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ORIGINAL ARTICLE

Isoflurane Use in the Treatment of Super-Refractory Status Epilepticus is Associated with Hippocampal Changes on MRI

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Abstract
Background Refractory status epilepticus (RSE) is associated with high morbidity and mortality. Experts recommend aggressive management with continuous intravenous infusions or inhaled anesthetics such as isoflurane. However, there is concern that MRI changes in RSE reflect isoflurane neurotoxicity. We performed a case–control study to determine whether isoflurane is neurotoxic, based on MRI signal changes.
Methods We performed a retrospective case–control study of the incidence of MRI changes in RSE treated with and without isoflurane. Charts were reviewed for demographic and treatment information. T1, T2, and FLAIR sequences of MRIs were reviewed independently by two neuroradiologists blinded to treatment group for presence or absence of signal change or atrophy in the meninges, cortex, white matter, basal ganglia, thalamus, hippocampus, brainstem, and cerebellum.
Results Eight cases of RSE receiving treatment with isoflurane were identified and double-matched with 15 controls who received only intravenous anesthetics. Baseline characteristics were similar. Hippocampal signal change was observed more frequently in cases receiving isoflurane ($p = 0.026$).
Conclusions Hippocampal signal changes were associated with isoflurane use in patients with RSE. They were also associated with number of seizure days prior to MRI and the use of multiple anesthetic agents. Similar changes have been seen as a result of RSE itself, and one cannot rule out the possibility these changes represent seizure-related effects. If isoflurane-related, these hippocampal signal changes may be the result of a direct neurotoxic effect of prolonged isoflurane use or failure of isoflurane to protect the hippocampus from seizure-induced injury despite achieving electrographic burst-suppression.

Keywords Isoflurane · Refractory status epilepticus · MRI · Hippocampus

Introduction

Refractory status epilepticus (RSE) confers high morbidity and mortality. It is defined as status epilepticus (SE) persisting after two first-line anticonvulsants are administered [1]. Super-refractory status epilepticus (SRSE) occurs when RSE continues for 24 h, or recurs upon withdrawal of anesthetic agents [2]. Approximately 15 % of all cases of SE become super-refractory [2]. Aggressive management using anesthetic agents is recommended, attempting to reduce the associated morbidity and mortality. Typically, continuous intravenous infusions such as midazolam, propofol, or pentobarbital/thiopental are used, or less commonly, inhaled anesthetics such as isoflurane.

Isoflurane has been proposed to be neurotoxic: Reversible MRI changes affecting the thalamus, brainstem, and

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cerebellum were reported in two patients receiving prolonged high-dose isoflurane therapy for RSE [3]. However, similar MRI changes have been seen as a result of SE itself [4, 5]. To investigate whether these MRI changes were the result of isoflurane use or RSE, we reviewed MRIs from cases of RSE treated with and without isoflurane to determine differences between these two groups.

Isoflurane is routinely used to treat RSE at London Health Sciences Centre (LHSC) in London, ON, Canada, whereas intravenous anesthetic agents alone are used at Columbia University Medical Centre (CUMC) in New York, NY. We sought to compare cases of RSE at LHSC to those at CUMC to determine whether MRI changes differed with and without isoflurane use.

Methods

We performed a retrospective case–control study of the incidence of MRI changes in SRSE in patients treated with and without isoflurane. Cases of SE at LHSC between 2001 and 2013 were identified through the ICU database and health records using the search term "status epilepticus." These results were compared to the ICU database of all patients who received isoflurane while hospitalized to ensure no cases were missed.

Cases were included if RSE was diagnosed and MRI was performed during or shortly after treatment with isoflurane. RSE was defined as seizures unresponsive to first- and second-line treatments with anticonvulsants. Patients were excluded if they did not receive MR imaging, imaging was not available for review, or MRI was not within 10 days of isoflurane treatment. Cases of RSE due to hypoxic–ischemic injury secondary to cardiac arrest were excluded due to poor prognosis and imaging changes potentially representing anoxic changes [6]. Once cases were selected, they were double-matched based on age (within five years), gender, and etiology of SRSE with controls at CUMC through their SE database.

Medical records were reviewed for demographic information, etiology of RSE, treatment characteristics, and mortality. The number of seizure days was calculated, which we defined as the duration of RSE prior to admission to LHSC or CUMC, plus the number of days with at least one seizure recorded on continuous EEG (cEEG) after admission to our centers. As many patients were transferred from peripheral hospitals without cEEG monitoring, we did not have accurate data regarding seizures prior to arrival at our centers, and thus assumed there was at least one seizure each day prior to transfer. Given that the population of patients we studied has severe SE using the previously validated Status Epilepticus Severity Score [7] with scores of >2, we used breakthrough seizure days as a surrogate for ongoing, poorly controlled RSE, reflecting more severe SRSE. Lateralized periodic discharges were not considered seizures, due to debate as to whether they constitute ictal or interictal phenomena [8, 9]. Anesthetics were titrated to achieve a burst-suppression pattern.

Isoflurane was administered using a Drager anesthetic machine, and an anesthesiologist supervised its administration in all cases. The protocol followed at LHSC has been previously reported [10, 11]. When isoflurane was added to the patient's intravenous anesthetic agents, attempts were made to wean other anesthetics. Total duration of isoflurane use, average end-tidal concentration (ETC), and duration of isoflurane use prior to MRI were calculated.

The MRIs were reviewed independently by two experienced neuroradiologists (DHL and AGK), who knew only that the patient has SRSE. Presence or absence of signal change (T2 or FLAIR hyperintensity) and atrophy was determined in the cortex, subcortical white matter, basal ganglia, thalamus, hippocampus, brainstem and cerebellum, and signal change or enhancement in the dura and leptomeninges. In cases where the radiologists disagreed, MRIs were jointly re-reviewed and interpretation agreed upon.

Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY). Means and standard deviations were calculated for baseline characteristics. Fisher's exact tests (two-sided) were performed to determine differences between cases and controls. Two-tailed *t* tests were performed to determine differences in characteristics of SRSE and MRI findings between cases and controls. Characteristics of SRSE evaluated were the total number of hospital days, hospital days before MRI, seizure days before MRI, days since last seizure prior to MRI, hemodynamic status, number of intermittent AEDs, number of anesthetic agents, and death. Two-tailed *t* tests were performed to determine differences between the duration and concentration of isoflurane and MRI findings among cases. As data were not normally distributed, Wilcoxon rank-sum exact test was performed where indicated.

Ethics approval within the guidelines for each institution was obtained for both sites.

Results

We identified 348 cases of SE at LHSC from 2001 to 2013. Of these, 293 were not refractory. In the remaining 43, 26 received isoflurane. The 17 patients who had RSE but did not receive isoflurane were excluded because cEEG recordings were not carried out (6), MRI was not carried out or not available (8), both cEEG and MRI were unavailable (2), or the etiology was anoxia (1). Sixteen

patients underwent MR imaging during treatment with isoflurane, and of these, eight patients' MRIs were available for review. These patients were then double-matched with patients at CUMC.

Baseline characteristics between cases and controls were similar (Table 1). Etiologies of SRSE included encephalitis, new-onset RSE (NORSE), known epilepsy, stroke, and trauma. The average patient age was 34.8 ± 11.3 in the cases and 34.9 ± 12.5 in the controls. The duration of SRSE prior to obtaining the MRI and the number of days without seizures prior to the MRI was not significantly different between cases and controls, although there was a trend toward more seizures prior to MRI in the cases ($p = 0.084$, Table 2).

Treatment characteristics, other than isoflurane use, did not differ between cases and controls (Table 2). Physiologic parameters were acceptable in all patients, and no significant difference was found in systolic blood pressure (SBP), mean arterial pressure (MAP), or oxygen saturation (Table 3). A statistically significant difference in diastolic blood pressure (DBP) was found between groups, with higher blood pressure in the cases (57 vs. 53 mmHg, $p = 0.04$). There were no differences in vasopressor use. No differences in metabolic abnormalities that could have resulted in brain damage and signal change on MRI occurred between groups. Three cases and four controls had renal failure requiring renal replacement therapy; however, this was transient and reversible in all cases.

A number of anesthetic medications and maintenance anticonvulsants were similar between groups. The average duration of isoflurane use was 220 h (range 5–820), with an average ETC of 1.3 % (range 0.59–2.1 %). The average isoflurane concentration-hours (isoflurane ETC times hours at each concentration) was 572.33 (range 7.82–1242.64). Mortality and severity of RSE were not different between groups.

Neuroimaging revealed more frequent hippocampal signal changes in the cases than controls by one radiologist, with discrepancies between radiologists seen in two cases and two controls (Fig. 1). Analysis after joint review of these four scans by both radiologists maintained cases having significantly more hippocampal signal changes than controls (5 vs. 2, respectively, $p = 0.026$, Table 4). No other brain area had significant differences in either signal change or atrophy.

Hippocampal signal changes occurred more frequently in patients who had a longer duration of SRSE prior to MRI and in those who required more anesthetic agents to treat their SRSE, regardless of treatment group ($n = 7$, Table 5). The average number of seizure days before MRI was 21.4 days in those with hippocampal signal change and 5.6 days in those without ($p = 0.01$). Patients with hippocampal signal changes used an average of 3.42 anesthetic agents, compared to 1.68 in those without ($p = 0.003$).

Duration of isoflurane use was associated with hippocampal signal change: Average duration of isoflurane treatment was 331 h in those with hippocampal signal change and 35.8 h in those without ($p = 0.03$). There was no association between average ETC and hippocampal signal change.

Table 1 Baseline characteristics

Baseline characteristics	Cases ($n = 8$)	Controls ($n = 15$)	Significance (Fisher's exact test)
Age, years (SD)	34.8 (11.3)	34.9 (12.5)	0.42
Male gender	6 (75)	9 (60)	0.66
Etiology			
Autoimmune	2 (25)	2 (13)	
Cerebrovascular	0	2 (13)	
Known epilepsy	0	3 (20)	
Idiopathic	1 (12.5)	2 (13)	
Infectious	0	1 (6.7)	
NORSE	3 (37.5)	3 (20)	
Post-traumatic	2 (25)	0	
Neoplastic	0	2 (13)	
Predominant seizure focus			
Right	2 (25)	3 (20)	
Left	3 (37.5)	3 (20)	
Generalized	1 (12.5)	4 (26.7)	
Bilateral	2 (25)	4 (26.7)	
None	0	1 (6.7)	

NORSE new-onset refractory status epilepticus

Table 2 Treatment characteristics

Characteristic	Cases ($n = 8$)	Controls ($n = 15$)	Significance
Length of hospitalization, days (SD)	63.4 (50.3)	48.7 (61.0)	0.97
Seizure days before MRI (SD)	16.8 (19.0)	7.0 (7.8)	0.084
Days since last seizure before MRI (SD)	1.4 (2.8)	7.1 (23.0)	0.21
Number of intermittent AEDs (SD)	4.8 (1.9)	4.3 (2.4)	0.9
Number of continuous anesthetic agents (SD)[a]	2.6 (0.9)	2.0 (1.7)	0.11
Mean total hours of isoflurane (SD, range)	220.0 (266, 5-820)	n/a	
Mean hours of isoflurane prior to MRI (SD)	97.7 (117.7)	n/a	
Mean number of days of isoflurane prior to MRI (SD)	1.8 (2.4)	n/a	
Mean isoflurane ETC (SD)	1.3 (0.6)	n/a	
Mean isoflurane concentration %-hours (SD, range)	572.33 (474.5, 7.82-1242.64)	n/a	
Renal failure requiring CRRT (%)	3 (38 %)	4 (26 %)	0.66
Mortality at discharge (deceased) %	3 (37.5 %)	4 (26.7 %)	0.67

ETC end-tidal concentration, *CRRT* continuous renal replacement therapy

[a] Anesthetic agents used included midazolam, propofol, ketamine, and pentobarbital

Table 3 Physiologic parameters

Parameter (SD)	Cases ($n = 8$)	Controls ($n = 15$)	Significance
Minimum systolic blood pressure (mmHg)	109 (5.6)	103 (8.3)	0.09
Minimum diastolic blood pressure (mmHg)	57 (4.1)	53 (5.4)	**0.04**
Minimum mean arterial pressure	72 (5.6)	70 (5.3)	0.48
Minimum SpO_2 (%)	95 (1.8)	96 (2.3)	0.30
Duration of vasopressor use	239 (272)	119 (219)	0.28
Number of pressors	2 (0.76)	1.4 (1.8)	0.38
Renal replacement therapy (%)	3 (37.5)	4 (26.7)	0.66

Bold value is statistically significant ($p \leq 0.05$)

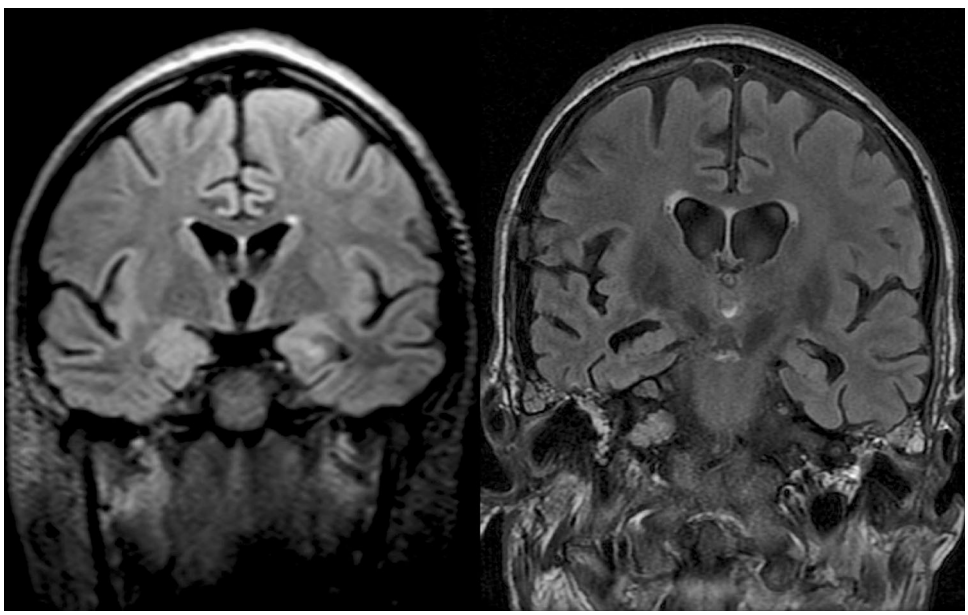

Fig. 1 Representative case–control showing hippocampal signal abnormalities seen more frequently in cases (*left*) than controls (*right*) on coronal FLAIR sequence

Table 4 Group differences in MRI changes

Brain area (cases vs. controls)	Radiologist 1	Radiologist 2	Combined review
Signal changes			
Dura & leptomeninges	ns	ns	–
Cortex	ns	ns	–
Subcortical white matter	ns	ns	–
Basal ganglia	ns	ns	–
Thalamus	ns	ns	–
Hippocampus	0.179	0.026	**0.026**
Brainstem	ns	ns	–
Cerebellum	ns	ns	–
Atrophy			
Dura & leptomeninges	ns	ns	–
Cortex	ns	ns	–
Subcortical white matter	ns	ns	–
Basal ganglia	ns	ns	–
Thalamus	ns	ns	–
Hippocampus	0.033	1	0.103
Brainstem	ns	ns	–
Cerebellum	ns	ns	–

Differences in each identified area were compared between cases and controls for any significant differences (Wilcoxon rank sum) independently by each radiologist or on combined review of discordant findings. *p* values are only reported if significant

Bold value is statistically significant ($p \leq 0.05$)

ns not significant

Table 5 Factors significantly associated with hippocampal signal change

Factors associated with hippocampal signal change (all patients)	Signal change present ($n = 7$)	Signal change absent ($n = 16$)	Significance (exact Wilcoxon)
Mean seizure days before MRI (SD)	21.4 (17.9)	5.6 (7)	0.01
Mean number of continuous anesthetic infusions (SD)	3.42 (0.79)	1.68 (1.4)	0.003
Factors associated with hippocampal signal change (isoflurane patients)	**Signal change present ($n = 5$)**	**Signal change absent ($n = 3$)**	**Significance (exact Wilcoxon)**
Total duration of isoflurane, hours (SD)	331 (287)	35.8 (41)	0.03

Discussion

Hippocampal signal change occurred more frequently in cases than controls and was not definitively explained by other between group differences. A statistically significant difference in DBP was seen; however, we feel this is unlikely to result in hippocampal MRI changes, as the MAP was similar between groups. Signal change was associated with the total duration of isoflurane treatment, but not the number of hours prior to obtaining MRI or the average ETC. This may indicate that longer use of isoflurane, which may act as a surrogate for increased difficulty treating seizures, rather than the total dose of isoflurane, influences the presence of hippocampal signal change. In our study, hippocampal signal change was not dose- or timing-related with respect to amount of isoflurane received prior to imaging; however, our numbers were small. This contradicts an association with dose and duration of isoflurane by Fugate et al. [3]. They reported two cases of RSE receiving prolonged isoflurane treatment who developed MRI changes in the thalamus and cerebellum that resolved upon isoflurane discontinuation. They suggested that there may be a critical point after which isoflurane is no longer neuroprotective and becomes neurotoxic. Their patients had prolonged exposure to isoflurane, with over 1250 concentration-hours, which was only present in two of our cases. One case with prolonged isoflurane use (1174 concentration-hours) with an average

ETC of 1.8 % had no hippocampal signal changes. The other case (1242 concentration-hours) demonstrated hippocampal signal changes that improved between scans done 18 days apart, despite continued isoflurane administration at an average ETC of 0.77 %. Overall, the concentration-hours and ETC of isoflurane were considerably lower in our patients than those reported by Fugate; however, our two cases with prolonged isoflurane use did not have the same signal abnormalities [3]. In particular, the case with no MRI changes received high-dose isoflurane (ETC $>$ 1.5 %) for the majority of the time he received isoflurane.

Unlike Fugate et al. [3], we did not find an association between isoflurane use and MRI changes in the cerebellum or thalamus. The hippocampal changes we observed could be due to SE itself, which has been well described [4, 5]. Seizure-related signal changes occur most frequently in the hippocampus and are often, but not always reversible. Other areas frequently involved include cortex, white matter, thalamus, basal ganglia, and brainstem [4, 5]. Signal changes can be seen as the result of recent seizure activity and does not require the presence of SE [12, 13]. This likely represents neuronal damage occurring as a result of seizures, and changes in these areas have been demonstrated pathologically [14, 15]. The hippocampus is the most vulnerable area to damage, which can occur in as little as 20 min of continuous seizure activity [15]. It is therefore possible that the hippocampal changes seen in this study could be the result of RSE rather than treatment with isoflurane, as our small numbers make any conclusions unreliable.

Our results suggest isoflurane may be neurotoxic, which could represent a direct neurotoxic potential or failure of isoflurane to protect the hippocampus from seizure-induced injury despite adequate electrographic control. Although more patients with hippocampal changes were in the isoflurane group, they could be explained by the known neuroimaging changes seen in RSE, particularly given the trend toward more seizure days before obtaining MRI. Additionally when disregarding treatment group, greater number of days before MRI was significantly associated with hippocampal signal changes. Cases with more intense and prolonged seizures would have received longer duration of treatment with isoflurane due to treatment resistance and may have resulted in delays acquiring imaging. While our data show a statistically significant association with isoflurane treatment and duration, this does not prove causation.

Unfortunately, follow-up imaging was not available in most of the cases treated with isoflurane, so we are unable to determine whether these effects are reversible. Three MRIs were available after resolution of RSE, two improved, and one worsened. Changes attributed to isoflurane have previously been shown to be reversible [3].

Whether isoflurane has neuroprotective or neurotoxic effects has been extensively debated, with evidence supporting both positions [16]. This neurotoxic potential has previously been shown in rats after SE where neuropathological changes were similar given treatment with isoflurane, thiopental, ketamine, or no anesthetic agent [17]. This may suggest isoflurane toxicity; however, this effect was not limited to isoflurane in this study.

Recently, it was demonstrated that rats receiving low-dose isoflurane for 1 week did not have any histological changes such as inflammation or neuronal death on neuropathology [18], suggesting it is safe to use for a prolonged period. However, postoperative cognitive decline (POCD) has become a significant clinical concern with volatile anesthetic use in both human and rat studies. Isoflurane appears to have a greater propensity to cause cognitive decline than other volatile anesthetics such as desflurane [19]; yet some studies have shown that surgery itself, rather than the type of anesthetic administered, is a risk factor for POCD [20]. Some rat studies demonstrate improved spatial memory after isoflurane administration [21, 22], whereas others find transient or persistent cognitive decline [22–25]. Memory impairments following isoflurane administration have been shown to be dose-dependent in both humans [26] and rats [27], with lower doses resulting in greater memory impairments. Proposed mechanisms include upregulation of proinflammatory cytokines IL-1β, IL-6, and TNF-α [28, 29]. Apoptotic neurodegeneration has also been seen following isoflurane administration, particularly in the hippocampal CA1 region [27]. Isoflurane can also inhibit hippocampal neuronal proliferation [30] and decrease neural progenitor cells [25]. Hippocampal neuronal nitric oxide synthase is downregulated after isoflurane exposure, which has been suggested to result in impaired memory [24]. The proclivity of damage localizing to the hippocampus and involving memory tasks lends support to our finding that increased hippocampal signal intensity in the isoflurane group is isoflurane-related, rather than SRSE-related.

Isoflurane has also had mixed results in treatment of ischemia. Kawaguchi et al. [31] demonstrated that isoflurane provided initial protection against ischemia, as there were smaller infarct size and fewer apoptotic cells up to 4 days after ischemia compared to rats who did not receive isoflurane. However, 7-day post-ischemia, the isoflurane-treated rats had increased apoptotic cells compared with control rats. More recently, isoflurane was shown to decrease the infarct volume and neurological deficits in rats 2 weeks following ischemic injury [32].

Inhalational anesthetics have been used successfully to treat RSE [10, 33, 34], and a recent systematic review found isoflurane effective in inducing burst-suppression in over 90 % of individuals [35]. However, it bears significant

systemic side effects, such as anasarca requiring dialysis, infection, paralytic ileus, and hypotension, which limit its usefulness [35]. Given the high mortality of SRSE, it still may have a role in the treatment of SRSE, especially if isoflurane is not neurotoxic and imaging abnormalities are the result of RSE.

Lidocaine was found to be effective in diminishing the negative effects of isoflurane in rats, such that rats receiving isoflurane and lidocaine performed almost as well as rats who did not receive anesthetics [36]. Lidocaine has also been used to treat RSE, with seizure response rates of up to 70 % [37]. If this finding is replicable, it may be beneficial in treating SRSE, offering dual benefits: controlling RSE and decreasing isoflurane neurotoxicity.

Limitations of this study include a small sample size and its retrospective nature. As SRSE is not common, the patient population is small and becomes smaller when examining specific aspects of treatment, such as isoflurane use, cEEG monitoring, and time to MRI. As numbers were small, differences in treatment effects are harder to determine and small but significant results may not be appreciated. Large variations or outliers within groups could skew results. Unfortunately, due to the nature of RSE, randomized controlled trials are difficult to perform.

Another significant limitation is that all patients in each group were treated at one facility due to local practice differences. LHSC routinely uses isoflurane to treat RSE, and patients who did not receive isoflurane at this center were excluded, as they did not have complete information required for this study, such as cEEG monitoring or MR imaging during treatment. In contrast, CUMC does not use isoflurane in the treatment of RSE, so obtaining additional isoflurane cases from this site was not possible. Using one center as the source for all cases another for all controls may have resulted in other treatment differences for which we could not control and limit the generalizability of these findings. However, we attempted to reduce reporting errors by having the MRIs reviewed by radiologists from each center rather than relying on radiology reports. There was only one brain area where the radiologists disagreed for a statistically significant result, which occurred in four of 23 subjects (17 %), and was resolved on joint review. Using a binary (present/absent) system for reporting MRI abnormalities cannot account for varying degrees of MRI abnormalities, which may over- or underestimate changes, and thus their significance and potential for neurotoxicity.

Long-term follow-up with neuropsychological outcomes would be useful in determining the impact of these signal changes on functioning after recovery from SRSE and whether they differ from those who do not receive inhalational anesthetics. This would be particularly important given the controversies as to whether isoflurane causes memory impairment.

Conclusion

Based on the results of this small, retrospective study, treatment of SRSE with isoflurane is associated with hippocampal signal change. The significance remains unknown, but could be a marker of neurotoxicity. It may also represent seizure-related damage known to occur in this context. The difference in signal change is limited to the hippocampus, not affecting the basal ganglia and cerebellum, as previously reported [3]. This suggests that signal change outside the hippocampus is the result of RSE. Further research is needed to address the relative roles of SE and isoflurane in producing hippocampal damage. Since hippocampal structure, anatomical and neurotransmitter connections are similar across numerous mammalian species, carefully controlled animal experiments should yield valid information on the potential for isoflurane neurotoxicity in RSE.

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Compliance with Ethical Standards

Conflicts of interest K.M.I, R.C, D.H.L, A.G.K, G.B.Y report no conflicts of interest. J.C has received funding from SAGE Pharmaceuticals for study planning.

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