Adenosine-Assisted Management of Intracranial Aneurysm

Bhoomika Thakore[1]   Shwetal Goraksha[1]   Joseph N. Monteiro[1]

[1]Neuroanaesthesia Program, Department of Anaesthesiology, P. D. Hinduja Hospital, Mumbai, Maharashtra, India

Address for correspondence Joseph N. Monteiro, MD, Neuroanaesthesia Program, Department of Anaesthesiology, P. D. Hinduja Hospital, D 61 Nirvana, Bhagoji Keer Marg, Mahim, Mumbai 400016, Maharashtra, India (e-mail: monteiro04@gmail.com).

Abstract

Cerebral aneurysms can be complex and variable in size, position, and morphology, resulting in difficult surgical exposure and secure clip placement. They have a high mortality rate when ruptured, and though endovascular techniques have emerged to tackle this, surgical clip ligation remains the preferred modality for some aneurysms. Various techniques that help the surgeon dissect the aneurysmal dome and apply the clip are temporary clip ligation of proximal vessels, deep hypothermic circulatory arrest, and balloon suction decompression. All of them require significant logistics and result in increased morbidity and mortality. Adenosine is a suitable alternative for inducing a temporary flow arrest, causing a short period of controlled hypotension. Its rapid onset and offset property along with low incidence of adverse events makes it an ideal agent in this regard. We present here a review on its use, contraindications, safety profile, and future applications.

Keywords
► adenosine
► cerebral aneurysm
► flow arrest

Introduction

The incidence of intracranial aneurysms is approximately 5% of the general population, and the mortality associated with subarachnoid hemorrhage is 40 to 50%.[1,2] This warrants prompt recognition and management of both ruptured and unruptured aneurysms. Although endovascular coiling has emerged as a less-invasive modality for aneurysm treatment, surgical clipping does remain the mainstay for many types of aneurysms, depending on their morphology and location. Clipping of cerebral aneurysms traditionally necessitated the placement of a temporary clip across a proximal feeding artery so that the intra-aneurysmal turgor reduces, which facilitates permanent clip placement. Certain intracranial aneurysm locations, such as a paraclinoid aneurysm, pose difficulty in exposing an anatomically suitable site for temporary clip placement.[3,4] In these cases, techniques, such as deep hypothermic circulatory arrest, extracranial to intracranial bypass, or endovascular balloon occlusion with suction, have been employed to clip the intracranial aneurysm.[5–7] However, these techniques require significant logistical support and are associated with complications such as dissection of friable arteries, cerebroembolic events, and coagulopathy-associated intracranial hematomas.[5] Other less-invasive modalities for achieving cardiac standstill are rapid ventricular pacing, and pharmacological methods such as administration of sodium nitroprusside (SNP), nitroglycerin, or adenosine.[8,9] Rapid ventricular pacing has regained its use in giant aneurysms, but it again has to be preplanned at the start of the case and requires the pacing wire in situ preoperatively. It cannot be used in emergent cases of intraoperative unanticipated ruptures.[10–12] SNP and nitroglycerin have several side-effects, such as cyanide toxicity, tachyphylaxis, rebound hypertension, increased intracranial pressure, and methemoglobinemia.[13] All this makes adenosine a good alternative for achieving temporary flow arrest. It provides predictable degree and duration of hypotension with few pharmacological side-effects; is easily available and simple to administer; and has low risk for procedure-related complications.[14] The main aim of this review is to provide a background on adenosine and its safe use in aneurysm clipping surgeries, both emergent and nonemergent.

Adenosine

Adenosine is an endogenous purine nucleoside, which comprises a molecule of adenine attached to a ribose sugar (ribofuranose) moiety via a b-N9-glycosidic bond. It serves as an inhibitory neurotransmitter in the central nervous system, playing a role in sleep and arousal.[15] Adenosine binds to cardiac A1 receptors, which initiates a cascade through activation of adenyl cyclase, decreasing intracellular cyclic adenosine monophosphate (cAMP), which results in decreased inward calcium conductance.[16] This results in depressed sinoatrial (SA) node activity (negative chronotropic effect), slowed atrioventricular (AV) nodal conduction (negative dromotropic effect), and decreased atrial contractility and ventricular automaticity.[17] The clinical effect is seen 10 to 20 seconds after bolus injection of adenosine, leading to AV nodal blockade, bradycardia, sinus pauses, and cardiac arrest; all of this causes a decrease in cardiac output and mean arterial pressure (MAP). In 1955, adenosine (as adenosine triphosphate) was used to terminate paroxysmal supraventricular tachycardia (PSVT). The Food and Drug Administration (FDA) first approved the use of adenosine for treatment of PSVT in 1989, and soon it replaced verapamil as the drug of choice for this indication.[18] Adenosine is rapidly cleared from blood by uptake into erythrocytes and vascular endothelial cells, having a short half-life of 0.6 to 20 seconds. This rapid onset and offset property helps a bolus of adenosine to cause flow arrest, decompresses the aneurysm sac, and improves visualization and clipping, all this without prolonged hypotension.

Adenosine also causes hyperpolarization of vascular smooth muscle cells, resulting in coronary arterial vasodilatation, by opening of potassium channels. This can produce a coronary steal phenomenon, and so it is very important to do a close cardiac monitoring when used in aneurysm surgery.[19]

Last but not the least, adenosine acts on $A_2\beta$-adenosine receptors on bronchial smooth muscles to cause contraction. This may induce bronchospasm, especially in patients with asthma or chronic obstructive pulmonary disease (COPD).[20,21]

Discussion

Adenosine use in humans was first studied by Sollevi et al in 1984.[22] They performed controlled hypotension in 10 patients undergoing cerebral aneurysm surgery with the help of adenosine and studied its cardiovascular effects. After pretreatment of patients with dipyridamole (0.3–0.4 mg/kg), an adenosine uptake inhibitor, adenosine infusion (0.14 ± 0.04 mg/kg/min) was given, which reduced the MAP by 43% and caused a mean hypotensive period of 32 minutes without any signs of tachyphylaxis. Hypotension was the result of profound decrease in the peripheral vascular resistance (61 ± 3%) and was accompanied by an increase in cardiac output (44 ± 9%). Pulmonary vascular resistance and central venous pressures remained unaffected. Whole-body oxygen consumption was decreased by 13 ± 4%, and there were no signs of lactate formation. They concluded that the rapidity of onset and termination, stability of action, maintenance of cardiac output, and a decrease in oxygen demand differentiate adenosine from other hypotensive agents and justify further clinical investigations.

Owall et al, in 1987, studied 47 patients (46 undergoing aneurysmal clip ligation and 1 arteriovenous malformation [AVM] resection).[23] Adenosine was infused, starting at 40 µg/kg/min and increasing by 40 µg/kg/min every 30 seconds until a desired MAP of 40 to 50 mm Hg was reached (range: 0.088–0.530 mg/kg/min). The hypotensive period lasted 29 minutes on an average. There were no changes in pulmonary arterial pressure, pulmonary capillary wedge pressure, pH, base excess, or partial pressure of carbon dioxide in arterial blood, and no reflex tachycardia or rebound hypertension was seen. The study, however, cautioned the use of adenosine hypotension in patients with ischemic heart disease as dysrhythmias occurred in the two patients with earlier history of myocardial infarction.

Both the above studies used adenosine in the form of infusions. In 1999, Groff et al[24] used adenosine as a bolus for the first time to clip an unruptured basilar tip aneurysm in one patient. In addition to adenosine, 6 mg, then 12 mg, and then another 12 mg, infusion of SNP was administered, which caused 8 to 13 seconds of profound hypotension (MAP ~15 mm Hg) and allowed the safe and successful placement of a clip. Powers et al,[25] in 2010, used adenosine by bolus for clipping anterior circulation aneurysms in six patients. They administered escalating doses of adenosine, until 30 seconds of asystole was achieved (6 mg, 12 mg, 18 mg, 24 mg, and 36 mg), concluding that a rate of 1 mg adenosine results in 1 second of asystole on an average.

Both the above studies failed to give a guideline for bolus dose and dosing. Two studies that helped establish the same were the ones conducted by Hashimoto et al and Bebawy et al.[14,26] Hashimoto et al used adenosine dosing for endovascular glue embolization of AVMs in five patients (four adults and one child). A series of adenosine test injections to establish a dose–response relation in each patient was given. The initial dose of adenosine was 0.25 to 0.35 mg/kg and was escalated by 10 to 20 mg for each injection with an interval of 3 to 10 minutes to achieve an endpoint of MAP of 25 to 30 mm Hg for 20 to 30 seconds. They also gave a continuous SNP infusion, titrated to reduce MAP by 10% of baseline and prevented post adenosine rebound hypertension. Data were analyzed by creating a scatter plot with weight-based dosing on the x-axis (mg/kg) and several variables on the y-axis: duration of asystole, duration of MAP < 50, duration of MAP < 30, and MAP for first 20 seconds. Results showed that both the duration of asystole and MAP < 30 to 50 are linearly correlated with adenosine dose, and an adenosine dose of 0.88 mg/kg is required for 45 seconds of moderate hypotension (MAP < 50) and 2.15 mg/kg for profound hypotension (MAP < 30).[14]

Bebawy et al[26] demonstrated the dose–response curve for adenosine during cerebral aneurysm clipping. They reviewed retrospectively 24 patients who had adenosine administration during aneurysm clipping, two-thirds of which were unruptured and one-third ruptured, and two-thirds were located in the anterior circulation and one-third in the posterior circulation. Results showed that a median dose of 0.34 mg/kg ideal body weight (IBW) (range: 0.29–0.44 mg/kg) resulted in

a systolic blood pressure (SBP) < 60 mm Hg for a median of 57 seconds (range: 26–105 seconds) and a linear correlation was noted between the dose of adenosine and the duration of SBP < 60 mm Hg. Patients were given anesthesia in the form of remifentanil infusion, low-dose volatile anesthetic, and propofol-induced burst suppression. IBW was used instead of actual body weight because the volume of distribution of adenosine is unlikely to change with obesity.[26] Unlike the study by Hashimoto et al, Bebawy et al needed 1/5 to 1/7 the dose of adenosine primarily because of remifentanil usage, which depresses SA node activation and AV node conduction, whereas the SNP used by Hashimoto et al can increase electrical conduction through these nodes.[14,26]

In 2011, Bendok et al[27] presented a retrospective review of 40 patients undergoing aneurysmal clipping with adenosine use, both anterior and posterior circulations, 10 of which were ruptured and 30 unruptured. They used bolus doses of 0.3 to 0.4 mg/kg, as suggested by Bebawy et al, with successful clip ligation in 35 out of 40 patients, a success rate of 87.5%.[27] In the same year, a retrospective study of 27 patients with primarily anterior circulation aneurysms was presented by Guinn et al.[28] Their results stated that a dose of 0.24 to 0.42 mg/kg is necessary to get 30 to 60 seconds of hypotension and bradycardia.[28] Also, one need not aim for asystole. The authors claim that hypotension is the single most important factor for adenosine success.

As with any drug, interpatient variability exists with adenosine dosing too, and sometimes one may have to give multiple doses to find the effective dose for the particular patient, which may not be possible in case of emergencies such as rupture of aneurysm. It also raises concern about safety of adenosine with repeated doses. Lee et al[29] compared a multiple, escalating dose regimen with a predetermined dose regimen, based on 0.3 to 0.4 mg/kg, and found equivalent safety profiles between the two groups. There were no major cardiac complications apart from occurrence of atrial fibrillation episode in two patients in the predetermined dose group. They were short lasting and self-limited. Vealey et al[30] administered six multiple precalculated large doses consecutively over a 12-minute period to achieve control of a left middle cerebral artery aneurysm that had ruptured. The repeated dosing did not cause any cardiac or neurological complications.

At our institute, we commenced using adenosine in craniotomies for clipping of cerebral aneurysms in early 2014. As per our unpublished data, adenosine was used in 116 out of total 134 such cases. Before application of permanent clip, adenosine in a carefully titrated dose of 0.3 to 0.4 mg/kg was administered; this achieved approximately 21 to 45 seconds of temporary flow arrest, followed by spontaneous return of rhythm. We had a few cases of transient self-resolving re-entrant arrhythmias. We did not observe any immediate or late adverse events related to administration of adenosine. Since action of adenosine is ultra short-acting and self-limiting in the most cases, we did not require any cerebral protection agents.

Indications and Contraindications

The decision to use adenosine-induced flow arrest during intracranial aneurysm clipping will depend on several factors, including the location, size of the aneurysm, its morphology, risk of rupture, and, importantly, absence of any contraindications to its use. As reported by Bendok et al[27] in their review, the primary reason for using adenosine is to decrease intra-aneurysmal tension or basically "soften the aneurysm." For a safe and effective clipping of intracranial aneurysms, the surgeon needs adequate exposure of the aneurysm and also its branches and perforators. This is difficult when the aneurysm is deep or very close to the paraclinoid segment of the carotid artery and basilar apex. In such cases, adenosine administration improves exposure. Broad neck aneurysms and giant aneurysms also are benefitted by intraoperative use of adenosine.[25,27] Intraoperative rupture of aneurysm is an emergent and catastrophic complication. Adenosine can be successfully used in such cases, especially when conventional suctioning fails to clear the field. The same was emphasized in a recent case series by Loustarnien et al,[31] which reported successful and uneventful clipping in 16 patients after adenosine flow arrest helped salvage intraoperative aneurysm rupture.

Action of adenosine on the A_{2B} receptors on bronchial smooth muscles causes muscle contraction.[32] This property need not cause concern in normal patients, as shown by Bebawy et al,[26] wherein there was no significant increase in peak airway pressures following bolus administration of adenosine in patients without reactive airway disease. Bronchospasm, however, can occur after adenosine administration, but this has been seen always in patients with active asthma or chronic obstructive lung disease.[20,21] Chronic smokers without the presence of severe reactive airway disease do not pose any risk of bronchospasm with adenosine.[33]

Another situation in which one needs to be cautious with adenosine use was pointed out by a study by Makaryus et al,[16] which reported development of a persistent AV block in patients with pre-existing right bundle branch block, when large doses of adenosine (47 mg over 5 minutes) were used and required postoperative permanent pacemaker implantation. Adenosine action on the coronary vasculature causes vasodilation, and this results in coronary vascular steal phenomenon in patients with cardiac ischemia.[34,35] Owall et al[23] in their case report mention the development of significant ST-segment depression and sustained ventricular tachycardia in one patient and atrial flutter in the other after administering adenosine. Both these patients had a history of previous myocardial infarction (9 and 13 years, respectively). Bebawy et al[26] too advocated avoidance of adenosine in patients with evidence of severe (80%) left main coronary artery stenosis or severe multi-vessel coronary artery disease (three vessels or grafts with 80% stenosis).

As far as renal function and use of adenosine are concerned, Zäll et al[13] advise against adenosine use in patients with impaired renal function because of its profound decrease in renal blood flow and glomerular filtration rate. The effect is

temporary and not associated with renin release and rapidly reverses once adenosine is discontinued. Exogenously administered adenosine is mostly eliminated by cellular uptake into vascular endothelium and erythrocytes. However, it can also be metabolized to uric acid and increase uric acid levels by 15%. This increase is clinically not significant to date, but one may exercise caution in its use in those with gout or purine metabolism defects.[23]

Last, adenosine breakdown and uptake are inhibited by dipyridamole,[22] nimodipine,[36] and methylxanthines,[18] resulting in increased levels of adenosine in these patients and the dosage may have to be adjusted accordingly. Therefore, to summarize adenosine is used as a preemptive drug for clipping of aneurysms, it is better to avoid certain patient groups as mentioned previously. However, in case of an emergency, such as an intraoperative aneurysm rupture or inability to clip the aneurysm due to technical difficulties, to salvage such a situation, the decision is best left to the judgment of the team of the neuroanesthesiologist and neurosurgeon involved.

Complications

Patient selection, if done adequately, results in few, if any, complications in the perioperative period. Tachyphylaxis can develop in patients subjected to repeated doses of adenosine. Bebawy et al[26] suggested avoiding the use of incremental dosing of adenosine to avoid tachyphylaxis.

Transient cardiac arrhythmias are occasionally seen, more so in patients with a preoperative history of myocardial ischemia.[23] They are clinically insignificant and recover spontaneously without any long-term sequelae.[26,27,29] Rarely, elevated troponins can occur postoperatively. Bendok et al[27] had two such patients, but neither showed acute changes on electrocardiogram (ECG) or echocardiogram. Bebawy et al also had two patients who had asymptomatic rise in troponin levels postoperatively but had no cardiac dysfunction on transthoracic echocardiogram.[26] Owing to these incidences, it is recommended placing external defibrillator pads on all patients who may receive adenosine as well as postoperative troponin levels monitoring.[24,26] To determine perioperative cardiac complications, such as myocardial ischemia or arrhythmias and 30-day mortality, Khan et al[19] retrospectively reviewed 64 cases of adenosine use during aneurysmal surgery and compared with 262 cases for which adenosine was not used. Results showed the outcome to be same in both the groups, and there was no difference in length of hospital or intensive care unit stay.

Deb et al, in 2014, reported a case in which intraoperative rupture of aneurysm led to 1.5 L of blood loss. Two sequential adenosine boluses were administered, to reduce the blood loss, which led to cardiac arrest and required electrical cardioversion. The patient woke up with lower cranial nerve palsy and needed tracheostomy and prolonged hospital stay. This patient had a history of interstitial lung disease, suggesting that patients with these comorbidities may be at higher risk for an adverse cardiac event after adenosine use.[37] In another case of intraoperative rupture with 500 mL of blood loss and hypotension, rapid redosing of adenosine, before full

recovery of cardiac function, prolonged the hypotensive period and required chest compressions.[28] Thus, if repeat dosing is required, it is important to have all the hemodynamics back to baseline and proper return of cardiac function.[9,19,28] A concern for neurological ischemic complications exists due to transient or prolonged duration of hypotension. Bebawy et al investigated the neurological safety profile of adenosine by comparing the incidence of neurological complications with and without adenosine use. Their results show that adenosine use was not associated with an increased neurological complication rate, defined as modified Rankin score > 2 at 48 hours postoperatively or at the time of discharge.[38]

Conclusion

The use of adenosine in clipping of complex cerebral aneurysms is a predictable, replicable, consistent, and hence a useful technique. In emergent cases of intraoperative rupture, it helps salvage the situation and has the advantage of readily being available and easy to administer. The available literature suggests that a proper selection of patients leads to minimum postoperative complications, and adenosine can be safely used. There have been no studies comparing the efficacy of adenosine administration and temporary clipping; however, studies show that it can be used in cases where temporary clipping carries a high risk of complications or is technically not feasible. Neuroanesthesiologists should familiarize themselves with this technique and its applications. A good understanding and collaboration between the neurosurgeon and the anesthesiologist are mandatory for a successful outcome.

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