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REVIEW

Adenosine-assisted neurovascular surgery: initial case series and review of literature

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Abstract Cerebral aneurysms in complex anatomical locations and intraoperative rupture of aneurysms are challenging for neurosurgeons and anaesthetists alike. Mechanical and non-mechanical methods to reduce blood flow into aneurysms are well-recognised techniques to facilitate aneurysm exclusion from the circulation. Mechanical methods like temporary clipping of parent arteries, carotid artery ligation and endovascular balloon occlusion are commonly used in clinical practice. However, non-mechanical techniques such as rapid ventricular pacing and adenosine-induced cardiac standstill with hypotension are still emerging strategies. The aim of this study is to report our units' experience in the use of adenosine in aneurysm clipping and arteriovenous malformation (AVM) resection and review the literature. The records of all patients who had adenosine-assisted clipping of intracranial aneurysms and AVM resections in our institute between November 2015 and December 2016 were extracted from prospectively maintained database. The following data were collected: patient demographics, comorbidities, size and location of the aneurysms or AVM, number of boluses and total dose of adenosine administered, duration of cardiac standstill and hypotension (systolic blood pressure < 60 mmHg), intraoperative and postoperative complications and outcome scores at discharge. Literature search on Embase and PubMed for the terms "adenosine and clipping", "adenosine and aneurysm" and "adenosine and AVM" was performed. Eight aneurysms and two AVMs were identified. While both AVMs were elective procedures, half of the aneurysm clippings were on urgent basis. We used adenosine safely with spontaneous return of rhythm in all cases. Temporary clips to the parent artery were applied for brief periods in 2 patients who had pre-adenosine intraoperative rupture. We did not observe any immediate or late adverse events related to administration of adenosine. From our literature review, a total of ten case series and four case reports were identified. There were no reports on the use of adenosine in AVM resection. Transient adenosine-induced asystole is a safe and effective technique in facilitating surgical treatment of complex aneurysms and AVMs. In addition, adenosine use reduces the need, duration, and associated complications of temporary clip applications to parent arteries.

Keywords Adenosine · Aneurysm · Arteriovenous malformation · Subarachnoid haemorrhage · Clipping

Introduction

With advances in endovascular techniques, most aneurysms are now treated endovascularly. However, the time tested surgical clipping remains the option when endovascular treatment is not feasible. In those cases, the aneurysm is often of a complex anatomy that usually requires proximal control to soften the aneurysm, reduce its turgor to facilitate clipping, and to achieve control in the event of premature rupture. In a subset of those cases, this may not be feasible due to the anatomical challenges or early rupture. It is in those cases that other methods can prove useful including mechanical and non-mechanical tactics. The mechanical ones include carotid artery ligation and endovascular balloon occlusion and non-mechanical such as hypothermic cardiac standstill, rapid ventricular pacing, and adenosine-induced cardiac standstill which rely on stopping the cardiac output and subsequent

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cessation of aneurysmal blood flow. Adenosine is a naturally occurring endogenous purine nucleoside composed of an adenine molecule attached to a ribose sugar moiety (ribofuranose) via a beta-N9-glycosidic bond (6-amino-9-b-D-ribofuranosyl-9-H-purine) [13]. Adenosine decreases heart rate and prolongs conductance through the sinoatrial and atrioventricular nodes [16]. When administered as an intravenous bolus, adenosine can produce transient asystole with concomitant flow arrest. It has a short half-life (<10 s) secondary to rapid reuptake by erythrocytes and vascular endothelial cells and enzymatic breakdown.

Adenosine administration emerged as a form of non-mechanical temporary flow arrest in various open and interventional procedures, including cardiac surgery, interventional cardiac procedures, endovascular aortic aneurysm repair, and embolization of cerebral arteriovenous malformations. Several reports have documented successful use in intracranial aneurysm surgery [4]. We are reporting our initial experience with the use of adenosine-assisted open neurovascular surgery over 1 year. In addition, we present a review of literature on such use of adenosine-assisted neurovascular surgery.

Materials and methods

We identified all cases in which the technique of adenosine-induced cardiac standstill was used and retrospectively reviewed their records. Data were gathered about patient demographics, comorbidities, size and location of the aneurysms/AVM, number of boluses and total dose of adenosine administered, duration of cardiac standstill and duration of induced hypotension (systolic blood pressure < 60 mmHg), intraoperative events, postoperative complications, and outcome scores at discharge.

Between November 2015 and December 2016, adenosine was used in ten patients for eight aneurysm clippings and two AVM resections. In all patients, necessary preparations were made preoperatively to use adenosine. All patients were closely scrutinised preoperatively to exclude contraindications for the use of adenosine which is listed in Table 1 before a decision was made on appropriateness and safety of adenosine administration in each case individually. Alternative strategies to facilitate surgery were employed in cases where use of adenosine was contraindicated or deemed unsafe.

Table 1 Contraindications for adenosine

Contraindications of adenosine in cerebral aneurysm clipping
1. Severe reactive airway disease
2. Severe coronary artery disease
3. Pre-existing cardiac conduction abnormalities
4. Allergy
5. Dipyridamole, methylxanthines and nimodipine (relative contraindication) administration may prolong adenosine duration of action

Maintenance of anaesthesia was accomplished with inhaled sevoflurane and intravenous remifentanil infusion or total intravenous anaesthesia according to the discretion of the anaesthetist. Attention was paid to maintenance of body temperature (36–36.5 °C) and electrolyte balance (magnesium 1.0–1.2 mmol/L, potassium 4.5–5.5 mmol/L, ionised calcium 2.25–2.5 mmol/L) perioperatively. All the patients in our study were corrected for any electrolyte imbalance and actively maintained at normothermia prior to administration of adenosine.

All patients included in this series had a test dose, typically 6 mg prior to microscopic dissection of the lesion to assess degree of hypotension and period of asystole achieved with the above dose. This facilitated prediction of the treatment dose required during dissection of the lesion and/or in the event of any intraoperative complications i.e. rupture of aneurysm/AVM. When requested by the surgeon, the predicted treatment dose of adenosine was administered as a rapid intravenous bolus to achieve systolic blood pressure less than 60 mmHg for at least 30 s. Further doses were repeated as necessary throughout the surgery until aneurysm successfully clipped or AVM resected. Full recovery between each bolus was allowed before further dose was administered. All boluses were given through a central line or a proximally sited peripheral cannula. Rapid saline flush followed all boluses to prevent peripheral metabolism of adenosine. Duration of cardiac standstill and profound hypotension (SBP < 60 mmHg) and increase in peak airway were closely monitored after each bolus.

All patients were discussed in the dedicated vascular neurosurgery multi-disciplinary team meeting where all the imaging and the morphology of the aneurysms were scrutinised. All patients operated by the senior author are assessed for potential use of adenosine, if indicated. In six of the aneurysms, the main reason for the use of adenosine was to reduce the aneurysm wall tension and facilitate dissection while minimising the risk of intraoperative rupture. In the reminder of the aneurysm cases and the two AVMs, the premature rupture of the lesion required the use of adenosine until the proximal control or the source of bleeding was controlled.

A literature search was performed using the electronic databases of PubMed and Embase for the terms “adenosine and clipping”, “adenosine and aneurysm” and “adenosine and AVM”. Results were then reviewed to exclude manuscripts not published in the English language; conference abstracts and duplicates were also removed. The abstracts of all remaining articles were reviewed to exclude irrelevant studies. The full texts of the remaining articles were then reviewed, creating a final group of articles from this search strategy for inclusion in our review.

Results

Cases were equally distributed between males and females. The median age of presentation was 56.5 years [range = 45–59]. There were six middle cerebral artery aneurysms (MCA), one anterior communicating artery aneurysm (ACom) and one pericallosal artery aneurysm. There were two AVMs; one frontal and one cerebellar. Four aneurysm clippings and both AVM resections were conducted electively. Table 2 summaries these findings.

The median stay in hospital was 16.5 days [range = 11–26.5] and patients achieved Glasgow outcome score and modified Rankin score medians of 4.5 [range = 4–5] and 1.5 [range = 1–2] respectively at discharge. It is prudent to note that the median range here is higher than the expected owing to the operational guidelines of the national health service in the UK where physiotherapy, occupational health clearance and social package of care have to be in place prior to patient discharge. All patients had intraoperative indocyanine green (ICG) angiogram confirming complete exclusion of aneurysms from circulation and total AVM resection. There were no unexpected intraoperative events, and all patients had an eventless immediate postoperative convalescence with no perioperative cardiac or respiratory complications.

Literature review

From our literature review, a total of ten case series and four case reports were identified (Table 3). To date and in total, 207 aneurysm surgeries were reported to have had adenosine-assisted aneurysm clipping, 154 (79.3%) occurred in the anterior circulation and none has reported adenosine-assisted AVM resection.

We have excluded in our count the case series by Guinn and co-workers [8] as the cases were included in the bigger study by Khan et al. [12]. The same was for the initial Bebawy et al. [2] case series and Bendok et al. [4] case series which were both included in the bigger Bebawy et al.'s [3] second case series published in 2013 which is more encompassing and comprehensive.

The earliest publications on the topic were three single-patient case reports by Groff, Nussbaum and Heppner in 1999, 2000 and 2007, respectively [7, 10, 17]. The earliest case series we identified in our search was that of Luostrinen and co-workers in 2009 [15]. Luostrinen detailed his experience with 16 patients (10 anterior circulation and 6 posterior circulation aneurysms) all of whom suffered intraoperative rupture. He concluded that adenosine-induced circulatory arrest could be a safe option to facilitate clipping in case of a sudden aneurysm rupture. In this series, cardiac arrest was achieved in most cases (12/16 patients) after a single dose of adenosine (median 12 mg) and all patients went on to have normal cardiac rhythm after restoration of spontaneous circulation. Luostrinen reported that the dose of adenosine did not seem to have deleterious effects on the patient outcomes [15].

Powers et al. [18] in 2010 reported his experience in six anterior circulation aneurysms using the individualised dose-response curve method recommended by Hashimoto [9] to determine the proper dose to administer prior to aneurysm clipping.

Bebawy and co-workers in 2010 [2] published a case series of 24 patients to establish the dose-response relationship and the safety profile of adenosine-induced transient flow arrest. He concluded that a dose of 0.3–0.4 mg/kg ideal body weight may be recommended for a 45-s systemic hypotension during remifentanil and low-dose volatile anaesthetic with propofol-induced burst suppression [2]. From the same institution (Department of Anaesthesiology, Northwestern University Hospital, Chicago, USA), Bendok et al. in 2011 reported a 2-year consecutive experience with 40 aneurysms. The case series detailed each aneurysm characteristics, reasons for use of this technique and clinical and cardiac complications as well as the long-term neurological follow-up of those patients. He reported a rise of troponin in two cases and clinically insignificant arrhythmias in five patients [4]. In 2013 Bebawy and co-workers published a more extended case series including the two previous cohorts. This was the first case-control series and focused on reporting neurological outcome. They reported that adenosine-induced flow arrest was associated with "between a 15.7% increase or a 12.7 decrease in incidence of poor neurologic outcome at 48 h or at time of discharge" and was not associated with cardiac morbidity in the perioperative period [3].

In a case series of 66 patients, Khan and colleagues in 2014 [11] evaluated the safety of adenosine-assisted intracranial aneurysm surgery. He reported the 30-day cardiac morbidity in patients undergoing adenosine-assisted clipping. He reported no increase in cardiac complications or mortality in patients with low risk of coronary artery disease. In his report, he included the cases reported by Guinn et al. [8]. In the same year, Benech et al. compared proximal temporary artery occlusion with adenosine-induced flow arrest. They observed adenosine administration allowed an easier clipping without cardiological adverse events [5].

Andrade-Barazarte et al. [1] exploited the adenosine-induced flow arrest in the specific case of contralateral clipping of ophthalmic segment aneurysms. He published in 2015 his experience with eight cases and reported no complications thus noting that this is an adjunct worth of note. In his series of 22 aneurysm clippings, Lee et al. [14] (2015) noted the use of estimated dose injection

Table 2 Patients in this study. *MRS* modified Rankin score, *GOS* Glasgow outcome score, *Difib.* defibrillator use, *WFNS* World Federation of Neurological Surgeons

Patient No	Age	Sex	ASA grade	Pathology	Location	Size of aneurysm (mm)	Emergency / Grade of SAH (WFNS)	Temp. clip time)	Adenosine total dose (mg) / number of boluses	Duration of cardiac pause in seconds/ systolic BP <60 mmHg	Peek airway pressure (CmH_2O)	Defib. use	Neurological outcome		Hospital stay (days)
													MRS	GOS	
1	33	F	1	Aneurysm	ACOM	7	Yes / 1	8	12 / 1	0 / 0	0	No	2	4	22
2	40	M	2	AVM	frontal	-	No	N/A	36 / 2	20 / 80	2	No	1	5	4
3	63	M	3	Aneurysm	pericallosal	5	No	6	42 / 3	26 / 105	3	No	4	3	14
4	59	M	2	Aneurysm	MCA	7	Yes / 3	N/A	12 / 1	8 / 30	1	No	2	4	51
5	59	F	2	Aneurysm	MCA	12	No	N/A	48 / 4	60 / 200	3	No	1	5	16
6	57	M	1	Aneurysm	MCA	11	No	N/A	24 / 2	6 / 70	2	No	1	5	10
7	56	F	1	AVM	cerebellar	-	No	N/A	12 / 1	2 / 30	1	No	1	5	17
8	44	M	2	Aneurysm	MCA	10	Yes / 2	N/A	12 / 1	8 / 40	2	No	4	3	34
9	48	F	2	Aneurysm	MCA	9	No	N/A	24 / 2	10 / 70	1	No	1	5	7
10	63	F	3	Aneurysm	MCA	7	Yes / 3	20	18 / 1	10 / 50	2	No	2	4	28

was more convenient than test incremental dose. He reported two transient atrial fibrillations.

Discussion

Adenosine-induced flow arrest for cerebral aneurysm surgery was first described by Groff et al. in 1999 in posterior circulation aneurysms. Since then, several studies explored and attempted to evaluate such use and to define the indications, use, dose, morbidities and side effects of its use. Luostrinen in 2009 established its value in case of a sudden aneurysm rupture. Powers in 2010 established its safety and re-emphasised Luostrinen's finding. Bendok in 2011 published his experience with the technique in 40 consecutive cases reporting the encountered complications. In 2013, Bebawy assessed the impact of the use of adenosine on the neurological outcome concluding that it was associated with no more that 15.7% increase or 12.7% decrease in the incidence of neurological outcome at 48 h or at the time of discharge noting that there was no cardiac morbidity. Lee on the other hand in 2015 pointed out that the estimated dose injection was more convenient than the test incremental method and again reported no serious cardiac issues. In 2015, Andrade-Barazarte established that this technique is a viable alternative to proximal control in selected cases in ophthalmic segment aneurysms via a contralateral approach.

A plethora of publications attempted to define the advantages of this technique. Table 4 details a list of those salient findings.

Very few case series have described the use of adenosine in intracranial aneurysm surgery. Data on appropriate dosing regimen for adenosine-induced flow arrest is limited. Response to adenosine, i.e., bradycardia and hypotension can vary widely with occasional unusual sensitivity or resistance. The ideal method of individualising drug administration may be based on an individual patient's dose-response relationship, which is determined by exposure to escalating drug doses. However, this may not always be a practical or safe option with adenosine. Administration of escalating adenosine doses required to determine an individual's dose response exposes the patient to multiple periods of flow arrest that have the potential to produce cardiac and neurologic injury. Also, exposure to repeated doses of adenosine may result in either a carryover effect or tachyphylaxis, either of which may lead to inaccuracy in estimating the dose required at the time when flow arrest is needed for clip placement [2]. Bebawy et al. in their case series recommended utilising a starting dose of 0.3–0.4 mg/kg ideal body weight to achieve approximately 45 s of profound systemic hypotension during a remifentanil/low-dose volatile anaesthetic with propofol-induced burst suppression. This is very similar to what Guinn et al. found in their review of 27 patients where adenosine was given in escalating

Table 3 Summary of the literature search

		Type		Anterior circulation	Posterior circulation	Aim of the study	Complications	Conclusion
GROFF	1999	CR	1	–	1	Case report	Nil	N/A
Nussbaum	2000	CR	1	1	–	Case report	Nil	N/A
Heppner	2006	CR	1	–	1	Case report	Death	N/A
Luostarinen et al.	2009	Series	16	10	6	Described the experience of adenosine use during intraoperative aneurysm rupture	Nil	• In case of sudden aneurysm rupture, adenosine-induced circulatory arrest could be a safe option to facilitate clipping.
Bebawy et al.	2010	Series	24	17	8	To determine the dose-response relationship and apparent perioperative safety profile of adenosine in intracranial aneurysm patients.	2 developed AF 2 increased troponine	• adenosine is capable of providing brief periods of profound systemic hypotension with low perioperative morbidity. • a dose of 0.3 to 0.4 mg/kg ideal body weight may be the recommended starting dose to achieve approximately 45 s of profound systemic hypotension during a remifentanil/low-dose volatile anaesthetic with propofol induced burst suppression.
Powers et al.	2010	Series	6	6	–	To assess the benefits of adenosine-induced transient asystole in complex anterior circulation aneurysms, to describe our experience in selected cases, and to provide the first experience of the use of adenosine in anterior circulation aneurysms.	Nil	• Transient adenosine-induced asystole is a safe and effective technique in select circumstances that may aid in safe and effective aneurysm clipping. Along. • adenosine-induced asystole facilitates circumferential visualisation of the aneurysm neck and is another technique available to cerebrovascular surgeons.
Bendok et al.	2011	Series	40	31	9	report our 2-year consecutive experience with 40 aneurysms in 40 patients for whom we used adenosine to achieve temporary arterial occlusion during aneurysm surgery.	2 cases of elevated troponin 2 cases of AF 2 cases of TACHYarrhythmia 1 case of BRADYarrhythmia	• Adenosine appears to allow safe flow arrest during intracranial aneurysm surgery. This can enhance the feasibility and safety of clipping in select circumstances.
Guinn et al.	2011	Series	27	23	4	Describes a method of temporarily decompressing the aneurysm via adenosine-induced transient asystole	NOT RELATED COMPLICATION	• Reasonable alternative method when temporary clipping is not desired or possible
Bebawy et al.	2013	Series	72	60	12	Determining if the use of intraoperative adenosine has a negative effect on the neurological outcome of the patient		• Associated with no more than 15.7% increase or 12.7% decrease in the incidence of poor neurologic outcome at 48 h. or at time of hospital discharge • No cardiac morbidity
Benech et al.	2014	Series	13	–	–	Comparing proximal temporary artery occlusion	Nil	• adenosine-induced arrest technique could be an

Table 3 (continued)

		Type		Anterior circulation	Posterior circulation	Aim of the study	Complications	Conclusion
						with adenosine-induced flow arrest		efficacious, harmless and reliable alternative strategy for surgical treatment of complex cerebral aneurysms
Khan et al.	2014	Series	66	49	17	Assessing the safety of adenosine-assisted intracranial aneurysm surgery	Nil	• Adenosine-assisted intracranial surgery is not associated with increased perioperative cardiac complications or mortality in patients with low risk for coronary disease
Lee et al.	2015	Series	22	19	3	Report on the dose, regimen, efficacy, and potential risk of adenosine.	AF 2 cases	• Safe and helpful for satisfactory clipping of a complicated aneurysm • Estimated dose injection was more convenient than test incremental method • No serious cardiologic problems.
Andrade-Barazarte et al.	2015	Series	8	8	–	To describe Adenosine transient cardiac arrest as an alternative tool to obtain proximal control and soften the aneurysm sac in selected patients.	nil	In selected patients, transient cardiac arrest induced by adenosine during a contralateral approach allows a brief flow arrest and softening of the aneurysm for safer exposure and clipping.
Vealey et al.	2017	CR	1	1		Case report	nil	NA

doses to achieve 30 s of asystole. (i.e. general dose range of 0.24 to 0.42 mg/kg of adenosine to provide about 30 to 60 s of hypotension and bradycardia).

In our study, the treatment dose of adenosine administered to achieve systolic blood pressure less than 60 mmHg for at least 30 s was typically around 0.2–0.3 mg/kg ideal body weight. Doses were repeated in about 50% of cases. This induced asystole and profound hypotension for 9 and 60 s, respectively, and was adequate for surgeons to successfully clip the aneurysm or resect the AVM. The total adenosine dose required in our study population was lower than those mentioned in the above studies.

Spontaneous return of sinus rhythm was successfully achieved in all cases following the use of adenosine. No patients developed post-adenosine arrhythmia. External defibrillator pads were available for use but not required in any case. Use of relatively small doses of adenosine, strict exclusion criteria for administration of adenosine, maintenance of perioperative normothermia and electrolyte balance may have contributed to this. Also, none of the patients developed prolonged hypotension requiring cardiac compression and vasopressors post adenosine, a complication reported by Guinn et al. as a consequence of adenosine redosing. Number of doses required to produce the desired effect in our study was 1.5 [1, 2], and as mentioned in methodology, full recovery

Table 4 Summary of adenosine use advantages

- Excellent circumferential visualisation of the aneurysm neck and safe clip application [17].
- This technique also allows the surgeon to have the maximum amount of space available to manipulate the aneurysm and place the clips, as no temporary clips are in the field of view [6].
- Temporary clips only decrease flow from the clipped inflow, whereas adenosine produces a more global hypotension and therefore often a better collapse of the aneurysm [6].
- 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 [7].
- Where the aneurysm ruptures before achieving proximal control [16].
- Facilitates clipping of giant and broad necked aneurysms [4].
- Avoids risks of coagulopathy, hyperglycemia and rebound hyperthermia associated with the use of hypothermic circulatory arrest and cardiopulmonary bypass as techniques to reduce blood flow into the aneurysm [2].
- Decrease intra-aneurysmal tension or "soften the aneurysm" [11].

between each bolus was allowed before further doses were administered to reduce carryover effect.

We found no significant increase in peak airway pressures following bolus administration of adenosine in patients without reactive airway disease. Although there are several case reports of bronchospasm after adenosine administration, they have always been in patients with active asthma or chronic obstructive lung disease [12].

In the two cases with intraoperative rupture, this occurred prior to administration of adenosine. Adenosine was administered and temporary clip applied to parent artery to achieve proximal control. Duration of temporary clip on the parent artery in both cases was significantly lower (90 and 160 s) than the recommended limits (10 min). Adenosine use reduces the need for temporary parent artery occlusion. However, if this is required, adenosine is equally helpful in reducing the duration of temporary clip application, and the complications associated with it.

Controlled hypotension is a well-recognised technique in neuro-anaesthesia to aid the neurosurgeon in achieving control of the source of bleeding in events where blood obscures the surgical field. However, we are not aware of any reports on the use of adenosine-induced cardiac standstill in cases of uncontrolled AVM bleeding, a technique we found extremely helpful in two cases to identify and control the source of bleeding swiftly. Adenosine offered the benefit of a short period of bloodless field where the source of bleeding was identified and controlled. In addition, a surge of CSF into the operative field was noted in all cases which helped in maximising the operative field without the need for retraction.

Our study is limited by using retrospective data and the small sample size and though the use of adenosine-assisted neurovascular surgery is not new, it is under represented in literature. Whether this is due to actual rarity of its use or under reporting remains to be established. However, the literature supports the safe use of adenosine.

Conclusion

Adenosine is safe, cheap, widely available and easily applicable in different scenarios within the neurosurgical practice including aneurysm and AVM surgery. It does not require complex or invasive preparation when compared to other alternatives. The global blood flow reduction associated with adenosine use will ensure a bloodless field as opposed to single artery control by temporary clip, and it reduces the need of temporary clipping and thus improves visualisation and maximises the space available for the surgeon to manipulate and clip the aneurysm.

With the knowledge of associated complications and appropriate precautionary measures, adenosine can be effectively used to decompress intracranial aneurysms, facilitating surgical exposure and aneurysm clip ligation. In the era of interventional neuroradiology, where only the more complex aneurysms and AVMs make their way to clippings and open resections, we think adenosine-assisted neurovascular surgery is an essential part of the armamentarium of a neurovascular neurosurgeon and a neuroanaesthetist, and all patients should be screened and prepared for potential use of adenosine intraoperatively.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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