

Sevoflurane augmentation in treatment-resistant depression: a clinical case study

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Abstract

Compared with other inhaled anaesthetics, sevoflurane has a faster onset and offset, causes less irritation to the mucous membranes, and has a better safety profile. These characteristics warrant investigating the effect of sevoflurane in depression. In this Case Report, we describe that sevoflurane treatment was feasible and well tolerated by a patient with treatment-resistant depression (TRD). Sevoflurane had rapid and durable antidepressant effects, with few adverse effects. Moreover, the patient showed significant improvements in neurocognitive measurements. Our preliminary results suggest that further clinical trials are needed to determine the independent efficacy and safety of sevoflurane in patients with TRD.

Keywords: antidepressant, sevoflurane, treatment resistant

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Introduction

Previous clinical studies on patients with treatment-refractory depression found that isoflurane anaesthesia produced rapid antidepressant effects similar to those of the *N*-methyl-d-aspartate (NMDA) receptor antagonist ketamine.^{1,2} Recently, Antila and Ryazantseva³ further confirmed that in rodents, single isoflurane anaesthesia administration produced rapid antidepressant-like effects similar to those of ketamine, including the activation of brain-derived neurotrophic factor receptor and an increase in the activity of gamma-aminobutyric acid (GABA) transmission.³

Sevoflurane is another inhaled anaesthetic that potentiates the functions of GABA receptors,⁴ and has similar rapid-acting antidepressant effects. Importantly, compared with other inhaled anaesthetics like isoflurane, sevoflurane has a faster onset and offset, causes less irritation to the mucous membranes, and has a better safety profile.^{5,6} Therefore, in view of this better safety profile, exploring the treatment effect of sevoflurane in depression is interesting.

Case summary

The patient was a 66-year-old man with a 29-year history of major depressive disorder (MDD). His depressive symptoms worsened after retirement, which occurred 6 years ago. He spoke few words every day and had strong suicidal ideations, which resulted in several attempts to kill himself. He initially responded to venlafaxine XR (225 mg/day) and mirtazapine (15 mg/day), but he subsequently experienced several residual symptoms and was re-hospitalized another four times. The symptoms persisted even after treatment with off-label prescription medications at a high dosage, including duloxetine (180 mg/day), venlafaxine XR (300 mg/day), escitalopram (30 mg/day), and eight sessions of electroconvulsive therapy.

At the time of hospitalization, he reported that he lost interest in everything and felt depressed. He also experienced severe headache and fatigue, which left him bedridden. He often thought of killing himself and he was certain he would in the future. He was administered a combination treatment including venlafaxine XR (150 mg/day),

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Table 1. Changes of depressive symptoms and cognitive functions of patients before and after the sevoflurane inhalation.

		Baseline	2 h	24 h	7 days	14 days
MADRS		24	14	7	7	10
HAMA		12	6	3	3	6
DSST		25	25	30	29	28
DST (proper)		7	10	6	7	8
DST (reversed)		4	4	4	4	4
Stroop test	Total	20	24	24	29	24
	Right	15	17	23	29	22
	Wrong	5	7	1	0	2
TMT-A	Time (s)	114	120	60	58	56
	Wrong times	0	0	0	0	0
	Remind times	3	1	0	0	0
	Pen-up times	3	5	2	2	0
TMT-B	Time (s)	148	200	124	106	99
	Wrong times	2	0	0	0	0
	Remind times	4	6	6	4	5
	Pen-up times	6	6	7	6	7

DST, Digit Span Test; DSST, Digit Symbol Substitution Test; HAMA, Hamilton Anxiety Rating Scales; MADRS, The Montgomery Åsberg Depression Rating Scale; TMT, Trail-Making Test.

flupentixol-melitracen (Deanxit®; one tab/day), sulphiride (0.1/d), lorazepam (1 mg/day), and an infusion of scopolamine (0.3 mg four times a day). However, he showed no response after 1 month of treatment during hospitalization.

Therefore, he was started on continuous sevoflurane inhalation at a low concentration flow (between 0.8 and 1.0 mac) *via* a mask under electrocardiogram monitoring for 1 h/session, after he was fully informed of the treatment and signed a written consent form. The treatment duration was selected, based on the findings of a previous clinical study on nitrous oxide and isoflurane for the treatment of patients with treatment-resistant depression (TRD).^{1,7} During the entire period of sevoflurane inhalation, the patient was evaluated repeatedly by monitoring the eyelash reflex, and the concentration of sevoflurane was adjusted to ensure he was kept in a twilight state where he was awake and could

communicate. After sevoflurane inhalation, he reported no other side effects except for slight dizziness. The depressive symptoms were remarkably relieved after 2 h and 24 h of treatment, respectively. Nevertheless, the depressive symptoms and cognitive functions were continuously evaluated over the following 2 weeks (Table 1). The patient has continued to do well on the same medications since his discharge from the hospital a couple of months ago. The patient also signed a written informed consent form agreeing to the publication of this case report.

Discussion

This case study showed that sevoflurane treatment is feasible and well tolerated by a patient with TRD. Sevoflurane had rapid and durable antidepressant effects with few side effects. Moreover, the patient showed significant improvements in neurocognitive measurements, and these improvements

probably resulted from the combined effects of the medications on decreased depressive symptoms.

Agents targeting GABA and NMDA glutamate antagonists, such as ketamine,⁸ nitrous oxide,⁷ propofol⁹ and isoflurane,² have been shown to have excellent antidepressive effects in clinical trials on patients with TRD. In addition, a low dose of ketamine can alleviate depressive effects in 2h, and these effects are maintained for 2 weeks;¹⁰ these findings are consistent with the current findings obtained using sevoflurane. Importantly, sevoflurane inhalation offers more benefits over intravenous treatment. For instance, from a safety perspective, the concentration of the inhaled drug can be easily controlled according to the physical state of the patient; the inert gas can be expelled from the body through rapid breathing once inhalation has stopped. Furthermore, previous clinical studies showed that ketamine causes adverse side effects such as hallucinations and delusions¹¹ and propofol causes hypotension (low blood pressure).⁹ Zacny and Janiszewski¹² conducted an interesting experimental study on moderate-drinking healthy volunteers to compare the reinforcing and subjective effects between sevoflurane and nitrous oxide. Their results showed that while nitrous oxide was chosen by 71% of the participants, sevoflurane did not function as a reinforcer in most of the participants. Moreover, nitrous oxide showed greater mood-altering effects than did sevoflurane, as evidenced by higher 'feel drug effect' and 'feel high' ratings. Furthermore, there is no evidence of neurotoxicity with sevoflurane usage, and it does not show any potential for addiction or abuse like nitrous oxide does,¹³ because sevoflurane seldom induces hallucination and euphoria like nitrous oxide does.

GABA concentration deficit has been proposed as a pathophysiological marker of depression, and current antidepressants aim to modulate GABA transmission. Experiments on rodent models revealed GABA_A receptor expression inhibition in the hippocampus during pregnancy, which also supported the pathophysiology of postpartum depression associated with GABA_A receptor plasticity deficit.¹⁴ A recent clinical trial also demonstrated that a GABA_A receptor modulator (brexanolone) showed a substantial treatment effect in patients with severe postpartum depression.¹⁵ Thus, it would be interesting to further investigate the treatment effect of sevoflurane in postpartum depression.

Conclusion

The present case highlights that sevoflurane has rapid and marked antidepressant effects in a patient with TRD. Further clinical trials are needed to determine the independent efficacy and safety of sevoflurane in patients with TRD.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical statement

Ethical approval was obtained from the 3rd Hospital in Huzhou Municipal, Zhejiang, China (approval number: AF015).

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