 doi: 10.2176/jns-nmc.2024-0331

NMC Case Report Journal 12, 115-119, 2025

Safety of Adenosine-assisted Clipping Surgery for Unruptured Cerebral Aneurysms: Interim Results of a Single-center, Single-arm Study

Tomohito HISHIKAWA,[1,2] Satoshi MURAI,[2] Masafumi HIRAMATSU,[1] Jun HARUMA,[1] Yuki EBISUDANI,[1] Takao YASUHARA,[1] Kenji SUGIU,[1] Kazuyoshi SHIMIZU,[3] Koji NAKAGAWA,[4] Aya KIMURA-ONO,[5] Katsuyuki HOTTA,[5] Hiroshi MORIMATSU,[3] and Isao DATE[1,6]

[1]*Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Okayama, Japan*
[2]*Department of Neurosurgery, Kawasaki Medical School, Kurashiki, Okayama, Japan*
[3]*Department of Anesthesiology and Resuscitology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Okayama, Japan*
[4]*Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Okayama, Japan*
[5]*Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Okayama, Japan*
[6]*Department of Neurosurgery, Okayama Rosai Hospital, Okayama, Okayama, Japan*

Abstract

The aim of this single-center, single-arm study was to evaluate the safety of adenosine-assisted clipping surgery for unruptured cerebral aneurysms. Five patients underwent aneurysmal clipping during adenosine-induced hypotension at ≤60 mmHg. The mean age of patients was 63.4±8.5 years, and the mean aneurysm size was 5.3±1.1 mm. The prevalence of patients with modified Rankin Scale scores of zero 30 days after surgery was 100%. The degree of aneurysm obliteration was complete in 4 patients and residual dome in 1 patient. The mean total dosage of adenosine was 37.4±18.8 mg. The mean duration of systolic blood pressure at ≤60 mmHg was 64.2±28.3 secs. No patients exhibited paroxysmal atrial fibrillation within 24 hours after adenosine administration or elevation of high-sensitivity cardiac troponin T on postoperative day 1. There was no reduction in either motor-evoked or somatosensory-evoked potential amplitude during surgery. Adenosine-induced hypotension is a safe procedure in clipping surgery for unruptured cerebral aneurysms.

Keywords: adenosine, clipping, safety, unruptured cerebral aneurysm

Introduction

In the era of endovascular treatment, some unruptured cerebral aneurysms (UCAs) are unsuitable for endovascular treatment and surgical clipping plays an important role in preventing UCA rupture.[1)] Decompressing aneurysms and visualizing the anatomy around them during surgical clipping is important to obliterate aneurysms completely and to preserve perforators close to aneurysms. The placement of a temporary clip at the main trunk proximal to the aneurysm is the standard procedure to decompress aneurysms. However, some aneurysm factors, such as large aneurysms, deep aneurysm location, and adjacence to the skull base bone, can make application of a temporary clip to the main trunk proximal to the aneurysm difficult. Moreover, application of a temporary clip is believed to be challenging in cases of intraoperative rupture, especially when rupture occurs early in the dissection. The American Heart Association/American Stroke Association consider adenosine for temporary cardiac arrest a technical advance in their guidelines for management of patients with UCAs.[2)] Adenosine-induced decompression of UCAs is an off-label use in Japan and we planned a single-center, single-arm study to evaluate the safety and feasibility of

Received December 14, 2024; Accepted January 7, 2025

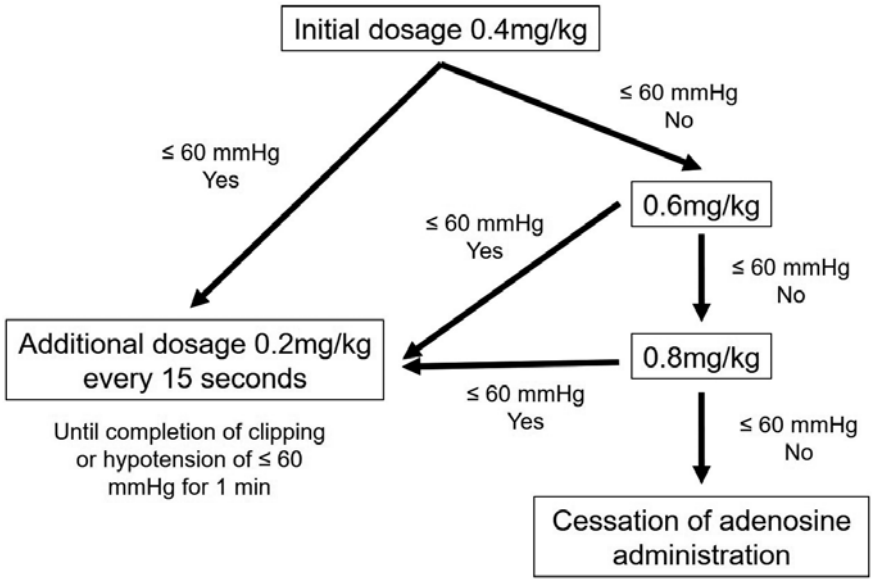

Fig. 1 The protocol for adenosine administration[3].

adenosine-assisted clipping surgery for UCAs as the first step.[3] The aim of this study was to present the interim results of this clinical trial.

Materials and Methods

Study design

This was a single-center, single-arm study to evaluate the safety and feasibility of adenosine-assisted clipping surgery for UCAs. This study was approved by the Okayama University Certified Review Board (approval number: CRB 20-003) and was registered in the Japan Registry of Clinical Trials (jRCT, registration no. jRCTs061200023). This trial was stopped owing to the transfer of the principal researcher (T.H.) from Okayama University to Kawasaki Medical School. The precise protocol of this study has been described previously.[3] Briefly, patients were enrolled if the surgeons judged that decompression of the aneurysm was effective for one of the following reasons: aneurysm size ≥7 mm; neck size ≥4 mm (≤2 in dome/neck ratio); adhesion of branches, perforators, or veins to the aneurysm; aneurysm buried in the brain; atherosclerosis of the aneurysm; or existence of a daughter sac that had undergone adenosine-assisted clipping surgery according to the protocol of adenosine administration (Fig. 1).[3] We planned to enroll 10 patients in this study.

Endpoints

The primary endpoint was the modified Rankin Scale (mRS) score 30 days after surgery. The secondary endpoints were (1) degree of aneurysm obliteration by the clip, which was evaluated by 3-dimensional computed tomography angiography on postoperative days 4-7; (2) total dosage of adenosine; (3) time between adenosine administration and termination of clipping; (4) mRS scores at discharge and at 90 days after surgery; (5) prevalence of maintaining systolic blood pressure at ≤60 mmHg between 30 secs and 1 min by adenosine administration and its duration; (6) adverse events related to adenosine (paroxysmal atrial fibrillation [Paf] within 24 hours after adenosine administration, prolonged hypotension at ≤60 mmHg in systolic blood pressure for >1 min, and elevation of high-sensitivity cardiac troponin T, which was defined as ≥0.014 ng/mL on postoperative day 1, and an increase of ≥20% compared with the preoperative value[4]); and (7) other adverse events (a reduction of amplitude <30% compared with the control in the motor-evoked potential [MEP] and <50% in somatosensory-evoked potential [SEP], new infarction detected by magnetic resonance imaging on the day after surgery).

Results

Recruitment commenced in October 2020, and data collection was completed on January 19, 2022. In this period, 21 patients underwent clipping surgery for UCAs. Seven patients with UCAs were enrolled in this study. Of these 7 patients, 1 patient withdrew informed consent. In another patient, adenosine-assisted clipping was deemed inadequate during the operation and clipping was performed using a temporary clip. Thus, a total of 5 patients underwent adenosine-assisted clipping surgery and were evaluated in this study (Fig. 2). The mean age of the patients (2 men and 3 women) was 63.4±8.5 years (range 52-76 years). Four aneurysms were located in the middle cerebral artery bifurcation and 1 in the internal carotid artery-anterior choroidal artery bifurcation. The mean aneurysm size was 5.3±1.1 mm (range 3.9-6.8 mm). All patients had a preop-

erative mRS score of zero. Table 1 lists the patient characteristics in this study.

The prevalence of patients with mRS scores of zero 30 days after surgery was 100% (Table 2). The degree of aneurysm obliteration was complete in 4 patients and residual dome in 1 patient. The mean total dosage of adenosine was 37.4±18.8 mg (range 20-65 mg). Two patients received a single adenosine bolus, whereas 1 patient each was administered 2, 3 and 4 adenosine boluses. The mean time between adenosine administration and completion of clipping was 52.6±14.3 secs (range 38-73 secs). All patients had mRS scores of zero at discharge and 90 days after surgery. The mean duration of systolic blood pressure at ≤60 mmHg was 64.2±28.3 secs (range 30-98 secs), and 3 patients had prolonged hypotension at ≤60 mmHg in systolic blood pressure for >1 min. No patients exhibited Paf within 24 hours after adenosine administration or elevation of high-sensitivity cardiac troponin T on postoperative day 1. There was no reduction in MEP or SEP amplitude during surgery. Brain magnetic resonance imaging revealed no new cerebral infarctions on postoperative day 1. One patient experienced pseudogout on postoperative day 7, which was deemed an adverse event unrelated to adenosine. The adenosine-related complication rate was 0% in this study.

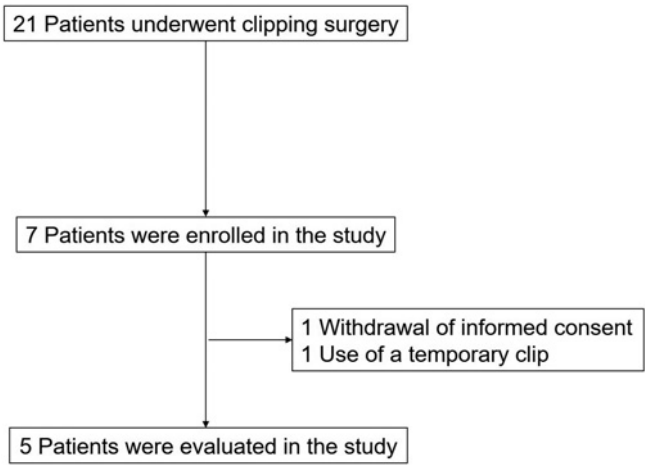

Fig. 2 Flow diagram in this study.

Discussion

Several studies have reported the successful use of adenosine during intracerebral aneurysm surgery.[5-9] Adenosine can induce hypotension or cardiac arrest by binding cardiac A1 receptors. Adenosine administration is expected as an alternative to applying a temporary clip owing to its rapid-acting effect and a short half-life. According to previous reports, the goals of adenosine administration during surgery are to induce cardiac arrest[6,9] and achieve systolic blood pressure of ≤60 mmHg with or without a heart rate ≤40.[5,7,10] The goal in this study was to maintain systolic blood pressure at ≤60 mmHg for between 30 secs and 1 min in consideration of patient safety. The mean total dosage of adenosine in this study was 37.4±18.8 mg (range 20-65 mg), and all patients exhibited a decrease in systolic blood pressure at ≤60 mmHg. The mean total dosage of adenosine in this study was comparable to those in previous reports (range 3-470 mg).[6-9] In case 3, the duration of systolic blood pressure at ≤60 mmHg was 98 secs, a longer duration than the study goal in this study, and we established a recovery protocol. The first step in the recovery protocol is prompt administration of ephedrine or phenylephrine if the duration of systolic blood pressure at ≤60 mmHg exceeds 1 min. When an increase in systolic blood pressure to >60 mmHg is not observed within 30 secs after administration of pressor agents, percutaneous pacing is performed in the second step. This recovery protocol was implemented in cases 4 and 5, and systolic blood pressure promptly increased to >60 mmHg after administration of pressor agents in both cases. Significant interpatient variability has been reported to exist in response to adenosine and duration of hypotension, and the optimal dose and manner of administration of adenosine have not yet been

Table 1 Patient characteristics

Case	Age, yr	Sex	Location	Maximum size, mm	mRS score	Body weight, kg	Reasons for adenosine use
1	76	Female	MCA	5.0	0	51	Neck size ≥ 4 mm Existence of a daughter sac
2	63	Male	MCA	4.9	0	67	Neck size ≥ 4 mm Existence of a daughter sac
3	62	Male	MCA	5.7	0	65	Neck size ≥ 4 mm
4	64	Female	IC-AChA	3.9	0	52	Existence of a daughter sac
5	52	Female	MCA	6.8	0	57	Neck size ≥ 4 mm Aneurysm buried in the brain

MCA, middle cerebral artery; IC-AChA, internal carotid-anterior choroidal artery; mRS, modified Rankin Scale

Table 2 Primary and secondary endpoints

Case	Primary endpoint	Secondary endpoint								
	mRS score 30 days post-surgery	Aneurysm obliteration	Total dosage of adenosine, mg	Time between adenosine administration and completion of clipping, s	mRS score at discharge/ 90 days	Duration of systolic BP at < 60 mmHg, s	Paf	Elevation of cardiac troponin T	Reduction in MEP/ SEP amplitude	New cerebral infarction
1	0	Complete	20	38	0/0	40	No	No	No/No	No
2	0	Complete	35	60	0/0	30	No	No	No/No	No
3	0	Complete	65	73	0/0	98	No	No	No/No	No
4	0	Complete	21	41	0/0	74	No	No	No/No	No
5	0	Residual dome	46	51	0/0	79	No	No	No/No	No

mRS, modified Rankin Scale; BP, blood pressure; Paf, paroxysmal atrial fibrillation; MEP, motor-evoked potential; SEP, somatosensory-evoked potential

established.[11] The rescue protocol is useful and important in adenosine-assisted clipping surgery, and the influence on circulatory dynamics of the protocol of adenosine administration in this study should be evaluated in more cases.

Cardiac ischemia and transient cardiac arrythmia have been reported to be important complications in adenosine-assisted clipping surgery.[5,6,8,11] Bendok et al.[6] reported that troponin levels were elevated postoperatively in 2 patients without acute changes observed on echocardiography, and clinically insignificant cardiac arrythmia was noted in 5 of 40 patients in their single-center study. Bebawy et al.[5] reported that in 2 patients, transient, hemodynamically stable atrial fibrillation developed, and 2 had postoperative troponin elevation without any evidence of cardiac dysfunction. None of the patients in the present study had troponin T elevation on postoperative day 1 or Paf intraoperatively or postoperatively. Although cardiac ischemia or arrythmia in adenosine-assisted clipping surgery is temporary and rarely causes serious sequelae, it is important to monitor cardiac ischemia and rhythm using troponin T and postoperative echocardiography. To the best of our knowledge, this study is the first to evaluate changes of MEP and SEP in adenosine-assisted clipping surgery. No patients showed reductions in MEP or SEP amplitude during surgery or new cerebral infarction on postoperative day 1. These data indicate that intraoperative adenosine-induced hypotension at ≤60 mmHg for approximately 1 min has little effect on cerebral hemodynamics.

There are several limitations in this study. First, the sample size was limited because the trial was stopped owing to the transfer of the principal researcher. Second, ease of clipping under adenosine-induced hypotension was not evaluated in this study. To overcome this limitation, adenosine-induced hypotension should be applied to large and deep aneurysms in narrow corridors where temporary clip ligation is difficult or not possible or in cases of intraoperative aneurysmal rupture. Third, this study was a single-arm study in patients who underwent adenosine administration to decompress aneurysms. To evaluate the feasibility of adenosine, a comparison study between temporary clipping and adenosine is warranted in a future study.

Conclusions

Adenosine-induced hypotension is a safe procedure in clipping surgery for UCAs. Establishing an adenosine administration protocol and rescue protocol and complying with these protocols are important in the clinical setting.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

References

1) Hishikawa T. Concept and management of cerebral aneurysms not suitable for endovascular treatment - from a viewpoint of hybrid neurosurgeon -. Jpn J Neurosurg. In press.
2) Thompson BG, Brown RD Jr, Amin-Hanjani S, et al. Guideline for the management of patients with unruptured intracranial aneurysms: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(8):2368-400. doi: 10.1161/STR.0000000000000070
3) 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):393-6. doi: 10.2176/nmc.st.2021-0018
4) Toda H, Nakamura K, Nakagawa K, et al. Diastolic dysfunction is a risk of perioperative myocardial injury assessed by high-sensitivity cardiac troponin T in elderly patients undergoing

non-cardiac surgery. Circ J. 2018;82(3):775-82. doi: 10.1253/circj.CJ-17-0747
5) 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):1406-11. doi: 10.1213/ANE.0b013e3181d65bf5
6) 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):815-20; discussion 820. doi: 10.1227/NEU.0b013e318226632c
7) Guinn NR, McDonagh DL, Borel CO, et al. Adenosine-induced transient asystole for intracranial aneurysm surgery. a retrospective review. J Neurosurg Anesthesiol. 2011;23(1):35-40. doi: 10.1097/ANA.0b013e3181ef2b11
8) Intarakhao P, Thiarawat P, Rezai Jahromi B, et al. Adenosine-induced cardiac arrest as an alternative to temporary clipping during intracranial aneurysm surgery. J Neurosurg. 2018;129(3):684-90. doi: 10.3171/2017.5.JNS162469
9) Niiya Y, Ito M, Itosaka H, et al. Efficacy of adenosine triphosphate-induced transient cardiac arrest for deflation of cerebral aneurysms during clipping surgery. Jpn J Neurosurg. 2014;23(11):889-96. doi: 10.7887/jcns.23.889
10) Lee SH, Kwun BD, Kim JU, et al. Adenosine-induced transient asystole during intracranial aneurysm surgery: indications, dosing, efficacy, and risks. Acta Neurochir (Wien). 2015;157(11):1879-86: discussion 1886. doi: 10.1007/s00701-015-2581-7
11) Desai VR, Rosas AL, Britz GW. Adenosine to facilitate the clipping of cerebral aneurysms: literature review. Stroke Vasc Neurol. 2017;2(4):204-9. doi: 10.1136/svn-2017-000082

Corresponding author: Tomohito Hishikawa, MD
Department of Neurosurgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan.
e-mail: thishi@med.kawasaki-m.ac.jp