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REVIEW

Anesthetic management of unruptured intracranial aneurysms: a qualitative systematic review

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Abstract

Intracranial aneurysms (IA) occur in 3–5% of the general population and may require surgical or endovascular obliteration if the patient is symptomatic or has an increased risk of rupture. These procedures carry an inherent risk of neurological complications, and the outcome can be influenced by the physiological and pharmacological effects of the administered anesthetics. Despite the critical role of anesthetic agents, however, there are no current studies to systematically assess the intraoperative anesthetic risks, benefits, and outcome effects in this population. In this systematic review of the literature, we carefully examine the existing evidence on the risks and benefits of common anesthetic agents during IA obliteration, their physiological and clinical characteristics, and effects on neurological outcome. The initial search strategy captured a total of 287 published studies. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 28 studies were included in the final report. Our data showed that both volatile and intravenous anesthetics are commonly employed, without evidence that either is superior. Although no specific anesthetic regimens are promoted, their unique neurological, cardiovascular, and physiological properties may be critical to the outcome in vulnerable patients. In particular, patients at risk for perioperative ischemia may benefit from timely administration of anesthetic agents with neuroprotective properties and optimization of their physiological parameters. Further studies are warranted to examine if these anesthetic regimens can reduce the risk of neurological injury and improve the overall outcome in these patients.

Keywords Intracranial aneurysm · Subarachnoid hemorrhage · Conscious sedation · Aneurysm, ruptured stroke · Craniotomy · Anesthesia, general · Anesthetics

Introduction

Anesthesia for UIA obliteration differs from routine craniotomies because of specific physiological challenges associated with the underlying neurovascular disease and the planned procedure. The margin of safety between high blood pressure leading to rupture and a low blood pressure provoking ischemia is narrow in these patients; hence, immediate management of hypertensive or hypotensive events is critical. Moreover, the anesthesiologist must balance the need to maintain cerebral perfusion pressure (CPP) to promote brain oxygenation with the risk of increasing the transmural pressure gradient that can promote aneurysm rupture [1, 2] (Fig. 1). Respiratory parameters must be carefully titrated to optimize oxygenation and carbon dioxide tension; coagulation and electrolyte balance, maintained; and intraoperative events and complications, rapidly managed to prevent risk for

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devastating neurological injuries (Fig. 2). Procedure-related challenges such as temporary occlusion of the parent vessel require special anesthetic consideration. Temporary clipping of the parent vessel may be needed to rescue or preempt IA rupture or to facilitate a surgical step in elective IA surgeries. However, temporary clipping can lead to ischemic stroke, dissection of the vessel, or rupture of the aneurysm [3–5]. Prolonged occlusion of the parent vessel leads to extended hypoperfusion in its corresponding territory; therefore, proper anesthetic management such as careful blood pressure augmentation and neuroprotection may be warranted. Various anesthetic agents reduce cerebral metabolism—as listed in this review—and, therefore, could be considered. However, it is essential to choose an anesthetic approach that preserves or ideally even augments cerebral blood flow (CBF)—in particular collateral flow to the ischemic territory—while reducing cerebral metabolic rate of oxygen ($CMRO_2$) (Table 1). Since temporary clipping during IA surgery may provoke cerebral vasospasm, cerebral function monitoring may be employed to guide blood pressure management and removal or reapplication of the temporary clip.

In some patients, it may become necessary to induce a transient circulatory arrest or severe hypotension in case of an aneurysm rupture or for decompression of the aneurysm to facilitate clip application. With appropriate safety precautions, adenosine boluses of up to 30 mg have been successfully used to induce a transient asystole in these patients [5]. Adenosine may also be considered when temporary clipping of proximal vessels is not desirable or possible. Although some recent reviews provide general guidelines on the anesthetic management of cerebral aneurysm surgery [1, 2, 8], there are no rigorously conducted studies or reviews to assess the intraoperative anesthetic risks and outcome effects for UIA obliteration. Therefore, we conducted a systematic review of the literature examining the hemodynamic, physiological and pharmacological effects of common anesthetic agents and regimens during endovascular and open procedures to obliterate UIA.

Methods

Study selection

All articles in English language, including adult patients, and published in indexed scientific journals were considered. Randomized controlled trials (RCT), prospective and retrospective cohorts, case series, and case reports, as well as cross-sectional studies involving patients with unruptured cerebral aneurysm or those who had undergone aneurysm obliteration or neurosurgical procedures were eligible for inclusion. Given the scarcity of studies on unruptured cerebral aneurysms, we also discuss relevant findings from selective studies on neurological effects of anesthetics and patients with aneurysmal subarachnoid hemorrhage.

Data extraction

We performed a systematic search on MEDLINE to identify studies. We used the participants, interventions, comparisons, and outcomes (PICO) search tool [9] to determine the following medical subject heading terms: "Aneurysm OR Aneurysm Surgery" AND "Nitrous Oxide OR Isoflurane OR Desflurane OR Sevoflurane OR Ketamine OR Propofol OR Barbiturate OR Thiopental OR Dexmedetomidine OR Opioids" AND "brain OR intracranial OR cerebral OR cranium" AND "Surgery OR Neurosurgery OR craniotomy OR endovascular OR Vascular Surgical Procedures" AND "Neuroprotection OR mortality OR morbidity" AND "anesthetics OR anesthesia." Additional reports were identified from reference lists of retrieved reports and Google Scholar searches.

Table 1 Effects of common anesthetic agents

Agent	CSF production	CSF absorption	CMR	ICP	CBF	CBV
Nitrous oxide	±	±	↓	↑	↑	±
Isoflurane	±	↑	↓↓↓	↑	↑	↑↑
Sevoflurane	?	?	↓↓↓	↑	↑	↑
Desflurane	↑	↓	↓↓↓	↑	↑	↑
Ketamine	±	↓	±	↑↑	↑↑	↑↑
Dexmedetomidine	?	?	↓	↓	↓	↓
Barbiturate	±	↑	↓↓↓↓	↓↓↓	↓↓↓	↓↓
Propofol	?	?	↓↓↓	↓↓	↓↓↓↓	↓↓
Opioids	±	↑	±	±	±	±

↑ indicates increase, ↓ indicates decrease, ± indicates little or no change, and ? indicates unknown effect. *CSF* cerebrospinal fluid, *CMR* cerebral metabolic rate, *ICP* intracranial pressure, *CBF* cerebral blood flow, *CBV* cerebral blood volume [6, 7]

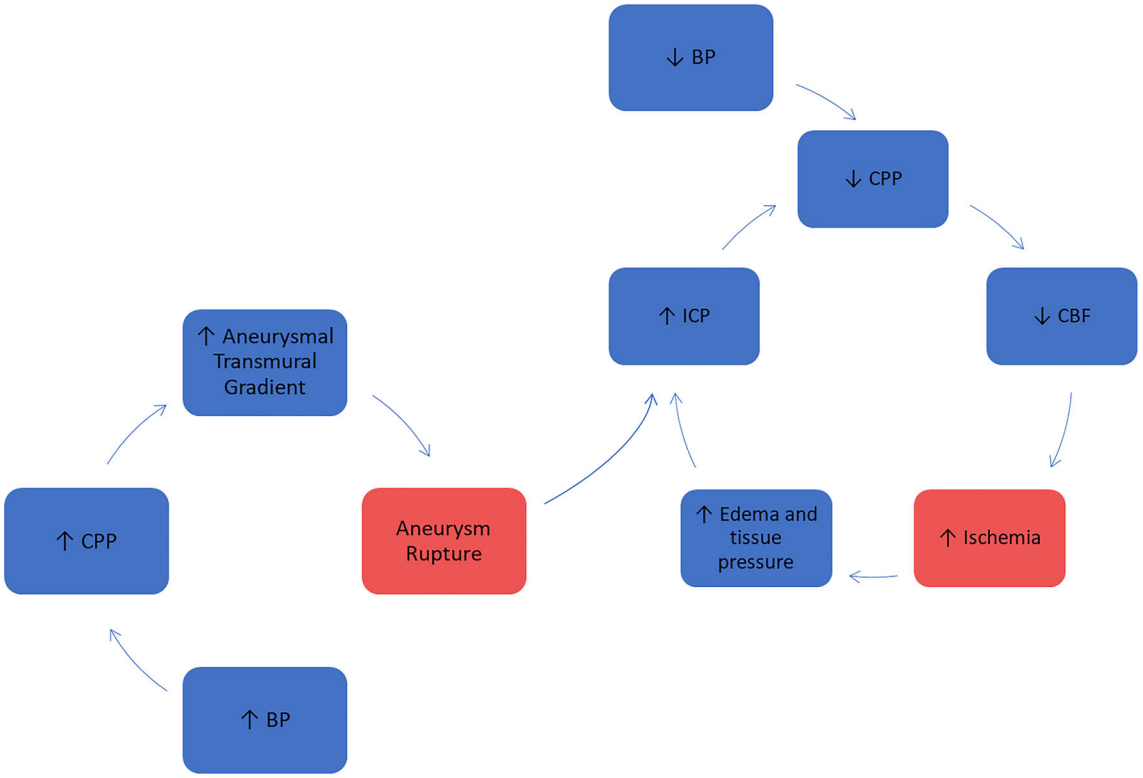

Fig. 1 Systemic blood pressure should be monitored closely and controlled to minimize risk of aneurysm rupture due to hypertension while avoiding low blood pressure that can provoke cerebral ischemia. *BP* blood pressure, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *CBF* cerebral blood flow

Method of synthesis

Two reviewers independently extracted the data from trial reports, with adherence to the PRISMA guideline [10]. Details of the patient population, type of surgery, anesthetic regimen, and outcomes were recorded. The data were extracted only from studies published in English.

Results of the review

The initial search strategy captured a total of 287 studies. From these, 28 studies were included in this study (Table 2 and Fig. 3) [10].

Anesthesia for cerebral aneurysms: intravenous or inhalational agents?

There is currently no clear consensus whether intravenous anesthesia, inhalational anesthesia, or a combination thereof should primarily be used for surgical or endovascular management of UIA. Inhalational agents commonly used for these procedures include volatile anesthetic agents such as isoflurane, desflurane, and sevoflurane, as well as nitrous oxide. Commonly used intravenous agents include propofol, ketamine, and dexmedetomidine, which are typically administered in combination with a short- or long-acting opioids. Thiopental sodium and other barbiturates are still used in certain countries, and benzodiazepines are also occasionally administered as perioperative anxiolytics or anesthetic adjuncts.

There are conflicting data on not only the perioperative risks and benefits of these agents, including direct neurotoxic effects or physiological side effects that can alter the outcome of the procedure, but also their neuroprotective properties, which become essential in cerebral aneurysm surgery due to the potential neurological insults associated with these complex procedures.

Inhalational anesthesia

Nitrous oxide

While nitrous oxide (N_2O) has been used continuously in clinical anesthesia for about 180 years, discussions about its neurological effects are still ongoing [39]. In 1992, Lam et al. described the important physiological effects of N_2O on cerebral metabolism and intracerebral steal [40]. Although little research has been carried out on the neurophysiological properties of N_2O, it is now generally accepted that N_2O lacks neuroprotective effects in anesthetic doses [41]. Furthermore, N_2O is known to increase cerebral metabolism,

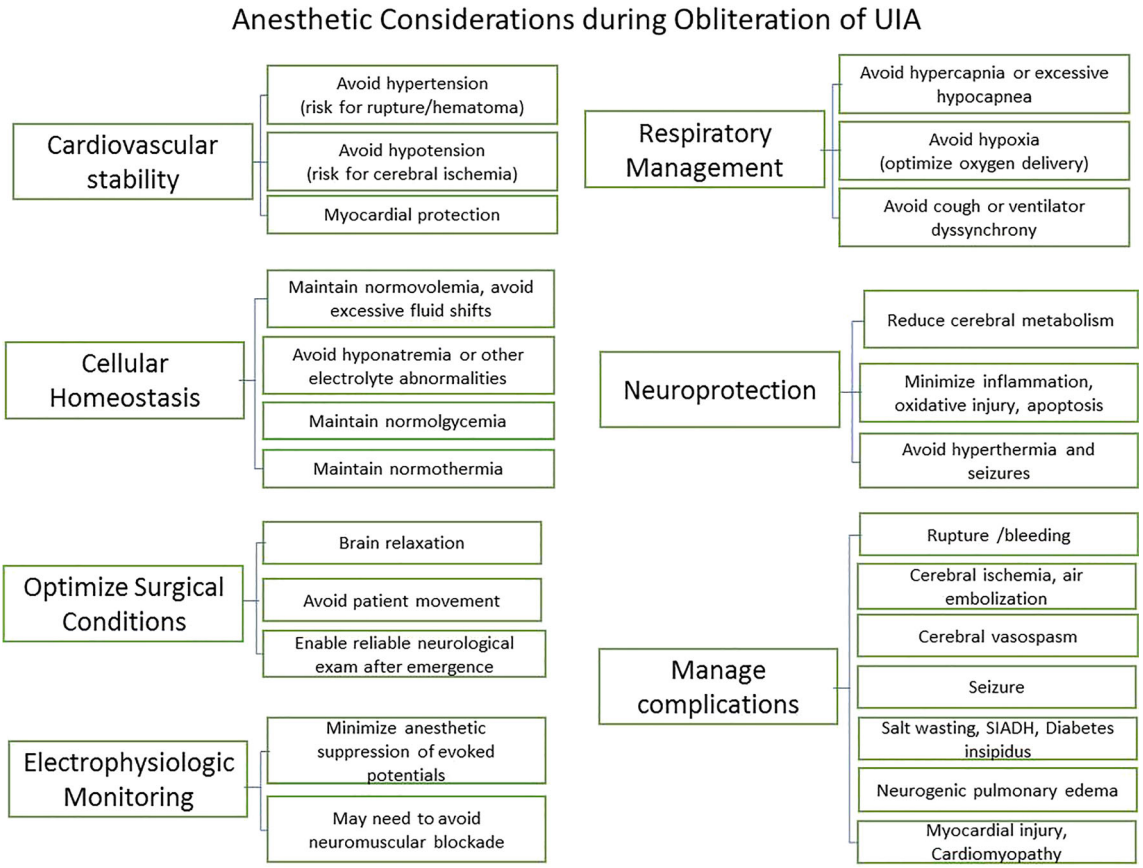

Fig. 2 Anesthetic considerations during obliteration of UIA (unruptured intracranial aneurysms)

CBF, and intracranial pressure (ICP) and can potentially exacerbate an ischemic insult, all undesirable effects in the setting of intracranial surgery [42].

The debate on N_2O safety has continued to simmer, mainly without any clinical neurological outcome data [42, 43]. In 2008, McGregor et al. assessed the clinical outcomes associated with N_2O by analyzing the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) data [11]. They evaluated neurological outcomes at two weeks (i.e., delayed ischemic neurologic deficit (DIND)) and three months after aneurysm surgery and found that in a population of patients potentially at risk for ischemic injury, the use of N_2O had no overall impact on neurological outcome [11]. A subgroup analysis of patients with temporary occlusion of a major cerebral artery for permanent clipping of the aneurysm provided a more granular analysis to capture patients who experienced ischemic events intraoperatively during exposure to N_2O. In this subgroup, intraoperative N_2O administration was associated with an increased risk of DIND. The long-term neurological outcome was, nevertheless, not affected [12].

To our knowledge, data from more recent studies assessing the effects of N_2O on neurological outcome after UIA surgery are lacking [8]. Although intraoperative use of N_2O is primarily based on the anesthetist's preference and differs between institutions, most experts agree that it is best avoided during endovascular procedures. In addition to its effects on CBF and ICP, it is well known that N_2O increases the risk of expansion of micro air bubbles in enclosed spaces. This expansion is due to N_2O's low potency, which results in high blood concentrations, and its low blood/gas partition coefficient, which causes N_2O to move into an air compartment faster than air moves out. Air embolization is rare during aneurysm obliteration but can happen during contrast injection or fluid irrigation; expansion of these air bubbles with N_2O can augment the risk for tissue ischemia and neurological injury [44]. Furthermore, it may be reasonable to avoid N_2O during open craniotomy for UIA clipping if it is difficult to achieve sufficient brain relaxation, or in patients with disrupted autoregulation, such as those with cerebral edema, ischemia, or vasospasm [45].

Isoflurane

Isoflurane is commonly used in neuroanesthesia due to its modest effects on CBF and cerebral autoregulation [46]. The neuroprotective effects of isoflurane have been studied widely in animal models. Isoflurane administration in rats during reperfusion after ischemia reduces brain injury, improves neurological outcome, and decreases neuronal apoptosis [47].

Isoflurane is generally associated with good blood pressure control without significant change in cardiac output or reflex

Table 2 Clinical studies of the effects of anesthetic agents on neurological outcomes following unruptured intracranial aneurysm surgery

Author	Journal/year	Design	Subjects	Focus	Aneurysm	End points	Outcomes
Nitrous oxide							
McGregor et al. [11]	*Anesthesiology*/2008	Retrospective post hoc data analysis	373 Pts in N_2O group vs 622 Pts in no N_2O group	General anesthesia for aSAH surgery	Ruptured	DIND, GOS, NIHSS, Rankin score	No difference was reported
Pasternak et al. [12]	*Anesthesiology*/2009	Retrospective post hoc data analysis	199 Pts in N_2O group vs 242 Pts in no N_2O group	General anesthesia for aSAH surgery with temporary occlusion of a major cerebral artery during surgery	Ruptured	DIND, GOS, NIHSS, Rankin score	Increased risk of DIND, but no negative effect on long-term neurological outcome
Isoflurane							
Madsen et al. [13]	*British Journal of Anesthesiology*/1987	Prospective cohort	10 Pts	Isoflurane-induced hypotension during intracranial aneurysm clipping	Ruptured	CMRo2, CBF	Decreasing levels of CMRo2 compared to baseline, CBF was maintained
Roth et al. [14]	*Cleveland Clinic Journal of Medicine*/1989	Prospective cohort	8 Pts	Isoflurane-induced hypotension during intracranial aneurysm clipping	Not indicated	lCoBF, lCoMRO2	Maintenance of a constant lCoBF and oxygen delivery
Meyer et al. [15]	*Journal of Neurosurgery* /1992	Case series	6 Pts	Isoflurane neuroprotection during complicated aSAH surgery	Ruptured	Neurological exam, daily TCD	Satisfactory outcomes in 5 of the 6 patients
Desflurane							
Wang et al. [16]	*Journal of Neurosurgical Anesthesiology*/2004	Prospective cohort	45 Pts	Desflurane anesthesia in patients undergoing intracranial aneurysm clipping	Unruptured	Endothelin, CGRP	Plasma endothelin decreased compared to baseline. CGRP decrease was not statistically significant
Ketamine							
Mayberg et al. [17]	*Anesthesia & Analgesia Journal*/1995	Prospective cohort	20 Pts (10 ruptured, 10 with supratentorial tumors)	Ketamine during isoflurane/N_2O anesthesia for craniotomy	Ruptured	ICP, MAP, $AVDO_2$, V_{MCA}, EEG power	No increase in ICP or MAP. No change in $AVDO_2$. Decreased V_{MCA} and EEG power
Von der Breile et al. [18]	*World Neurosurgery*/2017	Retrospective cohort	41 Pts in ketamine group vs 24 Pts non-ketamine group	Sedation in aSAH Pts	Ruptured	RASS, ICP, clinical parameters	Decreased ICP, vasopressor use and complications in the ketamine group
Dexmedetomidine							
Souza et al. [19]	*Revista Brasileira de Anestesiologia*/2004	Case report	1 Pt	Dexmedetomidine for surgical treatment of cerebral aneurysm in pregnant patient	Ruptured	Vital signs, uterus-placental blood flow, fetal vitality	Satisfactory clinical outcome, uterus placental blood flow, and fetal vitality optimal
Yokota et al. [20]	*Neurocritical Care Society*/2011	Retrospective cohort	50 Pts Dex group vs 50pts propofol group	Postoperative sedation after cerebral aneurysm surgeries	Unruptured	HR, BP	HR during sedation and systolic BP at 2 h after beginning sedation lower in the Dex group
Lee et al. [21]	*Journal of Korean Neurosurgical Society*/2014	Retrospective observational	12 Pts (11 ruptured, 1 unruptured)	Dexmedetomidine during intracerebral aneurysm coiling	Both	Vital signs, ICP, CPP	No significant changes in hemodynamic and respiratory parameters between time points
Tang et al. [22]	*Neuronal Regeneration Research Journal/2018*	RCT	60 Pts sevoflurane group vs 60 Pts sevoflurane with dexmedetomidine group	Sevoflurane combined with dexmedetomidine for intracranial aneurysm embolization	Unruptured	NSE, S100β	Decreased NSE and S100β levels in sevoflurane with dexmedetomidine group
Barbiturates							
McDermott et al. [23]	*Korean Neurosurgical Society Journal*/1989	Retrospective observational	29 Ruptured aneurysm Pts, 6 unruptured aneurysm Pts	Barbiturate neuroprotection in cerebral aneurysm surgery	Both	Clinical recovery	Satisfactory outcome
McConkey et al. [24]		Case report	1 Pt		Unruptured	Clinical outcome	Satisfactory clinical outcome

Table 2 (continued)

Author	Journal/year	Design	Subjects	Focus	Aneurysm	End points	Outcomes
	Anesthesia and Intensive Care Journal/2002			Thiopentone during combined carotid endarterectomy and clipping of intracranial aneurysm			
Propofol							
Ravussin et al. [25]	*Neurosurgery*/1993	Case series	42 Pts	Total intravenous anesthesia with propofol in cerebral aneurysm surgery with temporary clipping	35 Ruptured 7 Unruptured	Neurological exam, GCS	Propofol may be efficient in protecting the brain from ischemic injury
Schmieder et al. [26]	*European Journal of Anaesthesiology*/2003	Case series	69 Pts (47 tumors and 22 aneurysms and angiomas)	Propofol effects on CBF velocity in surgery for brain tumors and vascular malformations	Not indicated	Assessment of flow velocity with TCD	No changes were seen among aneurysm patients
Yamada et al. [27]	*Journal of Neurosurgical Anestheisology*/2003	Case report	A 65-year-old female	Effect of Propofol infusion and moderate hypothermia on aneurysm clipping	Unruptured	Postoperative complications, neurological exam	Functional outcome
Mahajan et al. [28]	Neurology India/ 2014	RCT	32 Pts control group and 34 Pts propofol group	Evaluate the effect of intraoperative brain protection with propofol on postoperative cognition among patients undergoing temporary clipping during intracranial aneurysm surgery.	Ruptured	BIS, HMSE score	Use of propofol was not beneficial in terms of cognition preservation
Karwacki et al. [29]	*Anaesthesiology Intensive Therapy*/2018	Case control	21 Anesthetized Pts with unruptured intracranial aneurysms and 21 patients as control group	Effect of propofol on MCA flow velocity in patients with unruptured intracranial aneurysm	Unruptured	Mean HR, $etCO_2$ and SpO_2; MAP	Propofol depresses the cerebral circulation during the induction of anesthesia
Ishibashi et al. [30]	*Journal of Clinical Monitoring and Computing*/2019	Prospective randomized crossover study	15 Pts undergoing coiling for cerebral aneurysm	Changes in cerebral circulation time with respect to propofol versus sevoflurane	Not indicated	Color-coded DSA to define TTP, travel time at an ROI	Propofol causes a decrease in overall cerebral perfusion, compared to sevoflurane
Guo et al. [31]	*International Journal of Neuroscience*/2019	RCT	60 Pts undergoing intracranial aneurysm clipping	Propofol post-conditioning after temporary clipping	Not indicated	Oxidative stress and cognitive function from blood samples drawn at six time points	Propofol post-conditioning can protect the brain from oxidative stress injury and improve cognitive function
Opioids							
Uchida et al. [32]	*Journal of Neurosurgical observational*		1380 Propensity-matched pairs ($n = 2760$)	Remifentanil during clipping of intracranial aneurysm	Not Indicated	In-hospital mortality	Significantly lower in-hospital mortality with remifentanil
General							
Lavine et al. [33]	*Neurosurgical Focus, JNS*/1997	Retrospective cohort	Pts treated with the intravenous agents, propofol, etomidate, and pentobarbital, administered individually or in combination, versus a group treated with the inhalational agent isoflurane	Compare effectiveness of brain protection anesthetics	Not indicated	Overall infarction rate, mean duration of temporary occlusion	Induction of focal iatrogenic ischemia during MCA aneurysm clip ligation is more advantageous compared to receiving isoflurane when patients are given pentobarbital as the primary neuroprotective agent or when they receive propofol or etomidate titrated to achieve electroencephalographic burst suppression

Table 2 (continued)

Author	Journal/year	Design	Subjects	Focus	Aneurysm	End points	Outcomes
Foroohar et al. [34]	*Surgical Neurology*/2000	Retrospective observational	297 aneurysms (190 ruptured and 107 unruptured)	Effects of blood pressure, temperature, and anesthetic agents on outcome in patients undergoing craniotomy for cerebral aneurysms	Both	Clinical outcome	Improved outcome as a result of decreased intraoperative blood pressure and propofol use
Allen et al. [35]	*Neurocritical Care*/2006	Case report	A 29-year-old pregnant female at 31 weeks' gestation in her second pregnancy	Diagnosis of an intracranial aneurysm during pregnancy	Unruptured	Diagnosis of aneurysm before rupture, resulted in early definitive treatment	Satisfactory clinical outcome, pregnancy was allowed to progress without intervention, full-term vaginal delivery
Magni et al. [36]	*Journal of Neurosurgical Anesthesiology*/2007	Prospective study	162 American Society of Anesthesiologists I to III Pts (82 females and 80 males, Glasgow 15) undergoing elective neurosurgical procedures	Compare patients anesthetized with sevoflurane-fentanyl versus propofol-remifentanil to study complications after neurosurgical procedures	Not indicated	High severity complications (respiratory events, neurological events), low severity complications (hypertension, hypotension, pain, shivering, nausea, and vomiting)	There is a great potential danger for patients during recovery period after neurosurgical procedures, due to postoperative complications
Karwacki et al. [37]	*Anaesthesiology Intensive Therapy*/2013	Case series	26 Pts for endovascular treatment of intracranial aneurysms	General anesthesia usefulness assessment for endovascular management of intracranial aneurysms	Unruptured	MAP, HR, BIS, $etCO_2$, SPO_2	Suitable conditions are achieved for endovascular treatment of intracranial aneurysms
Hoffman et al. [38]	*Neurosurgery*/1998	Prospective randomized study	20 Patients undergoing craniotomies for cerebrovascular surgery	Effect of thiopental and desflurane for brain protection	Not indicated	Brain tissue oxygen pressure (PO2), carbon dioxide pressure, and pH	Thiopental has a neutral effect on brain tissue gases and pH; desflurane enhances tissue oxygenation; both inhibit ischemic lactic acidosis and decreases in pH

Pts patients, *aSAH* aneurysmal subarachnoid hemorrhage, *HMSE* Hindi-language modification of mini mental state examination, *DIND* delayed ischemic neurologic deficit, *GOS* Glasgow outcome score, *NIHSS* National Institute of Health Stroke Scale, *CBF* cerebral blood flow, *UIA* unruptured intracranial aneurysm, *TCD* transcranial Doppler, *CMRo2* the cerebral metabolic rate of oxygen, *lCoBF* local cortical blood flow, *lCoMRO2* local cortical metabolic rate for oxygen, *CGRP* calcitonin gene-related peptide, $AVDO_2$ arterio-jugular differences in oxygen, V_{MCA} mean velocity in the middle cerebral artery, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *HR* hear rate, *etCO2* end-tidal carbon dioxide, *SpO2* peripheral capillary oxygen saturation, *MAP* mean arterial pressure, *DSA* digital subtraction angiography, *TTP* time to peak density of contrast medium, *ROI* region of interest, *BIS* bispectral index

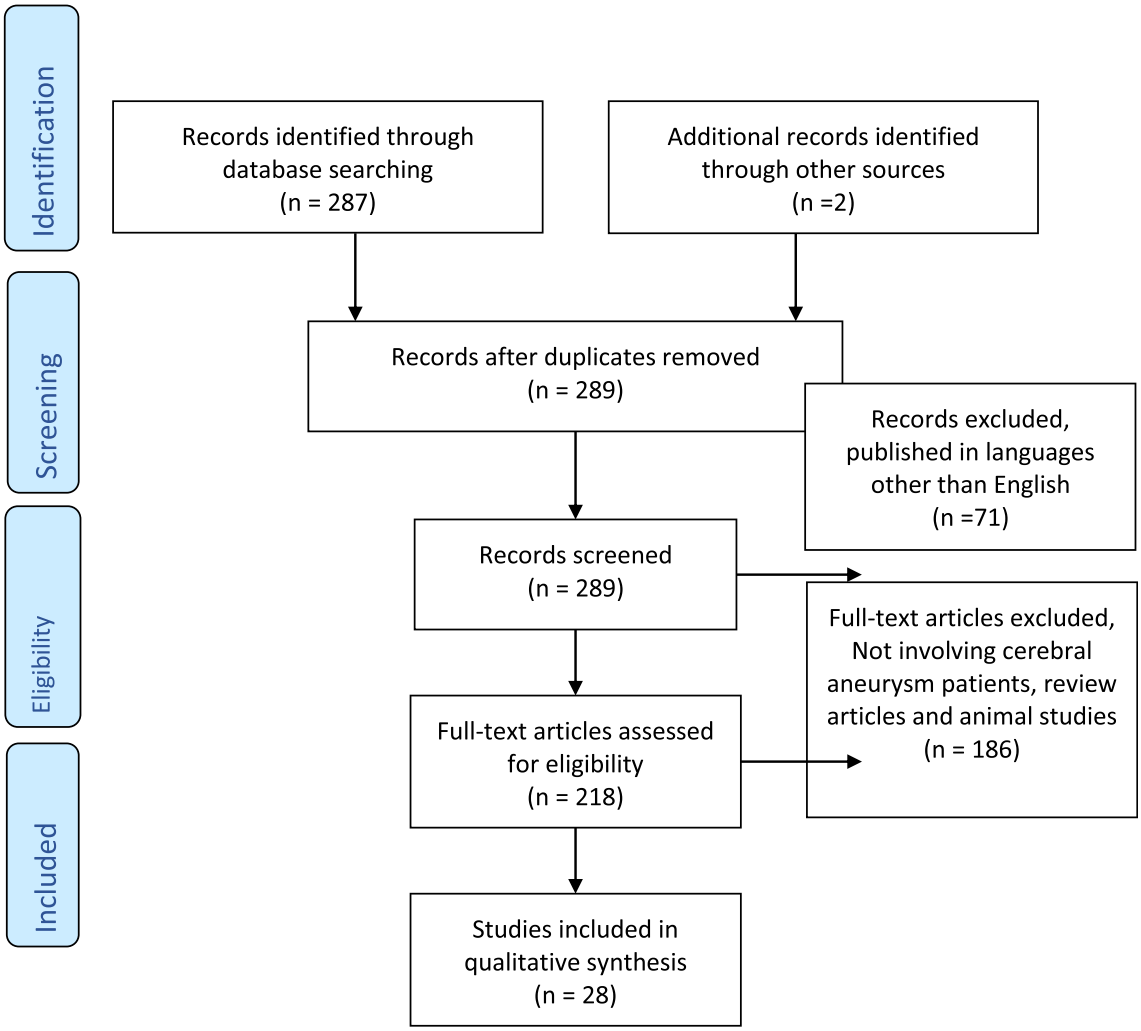

Fig. 3 PRISMA flow diagram showing the process of study inclusion

tachycardia when administered in anesthetic concentrations to normovolemic patients [48]. To further evaluate the cerebral effects of isoflurane, Madsen et al. measured CBF and $CMRO_2$ during isoflurane-induced controlled hypotension in ten patients undergoing craniotomy for clipping of a ruptured aneurysm. CBF and $CMRO_2$ were measured 5–13 days after aSAH. Controlled hypotension to an average mean arterial pressure (MAP) of 50–55 mmHg was induced by increasing the inspired concentration of isoflurane, which resulted in a significant decrease in $CMRO_2$ but no change in CBF. After clipping, the isoflurane concentration was reduced, and there was a significant increase in CBF. While $CMRO_2$ returned to baseline, CBF increased above its pre-hypotensive value. It was suggested that this advantageous supply-demand ratio can offer protection to the brain tissue during periods of induced hypotension [49]. Following prior clinical studies that emphasized the use of high concentrations of isoflurane to induce hypotension, decrease $CMRO_2$, and stabilize CBF, Meyer et al. used end-tidal isoflurane concentrations of 2.0 to 2.5 × minimum alveolar concentration (MAC) to induce electroencephalographic (EEG) ISO electricity (see below). At these high isoflurane concentrations, hypotension can occur due to myocardial depression and vasodilatation; therefore, a vasopressor agent was used to maintain blood pressure. The study included six patients with aSAH and extended temporary vessel occlusion time. Five of six patients made a good recovery despite prolonged occlusion of major cerebral arteries. Their findings supported the use of high dose isoflurane in selective patients to suppress cerebral metabolism during aneurysm surgery, as long as it is hemodynamically tolerated and when intraoperative EEG monitoring is used to carefully titrate the anesthetic concentration [15]. However, it should be noted that prolonged inhalation of isoflurane may reverse its protective effects, as was demonstrated by an aggravated brain injury in a rat model of transient focal ischemia [50].

Although more recent clinical studies looking at isoflurane for UIA surgeries are lacking, in 2019, a retrospective analysis of seven aSAH patients who underwent decompressive craniectomy due to a critically elevated ICP showed that deep sedation could rapidly be achieved after induction of general

anesthesia with isoflurane, without a critical increase in ICP. Adequate CPP was also achieved without a need for extended vasopressor treatment [51].

Sevoflurane

The general neurological profile of sevoflurane is largely comparable to isoflurane but with relatively smaller vasodilatory effects. At concentrations of 1 MAC or less, sevoflurane maintains global CBF (if MAP is unchanged), reduces $CMRO_2$, and minimally increases ICP, which can be blunted by mild hyperventilation [52]. Supported by animal studies, it is argued that sevoflurane may induce neuroprotection when administered during traumatic or ischemic events [53, 54]. In 2018, Xu et al. reported that early exposure to 3.4% sevoflurane for 5 h induced not only autophagy in rat hippocampal cells but also apoptosis of neurons, potentially leading to spatial learning deficits [55], raising questions about the neuroprotective role of sevoflurane. The fact that this high concentration of sevoflurane is seldom used in clinical practice, particularly without other medications such as opioid analgesics or intravenous anesthetics, makes it impossible to determine the clinical relevance of their findings. In fact, it is more likely that the co-administration of intraoperative anesthetics influences their effects on cerebral metabolism, inflammation, and injury, as was demonstrated by Bo et al. in 2018. They showed that the addition of dexmedetomidine to sevoflurane anesthesia could suppress the sevoflurane-induced cell cycle arrest, inhibition of brain-derived neurotrophic factor (BDNF), and tropomyosin receptor kinase B (TrkB) expression and concluded that dexmedetomidine could be used to prevent or mitigate sevoflurane-induced neurotoxicity [56]. The use of dexmedetomidine during sevoflurane anesthesia was also studied in a randomized clinical trial of 120 patients undergoing intracranial aneurysm embolization, and the addition of dexmedetomidine resulted in better neuroprotection, decreased incidence of postoperative delirium, faster recovery, and more stable hemodynamics [22].

Due to its bronchodilatory effects and relatively short duration of action (low blood-gas solubility coefficient), sevoflurane may be the ideal volatile agent for patients with underlying chronic obstructive pulmonary disease (COPD, Table 3). Conversely, it may not be the agent of choice in patients with kidney disease, although clinical trials have failed to confirm clinically relevant effects on renal function when higher fresh gas flows are maintained. There is currently no consensus on the neuroprotective or neurotoxic effects of sevoflurane. Specific clinical studies of the use of sevoflurane in open clipping or endovascular repair of UIA are lacking, and further investigation is warranted.

Desflurane

With its low blood-gas solubility coefficient, desflurane has favorable pharmacokinetic properties relative to isoflurane, including a more rapid emergence from anesthesia and postoperative recovery of cortical functions that have been noted in several in vitro, animal, and human studies. [57]

Several clinical and animal studies have looked at the effects of desflurane on cerebral hemodynamics. The effects of desflurane on ICP were assessed in a porcine model of intracranial hypertension, and at 0.5 to 1 MAC, desflurane was associated with cerebral vasodilatation and higher ICP levels compared to isoflurane and sevoflurane [58]. In humans, the same vasodilatory effect was observed in patients given desflurane, but the ICP did not increase significantly [59]. Although desflurane's cerebrovascular effects in patients with intracranial hypertension have not been thoroughly investigated, it is reasonable to avoid it in these patients to minimize the risk for significant vasodilation that could lead to ICP elevation [52, 60].

Evidence regarding the use of desflurane in aneurysm clipping is limited. In 2017, Lee et al. reported that the incidence of TCD-evident vasospasm in patients who underwent emergent clipping of cerebral aneurysms was higher with propofol as compared to desflurane, but the incidence of angiographic vasospasm, cerebral infarction, and interventions to treat vasospasm were similar between the groups [61]. Another study found that in patients undergoing intracranial aneurysm clipping, the plasma concentration of endothelin was lower when desflurane was used, suggesting a potential benefit in preventing acute cerebral vasospasm during aneurysm clipping [16].

The risks and benefits of desflurane should be considered carefully for each neurosurgical patients and procedure. As an example, given its association with adverse respiratory events, it may not be the ideal anesthetic agent in patients with severe asthma or COPD. While it has advantageous pharmacokinetic features, its physiological and neuroprotective properties are not superior to other common anesthetics, including sevoflurane and propofol. Although the associated side effects of desflurane remain theoretical or experimental, its physiological properties must be carefully considered during perioperative management of patients with UIA, especially those with poor brain relaxation or intracranial hypertension [62].

Intravenous anesthetic agents

Ketamine

The use of ketamine in neuroanesthesia, including UIA obliteration, is controversial. There is evidence that it may increase ICP, CBF, and $CMRO_2$ [63]; however, more recent animal and human studies suggest that ketamine may actually be

Table 3 Anesthetic relevance of common coexisting diseases in UIA surgery

	COPD	CKD	CLD	CHF
Isoflurane	++	++	++	++
Sevoflurane	+++	+	++	++
Desflurane	+	++	++	++
Propofol	++	++	+++	++
Ketamine	+++	++	++	++
Opioids	+	+	+	+++
Comments	Consider increased sensitivity to respiratory effects of analgesics and sedatives	Maintain higher fresh gas flows given the concern for fluoride nephrotoxicity or production of compound A with sevoflurane	Limit anesthetic dose minimize risk of hypotension-hepatic blood flow critically dependent on hepatic arterial blood pressure	Sensitive to hemodynamic effects of anesthetics

COPD chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CLD* chronic liver disease, *CHF* congestive heart failure. +++, preferred; ++, can be used; +, not preferred

beneficial to brain-injured patients due to its effects on NMDA receptors [64, 65].

Based on data from relevant randomized trials between 1994 and 2004, a systematic review suggested that with controlled ventilation and co-administration of a GABA receptor agonist, ketamine can be safely administered without raising the ICP [66]. In another study of 20 patients who underwent craniotomy for either brain tumor resection or cerebral aneurysm clipping, ketamine did not increase ICP during isoflurane or N_2O anesthesia. The same study also showed that middle cerebral artery blood flow velocity, mean arterial blood pressure (MAP), and bilateral fronto-occipital processed EEG remained stable after the administration of ketamine, suggesting it can be used safely during neurosurgical procedures [17].

Although clinical studies of ketamine use in the anesthetic management of UIA surgery are lacking, one retrospective, observational study published in 2016 found that among 65 patients with SAH, administration of ketamine decreased ICP and was not associated with a higher rate of neurological complications. This study also found that the rate of delayed cerebral ischemia (DCI)-associated cerebral infarction and the use of vasopressors for induced hypertension were lower when ketamine was administered [18]. Currently, ketamine is avoided in patients with elevated ICP, but based on available animal and human data, it may prove to be a valuable agent for UIA obliteration in the near future. A re-evaluation of its role in these patients is suggested, particularly in those who may benefit from its systemic effects (e.g., bronchodilation in patients with COPD).

Dexmedetomidine

Based on its favorable hemodynamic properties and an ability to attenuate the cardiovascular responses to intubation, pinning, and extubation, the introduction of dexmedetomidine was met with enthusiasm among clinicians. It significantly decreases both CBF and ICP [67, 68]. As an anesthetic adjunct, it decreases the amount of intravenous or volatile anesthetic agents required for induction and the need for opioid analgesics intraoperatively [69].

Dexmedetomidine is commonly used for intracranial procedures and cerebral aneurysm surgery. A retrospective analysis of 12 patients undergoing endovascular procedures for intracranial aneurysm management confirmed a stable hemodynamic profile when dexmedetomidine was used as an anesthetic adjunct. Vital signs and the Ramsey sedation scale for depth of sedation were analyzed every 10 min and showed no statistically significant differences between time points [21]. Another retrospective analysis of 49 patients admitted to the ICU after cerebral aneurysm surgery revealed a higher sedation level in the dexmedetomidine group, with only one patient requiring physical restriction as compared to ten controls [70]. Dexmedetomidine is effectively used in combination with other anesthetics such as sevoflurane to reduce the stress response during surgical clipping of intracranial aneurysms and has also been used in selected patients as the sole sedative agent during monitored anesthesia care for coil embolization of unruptured cerebral aneurysms [22]. Randomized trials with outcome data is, nevertheless, missing in this population.

Barbiturates

The neuroprotective properties of barbiturates have been well documented in many clinical settings, including status epilepticus and traumatic brain injury. Shapiro et al. described its effects on ICP reduction in 1973 [71]. Subsequent animal studies demonstrated its neuroprotective effects by reducing CBF, ICP, and $CMRO_2$ [72, 73]. In humans, however, these

effects have not consistently resulted in improved neurological outcomes. An RCT of 300 patients undergoing coronary artery bypass grafting (CABG) did not find a reduction in the incidence of postoperative neurological deficits with thiopental [74]. Another study of 182 CABG patients found that even though thiopental was associated with a significantly lower incidence of persistent neuropsychiatric complications, hemodynamic instability was more frequent, resulting in prolonged use of inotropic support [75].

Clinical studies of barbiturate usage in the UIA population are scarce. A study of 92 patients with cerebral aneurysms in which 23 received pentobarbitone during clipping showed that the complication rate was lower in the pentobarbital group (17%) than the non-barbiturate group (21%) [76]. A case report also documented how multiple thiopental boluses were used in a patient undergoing a combined procedure involving clipping of an intracerebral aneurysm and carotid endarterectomy with an encouraging clinical outcome and a rapid recovery with no postoperative neurological deficits reported [24].

Despite their suggested neuroprotective effects, barbiturates are rarely used in the perioperative setting because of a concern for adverse effects such as cardiorespiratory depression, prolonged duration of post-infusion clinical unresponsiveness, impaired white blood cell function, hypokalemia, and hepatic and renal dysfunction [77]. While this drug class should be used cautiously during cerebral aneurysm surgeries, it can result in satisfactory intraoperative conditions and good neurological outcomes if carefully administered.

Propofol

Because of its favorable hemodynamic, pharmacological, and physiological properties, propofol remains one of the most commonly used anesthetics for neurosurgical procedures, including endovascular and open approaches to securing intracranial aneurysms. It is well tolerated by most patients [78], and its hemodynamic effects are readily managed with common vasopressors. Propofol decreases CBF, $CMRO_2$, and ICP and has been shown to have neuroprotective effects in various models of neuronal injury. Animal models have demonstrated its direct antioxidant properties that can protect against oxidative stress as well as anti-inflammatory and antiapoptotic properties [79, 80]. Its rapid recovery profile also allows the possibility of prompt neurological examination postoperatively.

Propofol has been evaluated in aneurysm surgery in multiple studies. In 1993, Ravussin et al. evaluated 42 patients, including seven with unruptured aneurysms, who underwent cerebral aneurysm clipping using total intravenous anesthesia with propofol. The propofol infusion rate was reduced postoperatively to allow for early recovery and subsequent neurological examination, and they concluded that using a propofol infusion for maintenance of burst suppression could be a suitable alternative to isoflurane for aneurysm clipping [25]. Similarly, Guo et al. randomized 60 patients undergoing intracranial aneurysm clipping to propofol post-conditioning or sevoflurane and found improved mini mental status exam (MMSE) and Montreal Cognitive Assessment (MoCA) scores seven days after their surgery [31].

Due to its cerebral vasoconstrictive effects, propofol is generally considered to be an ideal anesthetic for effective brain relaxation during aneurysm surgery. A 2014 meta-analysis by Chui et al. showed that propofol-based anesthesia was associated with lower initial ICP values compared to maintenance with volatile anesthetics; however, this finding did not translate into better brain relaxation scores [2, 81]. A more recent study of 15 patients undergoing elective surgery for UIA found that cerebral circulation times were longer during propofol anesthesia compared to sevoflurane-based anesthesia, as were the circulation times in the internal carotid and middle cerebral arteries [30]. The presence of an unruptured intracranial aneurysm also did not affect the propofol-induced reactivity of cerebral vessels [29]. Multiple studies have compared propofol to other anesthetics for neurovascular procedures [29–31], but most have focused on the hemodynamic or neuroprotective effects of propofol, with only limited data regarding its effects on neurological outcomes.

Opioids

Among opioid receptors, the delta-opioid receptor (DOR) has received special attention for its proposed neuroprotective properties. Early animal studies suggested that opioid receptor agonists could increase survival rates during cerebral ischemia [82]. Zhang et al. further elucidated this concept using neuronal cultures from rat neocortex while studying glutamate-induced neuronal injury. These investigators found that activation of DORs reduced injury by half, whereas mu- or kappa-opioid receptors did not [83]. DORs are suggested to provide neuroprotection by different mechanisms such as inhibiting excitatory neurotransmitter release, increasing antioxidant capacity, and stabilizing ionic homeostasis [84].

In humans, however, mu-opioid receptor agonists are more commonly used for analgesia during surgery. Their perioperative use is limited primarily due to their respiratory depressant effects, which can lead to hypercapnia with cerebral vasodilation and increased ICP. Fentanyl can decrease CBF and $CMRO_2$, but if ventilation is not controlled, it can lead to hypercapnia and as a result an increase in ICP. Similarly, remifentanil can reduce CBF and $CMRO_2$, and although it is not demonstrated to directly increase the ICP, it can also cause respiratory depression and hypercapnia that can result in cerebral vasodilation [85].

Evidence from clinical studies on the use of opioids in UIA is scarce; however, a few have shed light on the subject. Degoute et al. found that remifentanil in combination with

propofol or an inhalational agent could produce reliable hypotension when needed for certain phases of aneurysm surgery [86]. In another study, Uchida et al. conducted a propensity score-matched analysis of more than four thousand patients who underwent open intracranial aneurysm clipping and found that the group who received remifentanil had significantly lower in-hospital mortality than controls [32]. Remifentanil can be a good adjunct to the anesthetic regimen if rapid recovery and postoperative neurological evaluation are desired or if opioid-induced respiratory depression is contraindicated (e.g., patients with severe COPD), but more clinical studies are needed to determine if its administration is associated with improved outcomes after UIA.

Discussion

Obliteration of UIA can result in devastating complications despite advances in surgical and endovascular techniques, careful preoperative optimization, and enhanced anesthetic and perioperative management of the patient. A thorough understanding of the anatomical features of the aneurysm, the technical approach, physiological and metabolic challenges, and the systemic and neurological effects of the anesthetic agents is crucial for reducing the risk of neurological injury in these patients. These cases also require preparedness for perioperative complications, and implementation of resuscitative and neuroprotective measures should these complications occur [87]. Animal and human studies have documented the neurophysiological and neuroprotective properties of common anesthetics, but there is only limited data regarding their effects on neurological outcomes, particularly in patients with UIA [41, 47, 62, 72, 73, 79, 80, 82, 88, 89]. Pharmacodynamic, cardiovascular, and neurophysiological effects of common anesthetics have been extensively studied, but not in the specific context of EVT or aneurysm clipping. Endovascular aneurysm coiling can be complicated by intraprocedural perforation by the microcatheter, guidewire, or coil [87]. Thromboembolic events or vasospasm can also occur and lead to cerebral ischemia with devastating neurological injury [90]. Intra-arterial vasodilators are sometimes administered, requiring careful titration of systemic vasopressors and anesthetics to avoid hypotension and cardiovascular collapse. Blood pressure fluctuations along with respiratory and other physiological parameters such as temperature and glucose levels must be meticulously controlled, and patient movement should be avoided [1, 2, 8]. Similar to EVT, successful open clipping of UIA is critically dependent on the perioperative control of hemodynamic perturbations, optimization of cerebral perfusion and metabolism, careful fluid management, and maintenance of cellular homeostasis. Blood pressure augmentation with common vasopressors such as phenylephrine may be required to improve the collateral blood supply by increasing the CPP and should be considered especially when the duration of temporary clipping is anticipated to exceed two minutes. Increasing brain tolerance for ischemia by pharmacologically inducing electroencephalogram (EEG) silence or burst suppression is another consideration. It is important to note, nevertheless, that despite supporting evidence in patients with prolonged (> 10 min) temporary clipping [91], pharmacological burst suppression or EEG silence is currently not recommended for routine use in cases with temporary arterial occlusion. Also, available literature provides limited data to support a specific anesthetic regimen, and our understanding of their physiological and outcome effects continues to evolve. It is unlikely that smaller trials will have the required power to identify significant outcome differences following uncomplicated procedures, as long as the above perioperative goals are met (Fig. 1). It is possible, however, that outcomes in a subgroup of patients at risk for perioperative neurological injury (e.g., those with aneurysm rupture, severe vasospasm, or prolonged temporary clipping) are critically dependent on the physiological and neuroprotective properties of the anesthetic agents used, in addition to perioperative hemodynamic, metabolic, and respiratory parameters [6, 7, 77, 92, 93]. This at-risk population would be an ideal target for future randomized trials to assess the protective effects of different anesthetic agents during UIA obliteration.

Conclusion

The existing literature does not support any specific anesthetic regimen during EVT or open craniotomy for the management of UIA. Further studies are needed to compare the perioperative physiological and clinical effects of different anesthetic regimens and define their influence on neurological outcomes.

Authors' contributions SE, JV, ABB, and SG: study design, data collection, data analysis, and writing up the first draft of the manuscript. LKB, ME, CF, RP, AT, CSO, SS, and AN: study design, data review and analysis, revision, and finalization of the manuscript.

Data availability The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Compliance with ethical standards

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

Ethical approval This hospital registry study was approved by the Institutional Review Board at the Beth Israel Deaconess Medical Center.

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References

1. Bruder N, Boussen S, Velly L (2019) Anesthesia for aneurysmal subarachnoid hemorrhage. In: Prabhakar H, Ali Z. (eds) Textbook of neuroanesthesia and neurocritical care. Singapore: Springer Nature Singapore Pte Ltd, pp 115–130
2. Lecours M, Gelb AW (2015) Anesthesia for the surgical treatment of cerebral aneurysms. Rev Colom Anestesiol 43:45–51
3. Abd-Elsayed AA, Wehby AS, Farag E (2014) Anesthetic management of patients with intracranial aneurysms. Ochsner J 14(3):418–425
4. Malinova V, Schatlo B, Voit M, Suntheim P, Rohde V, Mielke D (2017) The impact of temporary clipping during aneurysm surgery on the incidence of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Neurosurg 129(1):84–90
5. Desai VR, Rosas AL, Britz GW (2017) Adenosine to facilitate the clipping of cerebral aneurysms: literature review. Stroke Vasc Neurol 2(4):204–209
6. Inhalational anesthetics. In: Butterworth JF, IV, Mackey DC, Wasnick JD. (eds) Morgan & Mikhail's clinical anesthesiology, 5e. McGraw-Hill. https://accessmedicine.mhmedical.com/Book.aspx?bookid=2444. Accessed 22 Nov 2020
7. Drummond John C, Dao Andrew V, Roth David M, Cheng C-R, Atwater BI, Minokadeh A, Pasco LC, Patel PM (2008) Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. Anesthesiology 108(2):225–232. https://doi.org/10.1097/01.anes.0000299576.00302.4c
8. Chowdhury T, Petropolis A, Wilkinson M, Schaller B, Sandu N, Cappellani RB (2014) Controversies in the anesthetic management of intraoperative rupture of intracranial aneurysm. Anesthesiol Res Pract 2014:1–10
9. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S (2014) PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res 14:579–579. https://doi.org/10.1186/s12913-014-0579-0
10. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, Barbour V, Barrowman N, Berlin JA (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Chinese edition). J Chin Integrat Med 7(9):889–896
11. McGregor DG, William L, Pasternak J, Rusy D, Hogan K, Samra S, Hindman B, Todd MM, Schroeder DR, Bayman EO, Clarke W, Torner J, Weeks J (2008) Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. Anesthesiology 108(4):568–579. https://doi.org/10.1097/ALN.0b013e31816721fa
12. Pasternak JJ, McGregor DG, Lanier WL, Schroeder DR, Rusy DA, Hindman B, Clarke W, Torner J, Todd MM (2009) Effect of nitrous oxide use on long-term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. Anesthesiology 110(3):563–573
13. Madsen JB, Cold GE, Hansen ES, Bardrum B, Kruse-Larsen C (1987) Cerebral blood flow and metabolism during isoflurane-induced hypotension in patients subjected to surgery for cerebral aneurysms. Br J Anaesth 59(10):1204–1207. https://doi.org/10.1093/bja/59.10.1204
14. Roth S, Jones SC, Ebrahim ZY, Friel H, Little JR (1989) Local cortical blood flow and oxygen consumption during isoflurane-induced hypotension. Results in patients undergoing intracranial aneurysm clipping. Cleve Clin J Med 56(8):766–770. https://doi.org/10.3949/ccjm.56.8.766
15. Meyer FB, Muzzi DA (1992) Cerebral protection during aneurysm surgery with isoflurane anesthesia. J Neurosurg 76(3):541–543
16. Wang T, Luo F, Shan R, Zhen Y, Zhao J, Zhang S (2004) Changes of endothelin and calcitonin gene-related peptide during desflurane anesthesia in patients undergoing intracranial aneurysm clipping. J Neurosurg Anesthesiol 16(3):236–239. https://doi.org/10.1097/00008506-200407000-00009
17. Mayberg TS, Lam AM, Matta BF, Domino KB, Winn HR (1995) Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. Anesth Analg 81(1):84–89. https://doi.org/10.1097/00000539-199507000-00017
18. Von der Brelie C, Seifert M, Rot S, Tittel A, Sanft C, Meier U, Lemcke J (2017) Sedation of patients with acute aneurysmal subarachnoid hemorrhage with ketamine is safe and might influence the occurrence of cerebral infarctions associated with delayed cerebral ischemia. World Neurosurg 97:374–382. https://doi.org/10.1016/j.wneu.2016.09.121
19. Souza KM, Anzoategui LC, Pedroso WC, Gemperli WA (2005) Dexmedetomidine in general anesthesia for surgical treatment of cerebral aneurysm in pregnant patient with specific hypertensive disease of pregnancy: case report. Rev Bras Anestesiol 55(2):212–216. https://doi.org/10.1590/s0034-70942005000200008
20. Yokota H, Yokoyama K, Noguchi H, Nishioka T, Umegaki O, Komatsu H, Sakaki T (2011) Post-operative dexmedetomidine-based sedation after uneventful intracranial surgery for unruptured cerebral aneurysm: comparison with propofol-based sedation. Neurocrit Care 14(2):182–187. https://doi.org/10.1007/s12028-010-9485-4
21. Lee HH, Jung YJ, Choi BY, Chang CH (2014) Usefulness of dexmedetomidine during intracerebral aneurysm coiling. J Korean Neurosurg Soc 55(4):185–189. https://doi.org/10.3340/jkns.2014.55.4.185
22. Tang CL, Li J, Zhang ZT, Zhao B, Wang SD, Zhang HM, Shi S, Zhang Y, Xia ZY (2018) Neuroprotective effect of bispectral index-guided fast-track anesthesia using sevoflurane combined with dexmedetomidine for intracranial aneurysm embolization. Neural Regen Res 13(2):280–288. https://doi.org/10.4103/1673-5374.226399
23. McDermott MW, Durity FA, Borozny M, Mountain MA (1989) Temporary vessel occlusion and barbiturate protection in cerebral aneurysm surgery. Neurosurgery 25(1):54–61; discussion 61-52. https://doi.org/10.1097/00006123-198907000-00010
24. McConkey PP, Kien ND (2002) Cerebral protection with thiopentone during combined carotid endarterectomy and clipping of intracranial aneurysm. Anaesth Intensive Care 30(2):219–222. https://doi.org/10.1177/0310057x0203000217
25. Ravussin P, de Tribolet N (1993) Total intravenous anesthesia with propofol for burst suppression in cerebral aneurysm surgery: preliminary report of 42 patients. Neurosurgery 32(2):236–240 discussion 240. https://doi.org/10.1227/00006123-199302000-00013
26. Schmieder K, Schregel W, Engelhardt M, Harders A, Cunitz G (2003) Cerebral vascular reactivity response to anaesthetic induction with propofol in patients with intracranial space-occupying lesions and vascular malformations. Eur J Anaesthesiol 20(6):457–460. https://doi.org/10.1017/s0265021503000711
27. Yamada M, Nishikawa K, Kawahara F, Yoshikawa D, Saito S, Goto F (2003) Anesthetic management for clipping a giant basilar

artery aneurysm with moderate hypothermia, extracorporeal circulation assistance, and propofol infusion. J Neurosurg Anesthesiol 15(3):274–277. https://doi.org/10.1097/00008506-200307000-00018
28. Mahajan C, Chouhan RS, Rath GP, Dash HH, Suri A, Chandra PS, Mahajan A (2014) Effect of intraoperative brain protection with propofol on postoperative cognition in patients undergoing temporary clipping during intracranial aneurysm surgery. Neurol India 62(3):262–268. https://doi.org/10.4103/0028-3886.136908
29. Karwacki Z, Niewiadomski S, Witkowska M, Dzierzanowski J, Szczyrba S, Cichomska M (2018) The influence of propofol on middle cerebral artery flow velocity (VMCA) in patients with unruptured intracranial aneurysms during induction of general anaesthesia. Anaesthesiol Intensive Ther 50(5):349–358. https://doi.org/10.5603/ait.2018.0047
30. Ishibashi T, Toyama S, Miki K, Karakama J, Yoshino Y, Ishibashi S, Tomita M, Nemoto S (2019) Effects of propofol versus sevoflurane on cerebral circulation time in patients undergoing coiling for cerebral artery aneurysm: a prospective randomized crossover study. J Clin Monit Comput 33(6):987–998. https://doi.org/10.1007/s10877-018-00251-2
31. Guo D, Li Y, Wang H, Wang X, Hua W, Tang Q, Miao L, Wang G (2019) Propofol post-conditioning after temporary clipping reverses oxidative stress in aneurysm surgery. Int J Neurosci 129(2):155–164. https://doi.org/10.1080/00207454.2018.1483920
32. Uchida K, Yasunaga H, Sumitani M, Horiguchi H, Fushimi K, Yamada Y (2014) Effects of remifentanil on in-hospital mortality and length of stay following clipping of intracranial aneurysm: a propensity score-matched analysis. J Neurosurg Anesthesiol 26(4):291–298. https://doi.org/10.1097/ana.0000000000000039
33. Lavine SD, Masri LS, Levy ML, Giannotta SL (1997) Temporary occlusion of the middle cerebral artery in intracranial aneurysm surgery: time limitation and advantage of brain protection. Neurosurg Focus 2(6):e4. https://doi.org/10.3171/foc.1997.2.1.5
34. Foroohar M, Macdonald RL, Roth S, Stoodley M, Weir B (2000) Intraoperative variables and early outcome after aneurysm surgery. Surg Neurol 54(4):304–315. https://doi.org/10.1016/s0090-3019(00)00294-9
35. Allen G, Farling P, McAtamney D (2006) Anesthetic management of the pregnant patient for endovascular coiling of an unruptured intracranial aneurysm. Neurocrit Care 4(1):18–20. https://doi.org/10.1385/ncc:4:1:018
36. Magni G, La Rosa I, Gimignani S, Melillo G, Imperiale C, Rosa G (2007) Early postoperative complications after intracranial surgery: comparison between total intravenous and balanced anesthesia. J Neurosurg Anesthesiol 19(4):229–234. https://doi.org/10.1097/ANA.0b013e31806e5f5a
37. Karwacki Z, Witkowska M, Niewiadomski S, Wiatr A, Bukowski P, Wierzchowska J, Zapasnik A (2013) Anaesthetic management for endovascular treatment of unruptured intracranial aneurysms. Anaesthesiol Intensive Ther 45(3):145–148. https://doi.org/10.5603/ait.2013.0030
38. Hoffman WE, Charbel FT, Edelman G, Ausman JI (1998) Thiopental and desflurane treatment for brain protection. Neurosurgery 43(5):1050–1053. https://doi.org/10.1097/00006123-199811000-00026
39. Courville CB (1939) Untoward effects of nitrous oxide anesthesia with particular reference to residual neurologic and psychiatric manifestations. California: Pacific Press Publishing Association, p 174
40. Lam AM, Mayberg TS (1992) Use of nitrous oxide in neuroanesthesia: why bother? J Neurosurg Anesthesiol 4:284–284
41. Haelewyn B, David HN, Rouillon C, Chazalviel L, Lecocq M, Risso J-J, Lemaire M, Abraini JH (2008) Neuroprotection by nitrous oxide: facts and evidence. Crit Care Med 36(9):2651–2659
42. Culley DJ, Crosby G (2008) Nitrous oxide in neuroanesthesia: tried and true or toxin? Anesthesiology 108(4):553–554
43. Pasternak JJ, Lanier WL (2010) Is nitrous oxide use appropriate in neurosurgical and neurologically at-risk patients? Curr Opin Anaesthesiol 23(5):544–550. https://doi.org/10.1097/ACO.0b013e32833e1520
44. Varma MK, Price K, Jayakrishnan V, Manickam B, Kessell G (2007) Anaesthetic considerations for interventional neuroradiology. Br J Anaesth 99(1):75–85. https://doi.org/10.1093/bja/aem122
45. Frost EA (2017) Nitrous oxide in neuroanesthesia: does it have a place? In: Scher CS, Clebone A, Miller SM, Roccaforte JD, Capan LM (eds) You're wrong, I'm right: dueling authors reexamine classic teachings in anesthesia. Cham: Springer International Publishing, pp 207–208
46. Frawley G, Davidson A (2016) Inhaled anestheteic agents. In: Davis PJ, Cladis FP (eds) Smith's anesthesia for infants and children. Philadelphia: Elsevier Health Sciences, pp 200–213
47. Lee JJ, Li L, Jung H-H, Zuo Z (2008) Postconditioning with isoflurane reduced ischemia-induced brain injury in rats. Anesthesiology 108(6):1055–1062
48. Lam AM, Gelb AW (1983) Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62(8):742–748
49. MADSEN JB, COLD GE, HANSEN ES, BARDRUM B, KRUSE-LARSEN C (1987) Cerebral blood flow and metabolism during isoflurane-induced hypotension in patients subjected to surgery for cerebral aneurysms. BJA 59(10):1204–1207. https://doi.org/10.1093/bja/59.10.1204
50. Gaidhani N, Sun F, Schreihofer D, Uteshev VV (2017) Duration of isoflurane-based surgical anesthesia determines severity of brain injury and neurological deficits after a transient focal ischemia in young adult rats. Brain Res Bull 134:168–176. https://doi.org/10.1016/j.brainresbull.2017.07.018
51. Lehmann F, Müller M, Zimmermann J, Güresir Á, Lehmann V, Putensen C, Vatter H, Güresir E (2020) Inhalational isoflurane sedation in patients with decompressive craniectomy suffering from severe subarachnoid hemorrhage: a case series. J Neuroanaesthesiol Crit Care 7:27–33
52. Cottrell JE, Patel P (2017) Cottrell and Patel's neuroanesthesia, Sixth edn. Elsevier, Edinburgh
53. Brioni JD, Varughese S, Ahmed R, Bein B (2017) A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics. J Anesth 31(5):764–778. https://doi.org/10.1007/s00540-017-2375-6
54. Schifilliti D, Grasso G, Conti A, Fodale V (2010) Anaesthetic-related neuroprotection: intravenous or inhalational agents? CNS Drugs 24(11):893–907. https://doi.org/10.2165/11584760-000000000-00000
55. Xu L, Shen J, Yu L, Sun J, McQuillan PM, Hu Z, Yan M (2018) Role of autophagy in sevoflurane-induced neurotoxicity in neonatal rat hippocampal cells. Brain Res Bull 140:291–298. https://doi.org/10.1016/j.brainresbull.2018.05.020
56. Bo LJ, Yu PX, Zhang FZ, Dong ZM (2018) Dexmedetomidine mitigates sevoflurane-induced cell cycle arrest in hippocampus. J Anesth 32(5):717–724. https://doi.org/10.1007/s00540-018-2545-1
57. Eger EI 2nd, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB (1998) The effect of anesthetic duration on kinetic and recovery characteristics of desflurane versus sevoflurane, and on the kinetic characteristics of compound A, in volunteers. Anesth Analg 86(2):414–421. https://doi.org/10.1097/00000539-199802000-00037
58. Holmstrom A, Akeson J (2004) Desflurane increases intracranial pressure more and sevoflurane less than isoflurane in pigs subjected to intracranial hypertension. J Neurosurg Anesthesiol 16(2):136–143. https://doi.org/10.1097/00008506-200404000-00005

59. Sponheim S, Skraastad O, Helseth E, Due-Tonnesen B, Aamodt G, Breivik H (2003) Effects of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on intracranial and cerebral perfusion pressures in children. Acta Anaesthesiol Scand 47(8):932–938. https://doi.org/10.1034/j.1399-6576.2003.00199.x
60. Kundra S, Mahendru V, Gupta V, Choudhary AK (2014) Principles of neuroanesthesia in aneurysmal subarachnoid hemorrhage. J Anaesthesiol Clin Pharmacol 30(3):328–337. https://doi.org/10.4103/0970-9185.137261
61. Lee JW, Woo JH, Baik HJ, Kim DY, Chae JS, Yang NR, Seo EK (2018) The effect of anesthetic agents on cerebral vasospasms after subarachnoid hemorrhage: a retrospective study. Medicine (Baltimore) 97(31):e11666. https://doi.org/10.1097/MD.0000000000011666
62. Srivastava S (2017) Use of desflurane in neurosurgery: cons. J Neuroanaesthesiol Crit Care 04. https://doi.org/10.4103/2348-0548.199955
63. Urwin SC, Menon DK (2004) Comparative tolerability of sedative agents in head-injured adults. Drug Saf 27(2):107–133. https://doi.org/10.2165/00002018-200427020-00003
64. Luthra A, Rath G (2018) Ketamine: a neuroanesthesiologist's friend or foe? J Neuroanaesthesiol Crit Care 05:77–82. https://doi.org/10.1055/s-0038-1654746
65. Soriano FX, Papadia S, Hofmann F, Hardingham NR, Bading H, Hardingham GE (2006) Preconditioning doses of NMDA promote neuroprotection by enhancing neuronal excitability. J Neurosci 26(17):4509–4518. https://doi.org/10.1523/jneurosci.0455-06.2006
66. Himmelseher S, Durieux ME (2005) Revising a dogma: ketamine for patients with neurological injury? Anesth Analg 101(2):524–534, table of contents. https://doi.org/10.1213/01.Ane.0000160585.43587.5b
67. Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, Gage HD, Stump DA, James RL, Bennett J, Butterworth J (2002) Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg 95(4):1052–1059, table of contents. https://doi.org/10.1097/00000539-200210000-00048
68. Singh S, Chouhan RS, Bindra A, Radhakrishna N (2018) Comparison of effect of dexmedetomidine and lidocaine on intracranial and systemic hemodynamic response to chest physiotherapy and tracheal suctioning in patients with severe traumatic brain injury. J Anesth 32(4):518–523. https://doi.org/10.1007/s00540-018-2505-9
69. Batra A, Verma R, Bhatia VK, Chandra G, Bhushan S (2017) Dexmedetomidine as an anesthetic adjuvant in intracranial surgery. Anesth Essays Res 11(2):309–313. https://doi.org/10.4103/0259-1162.194555
70. Iwasaki Y, Nakamura T, Hamakawa T (2010) Retrospective evaluation of dexmedetomidine for postoperative sedation in patients for cerebral aneurysm surgery. Masui 59(11):1396–1399
71. Shapiro H, Galindo A, Wyte S, Harris A (1973) Rapid intraoperative reduction of intracranial pressure with thiopentone. BJA 45(10):1057–1062
72. Smith AL, Hoff JT, Nielsen SL, Larson CP (1974) Barbiturate protection in acute focal cerebral ischemia. Stroke 5(1):1–7. https://doi.org/10.1161/01.str.5.1.1
73. Hoff JT, Smith AL, Hankinson HL, Nielsen SL (1975) Barbiturate protection from cerebral infarction in primates. Stroke 6(1):28–33. https://doi.org/10.1161/01.str.6.1.28
74. Zaidan JR, Klochany A, Martin WM, Ziegler JS, Harless DM, Andrews RB (1991) Effect of thiopental on neurologic outcome following coronary artery bypass grafting. Anesthesiology 74(3):406–411. https://doi.org/10.1097/00000542-199103000-00003
75. Nussmeier NA, Arlund C, Slogoff S (1986) Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 64(2):165–170. https://doi.org/10.1097/00000542-198602000-00006
76. Belopavlovic M, Buchthal A, Beks JW (1985) Barbiturates for cerebral aneurysm surgery. A review of preliminary results. Acta Neurochir 76(3–4):73–81. https://doi.org/10.1007/bf01418464
77. Vuyk J, Sitsen E, Reekers M (2020) Intravenous anesthetics. In: Gropper MA, Cohen NH, Eriksson LI, Fleisher LA, Leslie K, Wiener-Kronish JP. (eds) Miller's anesthesia, 9th edition. Philadelphia: Elsevier Health Sciences, pp 638–679
78. Ravussin P, Revelly JP, Chiolero R (1991) clinical use of propofol in neuroanesthesia. Agressologie 32(8-9 spec):407–411
79. Acquaviva R, Campisi A, Murabito P, Raciti G, Avola R, Mangiameli S, Musumeci I, Barcellona ML, Vanella A, Li Volti G (2004) Propofol attenuates peroxynitrite-mediated DNA damage and apoptosis in cultured astrocytes: an alternative protective mechanism. Anesthesiology 101(6):1363–1371. https://doi.org/10.1097/00000542-200412000-00017
80. Sagara Y, Hendler S, Khoh-Reiter S, Gillenwater G, Carlo D, Schubert D, Chang J (1999) Propofol hemisuccinate protects neuronal cells from oxidative injury. J Neurochem 73(6):2524–2530. https://doi.org/10.1046/j.1471-4159.1999.0732524.x
81. Chui J, Mariappan R, Mehta J, Manninen P, Venkatraghavan L (2014) Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis. Can J Anesthesia 61(4):347–356
82. Hayward NJ, McKnight AT, Woodruff GN (1993) Neuroprotective effect of the kappa-agonist enadoline (CI-977) in rat models of focal cerebral ischaemia. Eur J Neurosci 5(7):961–967. https://doi.org/10.1111/j.1460-9568.1993.tb00947.x
83. Zhang J, Haddad GG, Xia Y (2000) Delta-, but not mu- and kappa-, opioid receptor activation protects neocortical neurons from glutamate-induced excitotoxic injury. Brain Res 885(2):143–153. https://doi.org/10.1016/s0006-8993(00)02906-1
84. He X, Sandhu HK, Yang Y, Hua F, Belser N, Kim DH, Xia Y (2013) Neuroprotection against hypoxia/ischemia: delta-opioid receptor-mediated cellular/molecular events. Cell Mol Life Sci 70(13):2291–2303. https://doi.org/10.1007/s00018-012-1167-2
85. Girard F, Moumdjian R, Boudreault D, Chouinard P, Bouthilier A, Ruel M (2009) The effect of sedation on intracranial pressure in patients with an intracranial space-occupying lesion: remifentanil versus propofol. Anesth Analg 109(1):194–198. https://doi.org/10.1213/ane.0b013e3181a3ea3a
86. Degoute CS (2007) Controlled hypotension: a guide to drug choice. Drugs 67(7):1053–1076. https://doi.org/10.2165/00003495-200767070-00007
87. Ihn YK, Shin SH, Baik SK, Choi IS (2018) Complications of endovascular treatment for intracranial aneurysms: management and prevention. Interv Neuroradiol 24(3):237–245. https://doi.org/10.1177/1591019918758493
88. Hoffman WE, Edelman G (2000) Enhancement of brain tissue oxygenation during high dose isoflurane anesthesia in the dog. J Neurosurg Anesthesiol 12(2):95–98. https://doi.org/10.1097/00008506-200004000-00004
89. Tsai YC, Huang SJ, Lai YY, Chang CL, Cheng JT (1994) Propofol does not reduce infarct volume in rats undergoing permanent middle cerebral artery occlusion. Acta Anaesthesiol Sin 32(2):99–104
90. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, Floyd J, Fornage M, Gillespie C, Isasi C (2017) Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 135(10):e146–e603
91. Lavine SD, Masri LS, Levy ML, Giannotta SL (1997) Temporary occlusion of the middle cerebral artery in intracranial aneurysm

surgery: time limitation and advantage of brain protection. J Neurosurg 87(6):817–824. https://doi.org/10.3171/jns.1997.87.6.0817

92. Hadler RA, Neuman MD, FLeisher LA (2020) Risk of anesthesia. In: Gropper MA, Cohen NH, Eriksson LI, Fleisher LA, Leslie K, Wiener-Kronish JP. (eds) Miller's anesthesia, 9th edition. Philadelphia: Elsevier Health Sciences, pp 892–917

93. Fukuda M, Vazquez AL, Zong X, Kim S-G (2013) Effects of the α2-adrenergic receptor agonist dexmedetomidine on neural, vascular and BOLD fMRI responses in the somatosensory cortex. Eur J Neurosci 37(1):80–95. https://doi.org/10.1111/ejn.12024