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Subarachnoid Hemorrhage and Sevoflurane

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ABSTRACT

AIM: To examine whether post-treatment sevoflurane is protective against early brain injury (EBI) after subarachnoid hemorrhage (SAH) and how this neuroprotective effect occurs at different concentrations and durations of administration in mice. Furthermore, we tested whether the neuroprotective effect of post-treatment sevoflurane is associated with inhibition of apoptosis.

MATERIAL and METHODS: SAH was induced in mice by endovascular perforation. Animals were randomly assigned to five groups in each study. Study 1, sham-operated; SAH+vehicle-air; and SAH+1.5% sevoflurane for 30, 60, and 90 min. Study 2, SAH+3% sevoflurane for 30, 60, and 90 min. Study 3, SAH+4.5% sevoflurane for 30, 60, and 90 min. Neurobehavioral function and brain edema (brain water content) were evaluated 24 h after SAH. Neuroglial cell death was examined by terminal deoxynucleotidyl transferase-mediated uridine 5′-triphosphate-biotin nick end-labeling (TUNEL) staining.

RESULTS: Administration of 1.5% sevoflurane for 60 min and 3% sevoflurane for 30 and 60 min significantly improved neurobehavioral function, brain edema, and attenuated neuronal cell death in the basal cortex at 24 h after SAH.

CONCLUSION: Administration of 1.5% sevoflurane for 60 min and 3% for 30 and 60 min sevoflurane application attenuated the development of EBI after SAH, implying its use for anesthesia during acute aneurysm surgery or intervention.

KEYWORDS: Subarachnoid hemorrhage, Early brain injury, Sevoflurane, Apoptosis, Mice

INTRODUCTION

Subarachnoid hemorrhage (SAH) remains a life-threatening disease despite progress in diagnostics and treatment with early neurosurgical intervention (4). Early brain injury (EBI) as a poor outcome occurs within 48 hours following cerebral aneurysm rupture that includes increased intracranial pressure (ICP), blood–brain barrier (BBB) disruption, brain edema formation, oxidative stress, and activation of inflammatory and apoptotic pathways (39,40). Early neuroprotective interventions for possible clinical use to treat EBI after SAH are needed urgently. Targeting apoptosis and inflammation may be an innovative treatment strategy to improve the outcome after SAH.

Available data indicate that anesthetic drugs such as barbiturates, propofol, xenon and most volatile anesthetics (halothane, isoflurane, desflurane, sevoflurane) show neuroprotective effects that protect cerebral tissue from adverse events without clear mechanisms, such as apoptosis, degeneration, inflammation, and energy failure (37). Designing the anesthetic plan for some surgical procedures (cardiopulmonary bypass, carotid surgery, and cerebral aneurysm surgery) and clinical situations (subarachnoid hemorrhage, stroke, brain trauma, and post-cardiac arrest resuscitation) for protecting the central neural system (CNS) is a priority (37). However, at present, available experimental data do not support the selection of any anesthetic agent over the others. Sevoflurane is gaining popularity in clinical neuroanesthesia practice in recent years. Considering the large number of surgical patients receiving sevoflurane anesthesia (29), it has proven to reduce perioperative morbidity and mortality (20,21).

When investigating animal studies in the literature, it is confusing to say which dose and duration of volatile anesthetic provides the largest therapeutic benefit. Also, to our knowledge no study exists of SAH treatment with sevoflurane. Therefore, we focused on the effects of sevoflurane application, and

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examined whether sevoflurane post-treatment is protective against EBI after SAH in mice and whether this neuroprotective effect depends on different concentrations with different exposure times and prevents brain apoptosis.

MATERIAL and METHODS

Experimental Design and Animal Groups

Animal care and all experiments were performed in concordance with the European Communities Council Directive of November 24, 1986 (86/609/EEC) on the protection of animals for experimental use. All experimental procedures performed were reviewed and approved by the ethical committee of Saki Yenilli Experimental Animal Production and Research Laboratory local authority (Decision no: 01; Date: 02.07.2018). We used 117 eight-week-old male BALB/c mice (30–38 g; Saki Yenilli Experimental Animal Production and Research Laboratory, Mamak, Ankara) for the study.

To examine whether sevoflurane (AbbVie, Queenborough Kent, England) application attenuated EBI after SAH and which dose and duration had an anti-apoptotic effect, we used three different concentrations and exposure times.

Animals were randomly divided into five groups in each study, and evaluated at 24 hours (h): Study 1 included sham-operated+30% O_2+70% medical air (O_2-medical air; 24-h, n=9), SAH+O_2-medical air (24-h, n=13), and SAH+1.5% sevoflurane+O_2-medical air (24-h) for 30 (n=12), 60 (n=11), and 90 (n=13) minutes (min). Study 2 included SAH+3% sevoflurane+O_2-medical air (24-hour) for 30 (n=11), 60 (n=11), and 90 (n=13) min. Study 3 included SAH+4.5% sevoflurane+O_2-medical air (24-hour) for 30 (n=8), 60 (n=8), and 90 (n=9) min.

Mouse SAH Model

An SAH endovascular monofilament model was produced, as previously described (1,2). Briefly, animals were anesthetized with an intraperitoneal injection of ketamine/xylazine (100/10 mg/kg). A sharpened 4-0 monofilament nylon suture was advanced through the internal carotid artery (ICA) to perforate the anterior cerebral artery. In the sham surgery, the filament was advanced 5 mm through the ICA without perforating the artery. Body temperature was kept constant (37.5°C ± 0.5°C) during the operation.

Drug Administration

The three concentrations of sevoflurane+O_2-medical air were administered continuously beginning 1 hour after SAH induction in the three study groups.

Severity of SAH

The severity of SAH was blindly evaluated using the SAH grading scale at sacrifice (1,2). For the SAH grading system, the basal cistern was divided into six segments, and each segment was allotted a grade of 0–3 depending on the amount of subarachnoid blood clot in the segment: grade 0, no subarachnoid blood; grade 1, minimal subarachnoid blood; grade 2, moderate blood clot with recognizable arteries; and grade 3, blood clot obliterating all arteries within the segment. The animals received a total score of 0–18 after adding the scores from all six segments. Four mice with SAH grading scores ≤7 and no significant brain injury were excluded (1,2).

Mortality and Neurologic Scores

We calculated mortality at 24 h after SAH. Neurologic score was blindly evaluated at 24 h after SAH as described previously (1,2). Evaluation consisted of six tests scored 0–3 or 1–3, including tests on spontaneous activity, symmetry in the movement of all four limbs, forelimbs outstretching, climbing, side stroking, and response to vibrissae (whisker stimulation). Animals were given a score of 3–18 in 1-number steps (higher scores indicated greater function).

Brain Water Content (BWC)

Brains were quickly removed and separated into the left and right cerebral hemispheres, cerebellum, and brain stem, and weighed (wet weight) at 24 h (n=6 per group) postoperatively. Next, brain specimens were dried in an oven at 105°C for 72 h and weighed again (dry weight). The percentage of BWC was calculated as ([wet weight-dry weight]/wet weight) ×100% (1,2).

Terminal Deoxynucleotidyl Transferase-mediated Uridine 5'-Triphosphate-biotin Nick End-labeling (TUNEL) Staining

Animals were euthanized 24 h postoperatively and brains were processed as described previously (1,2). Coronal sections (10-µm thick) at the level of the bregma 1 mm (caudally) were cut on a cryostat (Leica Microsystems, Wetzlar, Germany). TUNEL staining was performed with an in situ cell death detection kit (Roche, Mannheim, Germany). TUNEL-positive cells were counted in three fields per case at ×400 magnification and expressed as the mean number of TUNEL-positive cells/mm^2 with a fluorescence microscope.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). After confirming that each population being compared followed a normal distribution using Shapiro-Wilk W tests, statistical differences were analyzed using unpaired *t*-tests or one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc tests as appropriate. Differences in mortality were tested using Fisher's exact or χ^2 tests as appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Mortality and SAH Grade

There were no deaths in the sham-operated group. The mortality rate was not significantly different among the treatment groups given vehicle (4/13 mice, 30.7%), and 1.5% sevoflurane for 30 (3/12, 25%), 60 (2/11, 18.2%), and 90 (4/13, 30/7%) min in study 1; 3% sevoflurane for 30 (2/11, 18.2%), 60 (2/11, 18.2%), and 90 (4/13, 30.7%) min in study 2; and 4.5% sevoflurane for 30 (2/8, 25%), 60 (3/9, 33.3%), and 90 (3/9, 33.3%) min in study 3. No sham-operated mice died. There was no significant difference in SAH grade among the

vehicle and treatment groups at 24 h in each study (p=0.739, p=0.458, and p=0.612 in studies 1–3, respectively; Figure 1A–C).

Effects of Sevoflurane on Neurologic Score and BWC

In this study, neurologic score was not deteriorated in the sham group, and was significantly lower in the vehicle group compared to the groups given sevoflurane 1.5% for 60 min (p<0.001) and 3% for 30 and 60 min (p<0.001 and p<0.001, respectively). Therefore, a significant neurologic improvement was observed in these treatment groups at 24 h after SAH. However, there were no significant differences between the vehicle group and those given sevoflurane 1.5% for 30 and 90 min in study 1 (p=0.067 and p=0.810, respectively), 3% for 90 min in study 2 (p=0.730), and 4.5% for 30, 60, and 90 min in study 3 (p=0.943, p=0.999, and p=1.000, respectively; ANOVA; Figure 2A–C).

Brain edema is a common and important feature in EBI, is considered a major independent risk factor for poor outcome after SAH, and reflects disruption of the BBB evaluated with BWC (7). BWC was significantly higher in the vehicle compared to the sham groups and was significantly improved in the groups given sevoflurane 1.5% for 60 min (p<0.001) and 3% for 30 and 60 min (p<0.001 and p<0.001, respectively) compared to the vehicle group. However, the groups given sevoflurane 1.5% for 30 and 90 min in study 1 (p=1.000 and p=0.545, respectively), 3% for 90 min in study 2 (p=0.567), and 4.5% for 30, 60, and 90 min in study 3 (p=1.000, p=0.592, and p=0.792, respectively) did not show beneficial effects on BWC at 24 h after SAH (ANOVA; Figure 3A–C). These results suggested that specific concentration and exposure time attenuate the SAH-induced neurologic deficit and brain edema.

Effects of Sevoflurane on Apoptosis in the Basal Cortex after SAH

We quantified apoptosis in the basal cortex using TUNEL staining at 24 h after SAH only in studies 1 and 2, because in study 3 we did not find a significant difference in neurologic score and BWC between the groups. The numbers of TUNEL-positive cells were significantly higher in the vehicle than in the sham groups. Groups given sevoflurane 1.5% for 60 min (p=0.011) and 3% for 30 and 60 min (p<0.001, p<0.001, respectively) showed decreased numbers of positive cells compared to the vehicle group (Figures. 4A-B, 5A-B). These results indicated that specific dose and exposure time attenuated the apoptosis induced by SAH in the basal cortex in EBI after SAH.

DISCUSSION

Different volatile anesthetic dose and duration protocols may manifest changing brain conditions, which may have good

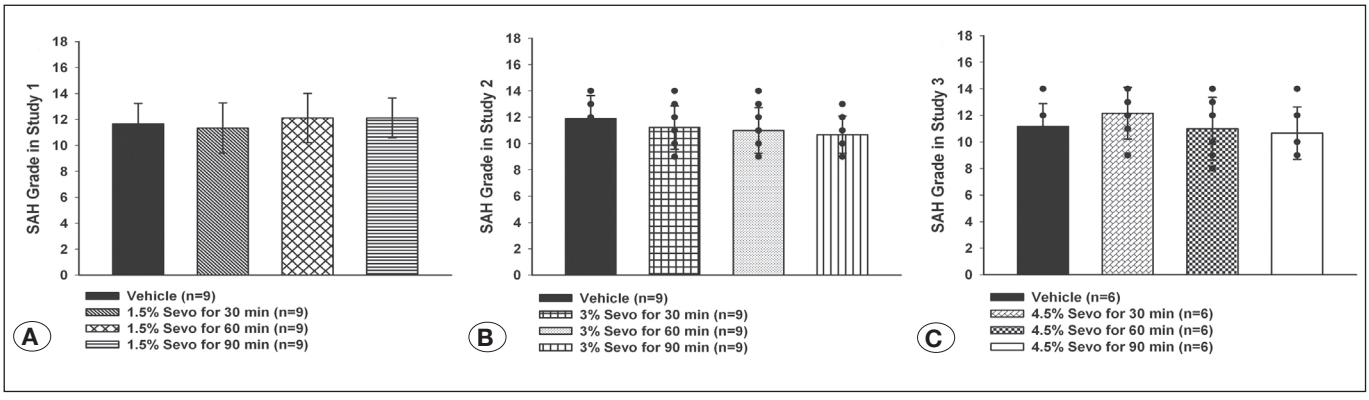

Figure 1: SAH grade (**A**, **B**, **C**) in studies 1, 2, 3 respectively, was evaluated at 24 hours after SAH. Values are mean ± SD; *p<0.05, ANOVA.

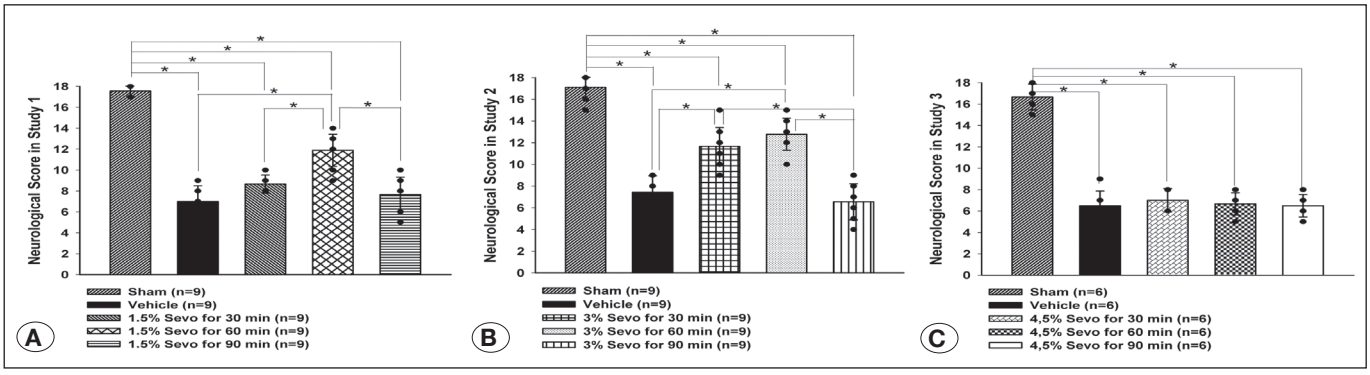

Figure 2: Neurologic scores (**A**, **B**, **C**) in studies 1, 2, 3 respectively, were evaluated at 24 hours after SAH. Values are mean ± SD; *p<0.05, ANOVA.

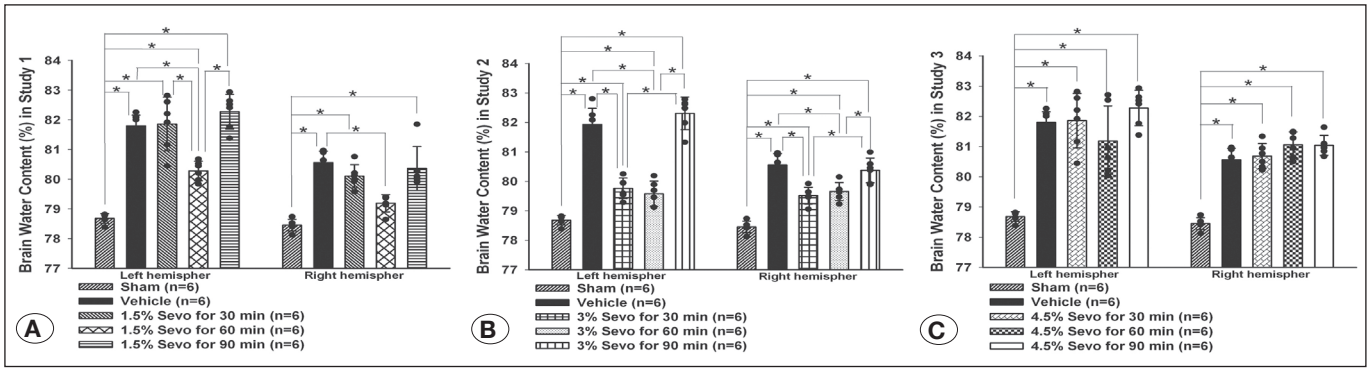

Figure 3: Brain water content (**A**, **B**, **C**) in studies 1, 2, 3 respectively, was evaluated at 24 hours after SAH. Values are mean ± SD; *p<0.05, ANOVA.

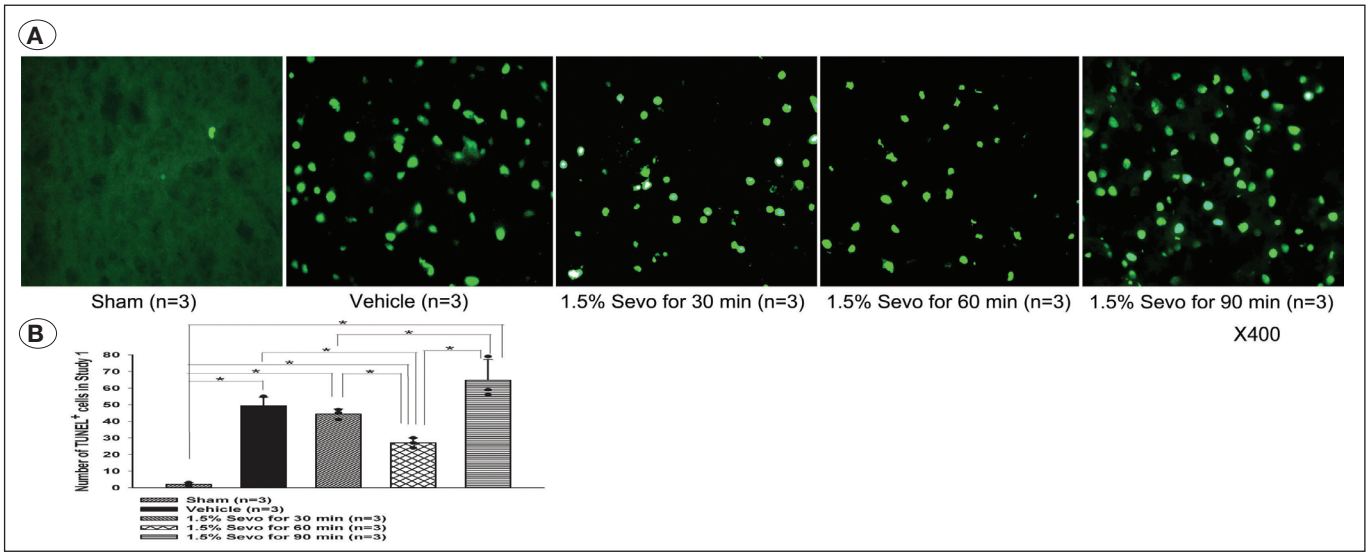

Figure 4: Evaluation of TUNEL-positive cells in the ipsilateral basal cortex at 24 hours after SAH (study 1). **B)** Immunofluorescence images showing the TUNEL (green)-positive cells. **B)** Quantitative analysis of TUNEL-positive neurons. Values are mean ± SD; *p<0.05, ANOVA.

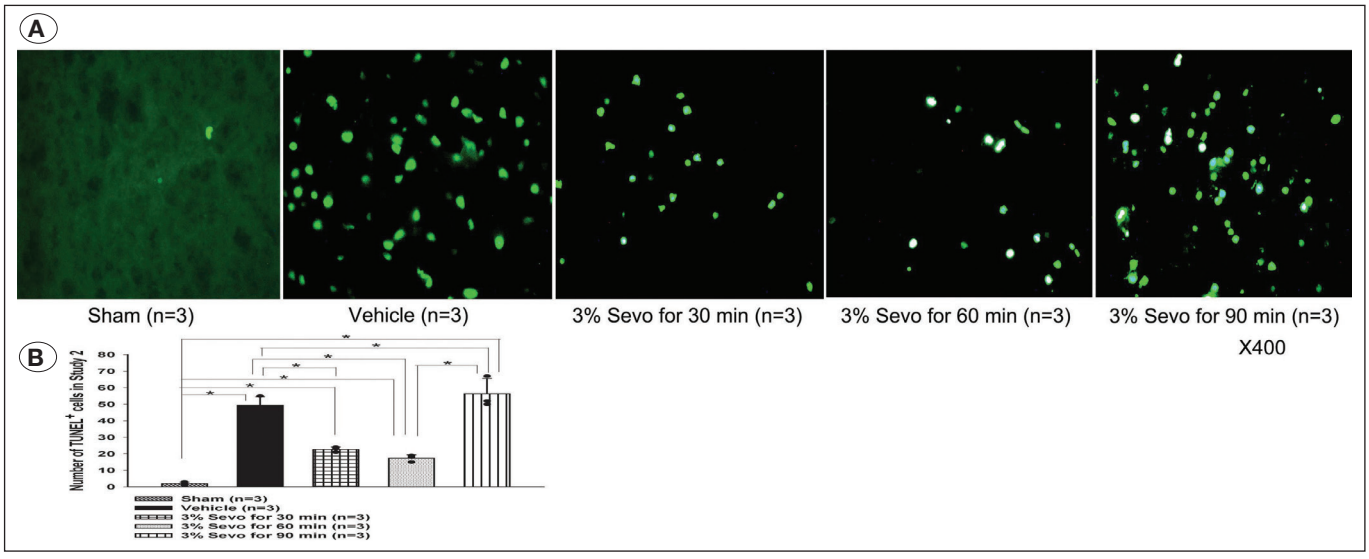

Figure 5: Evaluation of TUNEL-positive cells in the ipsilateral basal cortex at 24 hours after SAH (Study 1). **A)** Immunofluorescence images showing the TUNEL (green)-positive cells. **B)** Quantitative analysis of TUNEL-positive neurons. Values are mean ± SD; *p<0.05, ANOVA.

or bad effects on neuroglial cells. Therefore, there might be an optimal concentration and duration for neuroprotection, which also agrees with the results of one report showing that the neuroprotective effect of preconditioning with isoflurane depended on the doses (30). In our study, we confirmed that post-treatment sevoflurane reduced brain edema and improved neurologic scores after SAH in mice. We found that application of sevoflurane 1.5% for 60 min and 3% for 30 and 60 min had a neuroprotective effect against EBI after SAH. However, sevoflurane 1.5% for 30 and 90 min, 3% for 90 min, and 4.5% for 30, 60, and 90 min did not show a neuroprotective effect. We suggested that post-treatment sevoflurane has potential for future clinical application and that the neuroprotective effect of sevoflurane occurs depending on concentration and duration after SAH. Although whether a higher concentration of >4.5%, exposure time of >2 h, or multiple treatments for the long term, may provide better neuroprotection needs further study.

A growing number of studies have reported that pretreatment with 2.7% sevoflurane for 45 min (6), and 2% sevoflurane for 60 min significantly reduced neurologic deficit in rats after middle cerebral artery occlusion (MCAO) (23). Another study has reported that 2.4% sevoflurane pretreatment for 60 min effectively improved spatial learning and memory ability in a focal cerebral ischemia animal model (14). Also, pretreatment with 2.7% sevoflurane for 30 min conferred neuroprotective effects in *in vivo* global cerebral ischemia showed that 2.4% sevoflurane pretreatment for 1 hour inhibited microglial activation and alleviated neuronal apoptosis caused by inflammatory reactions (24,33).

In addition to pretreatment intervention, emerging evidence has demonstrated that post-treatment with sevoflurane also provided neuroprotection. It has been reported that 30 min of 2.5% sevoflurane post-treatment displayed neuroprotective effects via the phosphatidylinositide 3-kinase (PI3K)/AKT signaling pathway in neonatal hypoxia-ischemia–induced brain damage (19), and also 2.5% post-treatment sevoflurane for 60 min significantly reduced neurologic deficit after MCAO in rats (44). Likewise, post-treatment with sevoflurane (1.0 minimum alveolar concentration [MAC] and 1.5 MAC) for 30 min not only reduced infarct volume, but also improved learning and memory after MCAO in a rat model (42). In another study, 2.5% sevoflurane post-treatment for 90 min attenuates astrogliosis and glial scar formation after MCAO in a stroke model (45). Additionally, sevoflurane at 3% and 7% for 1 hour decreased TLR2 and TLR4 expression as well as significantly lowered tumor necrosis factor (TNF)–α and interleukin (IL)–6 levels in human endothelial cell culture media at 24 hours (35).

According to these data, animal studies have shown that pretreatment and post-treatment sevoflurane can provide neuroprotective effects (41). However, no consensus has yet been reached to guide clinical practice of concentration, duration, and conditioning with sevoflurane in terms of neuroprotection. This problem is at least partly due to the lack of information concerning the duration and timing of anesthetic conditioning in the human system (18, 27). However, pretreatment in clinical use is limited since ischemic and subarachnoid hemorrhagic insults are mostly unpredictable. Therefore, post-treatment is more clinically feasible and is not tied to a specific time point.

The limiting factors for using higher concentrations of inhalational anesthetics in patients undergoing neurosurgery are the agents' effects on cerebral blood flow (CBF) and cerebral blood volume (CBV), which are key determinants of ICP, and may add risk to neurosurgical patients (25). It has been reported that the average MAC was 1.71 ± 0.07% for isoflurane and 3.08 ± 0.4% for sevoflurane in domestic cats (38). No significant effect on CBF was reported by Fairgrieve et al. with 0.5, 1.0, and 1.5 MAC sevoflurane concentrations (9), and Satomoto et al. with 3% sevoflurane plus 60% oxygen for six hours (36). Kitaguchi et al. studied the effects of sevoflurane on the cerebral circulation of patients with symptomatic cerebrovascular disease and reported that carbon dioxide reactivity and pressure autoregulation were well maintained during 0.88 MAC sevoflurane/33% nitrous oxide anesthesia (17). However, Kaisti et al. reported that sevoflurane anesthesia is dose-dependent and induces a 36%–53% decrease in CBF in all regions of the brain at 1 MAC, and that 1.5 MAC sevoflurane does not significantly affect CBF velocity in healthy children (16). However, given the sustained increase in ICP, which persists in endovascular perforation models that mimic the clinical mechanism of artery rupture, sevoflurane might not contribute to ICP elevation for the rate of edema formation after SAH (22). However, effects of sevoflurane on CBF and CBV in the post-SAH brain remain undetermined. In addition, electroencephalographic (EEG) monitoring of normocapnic rabbits anesthetized with 1.0 MAC sevoflurane in 70% N_2O revealed no spike or seizure activity (37).

Proposed mechanisms related to the neuroprotective effect of volatile anesthetic agents include upregulation of antiapoptotic factors, activation of ATP-dependent potassium channels, upregulation of nitric oxide synthase, reduction of excitotoxic stressors and cerebral metabolic rate, and augmentation of peri-ischemic CBF (27).

Apoptosis is involved in the pathogenesis of EBI after experimental SAH (5). Many factors such as global ischemia (32), microcirculatory disturbance (3), and subarachnoid blood toxicity (28), are involved in apoptosis-related mechanisms, including the death receptor pathway, caspase-dependent and -independent pathways, as well as the mitochondrial pathway, which are believed to have a role in SAH (12). It has been thought that glial cells are activated by signals originated from dying neurons, and these activated glial cells produce toxic inflammatory mediators that are responsible for further neuronal cell death (10,11,31). As a result, these activated molecular apoptotic pathways in neuroglia may induce brain edema, neurologic deficit, and higher mortality.

Previous studies showed that apoptotic-related pathway modulation by treatment could improve outcome in EBI after SAH (1,5,34). Antiapoptosis is one pivotal common mechanism underlying the inhalational anesthetic-afforded neuroprotection against ischemic injury (1,13,26), and it has been reported that sevoflurane postconditioning reduced apoptosis

by regulating the expression of apoptotic and antiapoptotic proteins after global cerebral ischemia (15,46). TUNEL staining is used widely to examine the integrity of DNA fragmentation as a marker of apoptosis and has shown that the fluorescent spots indicating cell death mainly corresponded with the distribution of neuronal cell bodies (1,44). Apoptotic cell death detected by TUNEL was seen in the cortex, subcortex, and hippocampus, which is related to global ischemia (8,34).

We found that 1.5% sevoflurane for 60 min and 3% sevoflurane for 30 and 60 min decreased the number of TUNEL-positive cells compared to the vehicle group, which we showed in the basal cortex after SAH and which is consistent with the neurologic score and brain edema evaluations. In other words, sevoflurane bears the potential to delay or even prevent neurologic complications, thereby expanding the therapeutic window for other prospective neuroprotective agents (47).

CONCLUSION

We demonstrated that post-treatment sevoflurane has an anti-apoptotic effect on neuroglial cells at least for 24 hours after SAH. Identification of anesthetics with properties that help to attenuate neuroglial cell damage as a consequence of aneurysmal rupture is clinically highly relevant. Our results suggested that sevoflurane is a good candidate because the first step for intensive care of aneurysmal SAH patients is aneurismal obliteration under general anesthesia. Further studies are warranted to test the combination with other neuroprotectants for EBI after SAH.

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DISCLOSURE

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