. 2010;67(2 suppl operative):461-470.
13. Intarakhao P, Thiarawat P, Tewaritrueangsri A, et al. Low-dose adenosine-induced transient asystole during intracranial aneurysm surgery. *Surg Neurol Int*. 2020;11:235.
14. Khan SA, McDonagh DL, Adogwa O, et al. Perioperative cardiac complications and 30-day mortality in patients undergoing intracranial aneurysmal surgery with adenosine-induced flow arrest: a retrospective comparative study. *Neurosurgery*. 2014;74(3):267-271.
15. Intarakhao P, Thiarawat P, Jahromi BR, et al. Adenosine-induced cardiac arrest as an alternative to temporary clipping during intracranial aneurysm surgery. *J Neurosurgery*. 2018;129(3):684-690.
16. Sai Kiran NA, Mohan D, Sivaraju L, et al. Adenosine-Induced transient asystole during surgical treatment of basilar artery aneurysms. *Neurol India*. 2020;68(2):419-426.
17. Heppner PA, Ellegala DB, Robertson N, et al. Basilar tip aneurysm—adenosine induced asystole for the treatment of a basilar tip aneurysm following failure of temporary clipping. *Acta Neurochir (Wien)*. 2007;149(5):517-521.
18. Sheen JJ, Park W, Kwun BD, et al. Microsurgical treatment strategy for large and giant aneurysms of the internal carotid artery. *Clin Neurol Neurosurg*. 2019;177:54-62.
19. Rahme RJ, Adel JG, Bendok BR, et al. Association of intracranial aneurysm and Loeys-Dietz syndrome: case illustration, management, and literature review. *Neurosurgery*. 2011;69(2):E488-E493.
20. Layland J, Carrick D, Lee M, et al. Adenosine: physiology, pharmacology, and clinical applications. *JACC Cardiovasc Interv*. 2014;7(6):581-591.
21. Belardinelli L, Linden J, Berne RM. The cardiac effects of adenosine. *Prog Cardiovasc Dis*. 1989;32(1):73-97.
22. Gupta A, Lokhandwala Y, Rai N, et al. Adenosine—a drug with myriad utility in the diagnosis and treatment of arrhythmias. *J Arrhythm*. 2021;37(1):103-112.
23. Guinn NR, McDonagh DL, Borel CO, et al. Adenosine-induced transient asystole for intracranial aneurysm surgery: a retrospective review. *J Neurosurg Anesthesiol*. 2010;22(4):435-436.
24. Nimjee SM, McDonagh DL, Agrawal A, et al. A case of high-dose adenosine usage for anterior communicating artery aneurysm clip ligation: what is the dose limit for a resistant response? *Asian J Neurosurg*. 2017;12(4):783-786.
25. Bebawy JF, Gupta DK, Bendok BR, et al. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation: dose-response data and safety profile. *Anesth Analg*. 2010;110(5):1406-1411.
26. Bebawy JF, Zeeni C, Sharma S, et al. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation does not worsen neurologic outcome. *Anesth Analg*. 2013;117(5):1205-1210.
27. Vealey R, Koht A, Bendok BR. Multidose adenosine used to facilitate microsurgical clipping of a cerebral aneurysm complicated by intraoperative rupture: a case report. *A A Case Rep*. 2017;8(5):109-112.
28. Quiroz-Murga E, Simon-Scamarone G. Atrial fibrillation with hemodynamic instability after the use of the third dose of adenosine during surgery for 7 intracranial aneurysms: case report. *Colombian J Anesthesiol*. 2019;47(2):124-127.
29. Meling TR, Romundstad L, Niemi G, et al. Adenosine-assisted clipping of intracranial aneurysms. *Neurosurg Rev*. 2018;41(2):585-592.
30. Chowdhury T, Petropolis A, Wilkinson M, et al. Controversies in the anesthetic management of intraoperative rupture of intracranial aneurysm. *Anesthesiol Res Pract*. 2014;2014:595837.
31. Burkhart KK. Respiratory failure following adenosine administration. *Am J Emerg Med*. 1993;11(3):249-250.

32. Konczalla J, Platz J, Fichtlscherer S, et al. Rapid ventricular pacing for clip reconstruction of complex unruptured intracranial aneurysms: Results of an interdisciplinary prospective trial. *J Neurosurg*. 2018;128(6):1741-1752.
33. Kienzler JC, Diepers M, Marbacher S, et al. Endovascular temporary balloon occlusion for microsurgical clipping of posterior circulation aneurysms. *Brain Sci*. 2020;10(6).
34. Lee KS, Zhang JJY, Nguyen V, et al. The evolution of intracranial aneurysm treatment techniques and future directions. *Neurosurg Rev*. 2022;45(1):1-25.
35. Hishikawa T, Murai S, Hiramatsu M, et al. An evaluation of the safety and feasibility of adenosine-assisted clipping surgery for unruptured cerebral aneurysms: study protocol. *Neurol Med Chir (Tokyo)*. 2021;61(7):393-396.

To earn CME credit, you must read the CME article and complete the quiz and evaluation on the enclosed form, answering at least 7 of the 10 quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope.Your answer form must be received by Lippincott CME Institute, Inc., by **November 14, 2024.** Only two entries will be considered for credit. For more information, call (800) 638-3030.

Online quiz instructions: To take the quiz online, **log on to your account** at **www.contempneurosurg.com**, and click on the "CME" tab at the top of the page. Then click on "Access the CME activity for this newsletter," which will take you to the log-in page for **http://cme.lww.com**. Enter your *username* and *password*. Follow the instructions on the site. You may print your official certificate ***immediately.*** Please note: Lippincott CME Institute, Inc., **will not** mail certificates to online participants. **Online quizzes expire on the due date**.

The American Association of Neurological Surgeons (AANS) manually tracks *AMA PRA Category 1 Credits*™ earned from neurosurgery activities not sponsored or joint-sponsored by the AANS. As a service to AANS members, Lippincott CME Institute will continue to provide the AANS a monthly listing of their participants and the CME credits they earned so that AANS members do not have to send their individual certificates to the AANS for tracking.

1. Adenosine administration has only shown benefit in cases of intraoperative rupture, but its use should be avoided otherwise.

True or False?

2. The predominant metabolites of adenosine are excreted by the kidneys.

True or False?

3. Total adenosine doses frequently exceed 500 mg.

True or False?

4. Activation of A2 receptors by adenosine on vasculature produces vasodilation; therefore, expected effects of adenosine include peripheral and coronary vasodilation.

True or False?

5. When using adenosine as management for IAR, the time window of flow rest is usually limited to 10 to 30 seconds.

True or False?

6. Perioperative cardiac arrhythmias are often permanent and require lifelong medical treatment as a result from adenosine use.

True or False?

7. Atrial fibrillation is the most common perioperative cardiac arrhythmia seen following adenosine administration.

True or False?

8. Adenosine has no effect on the lungs; therefore, pulmonary comorbidities are of no concern when accessing if a patient is a candidate for adenosine use.

True or False?

9. The use of adenosine for clipping of intracranial aneurysms is currently approved by the FDA.

True or False?

10. Alternatives to adenosine to reduce intra-aneurysmal pressure include rapid ventricular pacing, deep hypothermic circulatory arrest, endovascular balloon occlusion with suction, and temporary clipping.

True or False?