

Adenosine-induced Flow Arrest to Facilitate Intracranial Complex Aneurysm Clip Ligation: Review of the Literature

Abstract

Complex intracranial aneurysms (CIAs) rank high among the most technically demanding neurosurgical pathologies. Microsurgery and clip ligation can be challenging in CIAs 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 CIAs. We reviewed the literature and PubMed advanced search showed 13 results of adenosine-induced flow arrest to facilitate intracranial complex aneurysm clip ligation which included three independent case reports and ten cases in a case series from 1999 to May 2016. Few case series have described the use of adenosine in intracranial aneurysm surgery. Satisfactory aneurysm decompression was achieved in all cases, and all aneurysms were clipped successfully. We recommend that 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.

Keywords: Adenosine-induced flow arrest, clip ligation, complex intracranial aneurysms

Introduction

Complex intracranial aneurysms (CIAs) include not only giant aneurysms (classically larger than 25 mm in diameter) but also smaller aneurysms in difficult locations of the human brain and cranial base.^[1] Such lesions are associated with a high risk of subarachnoid hemorrhage and progressive neurological deterioration or death caused by mass effect or stroke. 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. Microsurgery and clip ligation can be challenging in CIAs 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. Adenosine-induced flow arrest briefly reduces cerebral perfusion pressure and

reduces the turgor of the aneurysm, thereby facilitating the clip ligation. 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 an alternative method of flow arrest.

We reviewed the literature and Pubmed advanced search showed 231 cases of intracranial aneurysms which used adenosine-induced flow arrest during microsurgery and clip ligation from 1999 to May of 2016 (Bebawy *et al.* have 3 published papers, there are some repeated cases in these 3 papers).

Adenosine-induced Transient Asystole

Adenosine is a nucleoside analog that decreases heart rate and prolongs conductance through the atrioventricular (AV) node. Adenosine binds to cardiac A1 receptors, decreasing adenylate cyclase activity and intracellular cyclic adenosine monophosphate. This results in decreased inward calcium conductance and diminishes the pacemaker

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How to cite this article: Wang X, Feletti A, Tanaka R, Yamada Y, Suyama D, Kawase T, *et al.* Adenosine-induced flow arrest to facilitate intracranial complex aneurysm clip ligation: Review of the literature. *Asian J Neurosurg* 2018;13:539-45.

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Access this article online

Website: www.asianjns.org

DOI: 10.4103/ajns.AJNS_207_16

Quick Response Code:



current. Adenosine, which has a half-life between 0.6 and 10 s, is rapidly cleared from the circulation by uptake into erythrocytes and vascular endothelial cells. After a bolus injection of adenosine, the heart rate is reduced in a dose-dependent manner until complete AV node blockade occurs. The clinical effect of adenosine is seen 10–20 s after delivery of the bolus. The adenosine dose has a linear relationship with the duration of asystole that reaches a plateau between 40 and 60 s at 1 mg/kg.^[2] After the period of asystole, there is a variable duration of relative hypotension that lasts up to 1 min. Clinically, adenosine is most commonly used for the treatment of supraventricular tachycardia.^[3] Surgical uses for transient adenosine-induced asystole include endovascular aortic aneurysm repair^[4,5] and endovascular arteriovenous malformation treatment.^[6,7]

Which are Indications of Adenosine-induced Flow Arrest Using for Complex Aneurysm?

There are 3 earlier single patient case reports during 1999–2007. In the first reported case by Groff *et al.*,^[8] adenosine was safely administered to facilitate clipping of a basilar apex aneurysm. The patient received 3 doses of adenosine, and no complications were encountered. The second case was reported by Nussbaum *et al.*^[9] In this case, the authors used adenosine to control intraoperative rupture of an anterior communicating artery aneurysm after traditional methods of tamponade and temporary arterial occlusion failed to achieve adequate hemostasis. Adenosine allowed successful clipping in this case. The patient recovered without deficits, and no complications related to adenosine were reported. The third case reported by Heppner *et al.*^[10] involved a giant basilar apex aneurysm. Temporary occlusion of the basilar artery above the superior cerebellar arteries failed to provide sufficient softening of the aneurysm to allow perforator visualization and clip placement. The authors then resorted to 3 sessions of adenosine-induced flow arrest. The first episode allowed perforator dissection; the second allowed permanent clip placement; and the third allowed readjustment. Unfortunately, this patient had a poor outcome, but it was judged to be unrelated to adenosine administration.

Recently, there are 10 case series describing the use of adenosine to facilitate intracranial aneurysm repair during 2010–May 2016.

For CIAs clip ligation, it is often difficult to find an anatomically suitable place for temporary arterial occlusion, such as aneurysms of the intracranial carotid artery proximal to its bifurcation into the middle and anterior cerebral arteries.^[11,12]

These aneurysms have required temporary extracranial cross-clamp of the carotid artery in the neck to facilitate intracranial clip ligation. There are alternative techniques, such as endovascular balloon occlusion with suction decompression or deep hypothermic circulatory arrest, but

they require significant logistical support.^[13,14] In addition, these procedures may be associated with significant patient morbidity; endovascular procedures may result in dissection of friable arteries or distal arterial embolic occlusion, whereas cardiopulmonary bypass may result in arterial injury at the site of cannulation or arterial embolic phenomena related to aortic plaque. Furthermore, coagulopathies induced by cardiopulmonary bypass, independent of the required anticoagulation, result in a high incidence of postoperative intracranial hematomas.^[15] When temporary arterial occlusion is impractical or difficult for anatomical reasons, adenosine administration can produce brief, profound systemic hypotension, and flow arrest as an alternative to logistically complex methods of decreasing parent artery blood flow.^[8,10,16–19]

At the same time, 57 (24.7%) of 231 patients who were given adenosine underwent surgery of posterior circulation aneurysm, which include 25 (10.8%) basilar artery aneurysm and 29 (12.55%) unsorted posterior circulation aneurysm. This probably refers to the fact that these operations are technically the most challenging ones [Table 1].^[8,10,20–26]

Bendok *et al.*^[23] reported a series of 40 patients using adenosine to facilitate surgery for intracranial aneurysms, they pointed out that use of temporary clips remains the gold standard. Adenosine should be regarded as an additional and potentially synergistic tool with temporary clips, not a replacement for them.

In conclusion, for intracranial aneurysms in which temporary occlusion is impractical or technically difficult, adenosine is a viable option to provide brief periods of flow arrest for facilitating aneurysm clip ligation with apparently low neurologic and cardiopulmonary morbidity in the perioperative period.

Table 1: Location of the aneurysms (231 patients)

Aneurysms	Patients, n (%)
ICA	50 (21.64)
MCA	13 (5.63)
Ophthalmic artery	9 (3.90)
ACA	3 (1.30)
AcoA	35 (15.15)
PcoA	14 (6.06)
Pericallosal artery	2 (0.87)
Unsorted anterior circulation	35 (15.15)
BA	25 (10.8)
PICA	1 (0.43)
Posterior cerebral	1 (0.43)
Vertebral artery	1 (0.43)
Unsorted posterior circulation	29 (12.55)
Several AN	13 (5.63)

ICA – Internal carotid artery; MCA – Middle cerebral artery; AcoA – Anterior communicating artery; PcoA – Posterior communicating artery; BA – Basilar artery; PICA – Posterior inferior cerebellar artery; AN – Aneurysms

About the Use of Adenosine-induced Flow Arrest for Unruptured Aneurysms and Ruptured Aneurysms

As we all know, the first reported case by Groff *et al.*,^[8] adenosine was safely administered to facilitate clipping of an unruptured basilar apex aneurysm. One hundred and sixty-one (69.7%) of 231 patients who were given adenosine underwent surgery of unruptured aneurysm, 70 (30.3%) of 231 patients who were given adenosine underwent surgery of unruptured aneurysm [Table 2].

Early rupture of an aneurysm may make temporary clip application unfeasible and potentially dangerous owing to poor exposure and visualization of the relevant proximal and distal vasculature. Hence, intraoperative rupture is the clearest indication for adenosine, particularly when rupture occurs early in the dissection before proximal and distal control have been achieved.

In the series of Bendok *et al.*,^[23] adenosine was used for the purpose of controlling intraoperative rupture in 6 cases. In all 6 cases, the aneurysm was successfully clipped during adenosine-induced flow arrest.

Adenosine-induced flow arrest can clear the field for a long enough period to allow either definitive clipping or a corrective maneuver such as placing a pilot clip on the rupture site or trapping the aneurysm with temporary clips.

Careful Patient Selection

Do not administer adenosine to patients with evidence of severe (>80%) left main coronary artery stenosis, severe multivessel coronary artery disease (3 vessels or grafts with >80% stenosis),^[21,22,25] AV conduction defects (second degree AV block), or pacemakers.^[21]

In addition, patients with severe reactive airway disease (i.e., requiring hospitalization in the previous 6 months and active perioperative wheezing) do not receive adenosine.^[21,22]

Patients are excluded from undergoing this procedure if they have a history of severe asthma, symptomatic asthma, or sick sinus syndrome/heart block.^[27]

Careful patient selection in regard to cardiac history includes 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.^[22]

About the Selection of an Appropriate Initial Dose: Single Dose or Multiple Boluses of Adenosine?

The optimal dose and administration manner of adenosine have not yet been established. Luostarinen *et al.* reported the first series of 16 patients demonstrating its safety and efficacy during surgery for ruptured intracranial aneurysm.^[20] 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 clip.^[21] They recommended an initial dose between 0.3 and 0.4 mg/kg ideal body weight as the starting dose to achieve

Table 2: Review of adenosine for temporary flow arrest during intracranial aneurysm surgery cases

Year	Author	Number of cases	Male/female (n)	R/URA (n)	IDOA (mg)	SD/MB (n)	Median dose of adenosine	Dose range	MDOF (s)
1999	Groff <i>et al.</i>	1	0/1	0/1	6	0/3		6-12 mg	8-13
2000	Nussbaum <i>et al.</i>	1	1/0	1/0	12	0/1		12 mg	25
2007	Heppner <i>et al.</i>	1	0/1	0/1	6	0/3		6-36 mg	10-52
2010	Luostarinen <i>et al.</i>	16	6/10	16/0	6	12/4	12/27 mg	6-18/18-87 mg	-
2010	Bebawy <i>et al.</i>	24	3/21	8/16	-	10/14	0.34 mg/kg	0.29-0.44 mg/kg	57
2010	Powers <i>et al.</i>	6	4/2	3/3	6	0/6	78 mg	18-112 mg	30
2011	Guinn <i>et al.</i>	27	7/20	7/20	6	12/15	15 mg	3-285 mg	30
2011	Bendok <i>et al.</i>	40	5/35	10/30	0.3-0.4 mg/kg	19/21	24 mg	6-60 mg	57
2013	Bebawy <i>et al.</i>	72	11/61	19/53	0.3-0.4 mg/kg	-	-	-	-
2014	Khan <i>et al.</i>	64	18/46	20/44	6-12 mg	-	61.5 mg	36-135 mg	-
2014	Benech <i>et al.</i>	13	*	0/13	*	*	*	*	*
2015	Andrade-Barazarte <i>et al.</i>	8	2/6	0/8	0.2-0.4 mg/kg	5/3	22.5 mg	5-50 mg	20-40
2015	Lee <i>et al.</i>	22	6/16	4/18	6-12 mg/0.3-0.4 mg/kg**	13/9	-	-	19/24

*Not available; **6-12 mg/0.3-0.4 mg/kg: Adenosine was administered in a test-incremental manner starting with the minimal testing dose in the first 11 cases, and a bolus manner with an estimated dose based on body weight was used in the latter 11 cases. R/UNR – Ruptured/unruptured; IDOA – Initial dose of adenosine (mg); SD/MB – Single dose/multiple boluses of adenosine; MDOF – median duration of flow arrest

approximately 45 s of profound systemic hypotension. The third case series reported by Powers *et al.* Case series included 6 patients, including 3 unruptured, 2 ruptured, and 1 intraoperative aneurysm ruptured. An adenosine dose-response curve is approximated for each patient. To do this, escalating doses of adenosine are given (6, 12, 18, 24, and 36 mg) and titrated to determine the dose that would result in approximately 30 s of asystole. Typically, the dose of adenosine is about 1 mg/s asystole. Moreover, they reported that they had not observed any complication from repeated adenosine dosing in patients with normal preoperative cardiac function who are allowed to fully recover between doses. Furthermore, although doses of adenosine as high as 90 mg have been reported for endovascular aortic aneurysm repair,^[4] they have not had to give >60 mg as a single bolus during cerebral aneurysm clipping. Lee *et al.* reported their study, and they found that there was a linear relationship between the dose and the duration of asystole.^[26]

About the dose of adenosine, because individual responses to adenosine vary, so, different patients may need different doses of adenosine.^[20-29] We recommend we should establish an individual dose-response relationship for each patient by injecting escalating doses of adenosine [Table 3].

Advantages of Adenosine-induced Transient Asystole

1. Temporary flow arrest into the parent vessel, facilitating the circumferential exposure of the aneurysm and decreasing the risk of premature rupture during the dissection, and finally safe clip placement
2. Short half-life and recovery of the normal circulation with almost no need for additional medications
3. Adenosine may be administered repeatedly after recovery from the initial dose.

Potential Risks, Complications of Adenosine-induced Transient Asystole

Transient atrial fibrillation during cardiac rhythm recovery was reported with an incidence of 2.6%.^[21,23,26] One of these patients required intraoperative treatment with amiodarone for conversion to sinus rhythm.^[21] Troponin I elevation has been reported with an incidence of 1.73%,^[21,23] neither of these patients demonstrated any clinical (e.g., chest pain) or transthoracic echocardiographic evidence of cardiac dysfunction (e.g., decreased contractility and regional wall motion abnormality) in the postanesthesia care unit.

Khan *et al.* reported that 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.^[25] However, in a large series of patients with abdominal aortic aneurysms who underwent adenosine-induced

transient asystole, there was self-limited depression of the ST segment.^[4] In another report on adenosine-induced cardiac arrest, ventricular tachycardia and atrial flutter were reported in patients who had a history of myocardial infarction.^[17] Although most reported cardiac problems were safely controlled with medication, a medical history of coronary artery disease is a relative contraindication to this procedure.^[22] Adenosine can also induce pulmonary problems such as bronchospasm.^[30] In addition, caution is needed in patients with renal problems or purine metabolism abnormalities (in particular, gout) because adenosine is eliminated not only by cellular uptake but also through the kidney.^[17] Close examination is crucial for the prevention of medical complications. If there is no choice but to use adenosine intraoperatively without a preoperative cardiopulmonary evaluation, particular attention is required.

Repeat administration of adenosine has another potential risk. Adenosine is rapidly metabolized and eliminated from the body; however, there was a report of prolonged hypotension (11 epochs or >5.5 min), following repeat doses of adenosine before hemodynamic recovery in a case of uncontrolled, intraoperative aneurysm rupture.^[22] Because the situation was accompanied by massive blood loss and the cardiac rhythm was maintained, adenosine may not have been the only reason for the prolonged hypotension. However, it is generally understood that complete hemodynamic recovery is recommended before a repeat dose of adenosine is given.^[22] If possible, sufficient arachnoid dissection, aneurysm exposure, and selection of the appropriate aneurysm clip should be achieved before the first administration to minimize the number of administrations needed.

Prolonged bradycardia or asystole is one of the potential risks; so several authors recommend the addition of the placement of transcutaneous pacemakers as a precaution for prolonged bradycardia or asystole.^[27] We think it necessary to do so, because we think we should maximize the safety of patients and reduce potential risk during surgery.

Conclusion

Given the limited number of studies that have reported on this topic, there is no consensus regarding the dose, regimen, efficacy, and potential risks of adenosine. We recommend that adenosine be available during intracranial aneurysm surgery and be used judiciously for scenarios in which temporary occlusion with clips is impractical, unsafe, or difficult. Further studies are warranted to further refine our understanding of the utility of adenosine during intracranial aneurysm surgery.

At the same time, in some countries, authorization from the Institutional Review Board (IRB) may be necessary in

Table 3: Preexisting medical conditions at admission and intraoperatively, postoperative complications

Year	Author	Number of cases	CAD	Hypertension	Cardiac arrhythmias	ECG ischemia	Universal atherosclerosis	Asthma	COPD	OSA	Intraoperatively complications of adenosine	Postcomplications of adenosine
1999	Groff <i>et al.</i>	1	No	Yes	No	No	No	No	No	No	No	No
2000	Nussbaum <i>et al.</i>	1	No	No	No	No	No	No	No	No	No	No
2007	Heppner <i>et al.</i>	1	No	No	No	No	No	No	No	No	No	No
2010	Luostarinen <i>et al.</i>	16	2	7	1	4	3	0	0	0	No	No
2010	Bebawy <i>et al.</i>	24	0	0	0	0	0	0	0	0	2 developed transient atrial fibrillation	2 mild increases in troponin levels
2010	Powers <i>et al.</i>	6	0	0	0	0	0	0	0	0	No	No
2011	Guinn <i>et al.</i>	27	2	18	0	0	0	0	3	0	1 prolonged hypotension (>5.5 min)	No
2011	Bendok <i>et al.</i>	40	0	0	0	0	0	0	0	0	1 atrial fibrillation	1 atrial fibrillation, 2 sinus tachycardia
2013	Bebawy <i>et al.</i>	72	3	33	0	0	0	0	0	0	-	1. Transient bradycardia 2. Increases in troponin levels
2014	Khan <i>et al.</i>	64	1	43	2	-	-	6	3	5	No	5 arrhythmia
2014	Benech <i>et al.</i>	13	*	*	*	*	*	*	*	*	No	No
201	Andrade-Barazarte <i>et al.</i>	8	0	1	0	0	0	0	0	0	No	No
2015	Lee <i>et al.</i>	22	0	0	0	0	0	0	0	0	2 atrial fibrillation	No

*Not available. CAD – Coronary artery disease; COPD – Chronic obstructive pulmonary disease; OSA – Obstructive sleep apnea; ECG – Electrocardiogram

using adenosine at least in elective aneurysm surgery, so it needs to obtain the IRB's permission and it should be according to the IRB regulations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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