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ORIGINAL RESEARCH

Effects of Glutathione Tablets on Ferroptosis Pathway and Oxidative Stress-Related Indexes in Serum of Patients Undergoing Sevoflurane Inhalation General Anesthesia and Its Clinical Significance

Hongxia Liu, BM; Lihui Yan, BM; Huiyang Niu, BM; Zhenhua Miao, BM

ABSTRACT

Objective • To explore the effect of glutathione on serum oxidative stress, inflammatory reaction, and brain injury in patients with Sevoflurane inhalation general anesthesia based on iron metabolism pathway.

Methods • From January 2018 to January 2023, 120 patients undergoing Sevoflurane inhalation anesthesia in Xingtai Third Hospital were divided into a control group and an observation group. The control group was given routine treatment, and the observation group patients were given oral glutathione tablets 2 weeks before anesthesia based on the control group. Relevant basic data of patients were collected 3 days before operation (T0), 1 day after the operation (T1), 3 days (T2), and 7 days (T3) respectively, and the serum oxidative stress indicators of patients in each group were measured by ELISA: SOD, MDA, GSH, Hif-1α, ferroptosis related indicators: SIRT3, GPX4; related inflammatory indicators: IL-1β, TGF-β, IL-33; neuronal injury related proteins: MBP, NGF, and statistical analysis of the data.

Results • There was no significant difference in general conditions and operation time between the two groups ($P > .05$). Compared with the control group, the observation group showed significant differences in oxidative stress indicators: SOD in the observation group at T1, SOD, and Hif-1α in the observation group at T2, and SOD, MDA, GSH and Hif-1α in the observation group at T3. 1α, there were significant differences compared with the indicators of the control group at the same time ($P < .001$). In terms of inflammatory factor indicators, compared with the control group, there were significant differences in IL-1β at T1, TGF-β, and IL-33 at T2, and IL-1β, TGF-β and IL-33 at T3. ($P < .001$). In terms of ferroptosis indicators, compared with the control group, there were significant differences in SIRT3 at T1, SIRT3, and GPX4 at T2, and SIRT3 and GPX4 at T3 ($P < .001$). In terms of nerve injury-related proteins, in patients, MBP levels were negatively correlated with SIRT3 (r=-0.8979, $P < .0001$), MBP levels were positively correlated with GPX4 (r=0.528, $P < .0001$), and NGF levels were positively correlated with SIRT3 (r=0.8979, $P < .0001$), NGF level was negatively correlated with GPX4 (r=0.528, $P < .0001$).

Conclusion • Glutathione tablets can alleviate sevoflurane-induced ferroptosis and oxidative stress by elevating GPX4 protein levels, and glutathione tablets have an ameliorative effect on brain injury in patients with sevoflurane inhalation anesthesia. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Tens of millions of patients worldwide receive general anesthesia every year for different medical conditions, and whether early general anesthetic exposure damages the neurological aspects of the brain system or even triggers long-term intellectual and cognitive deficits has become one of the focuses of interest in anesthesiology, neuroscience, and other fields.[1,2] Previous studies have confirmed that inflammation, neurotoxic agents, and oxidative stress are important factors in inducing neuronal death.[3] Early basic experiments have shown that sevoflurane can lead to abnormal apoptosis of neurons in the rat brain, and the apoptotic region is concentrated in the hippocampus of the brain.[4] Sevoflurane is currently the most commonly used inhalational anesthetic drug, and patients lose consciousness within 2 min when 4% of sevoflurane is inhaled through an oxygen mask. Sevoflurane has potential toxic effects on neurons. It was found that sevoflurane may induce abnormal development of neuronal dendritic spines in

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newborn rats by regulating the expression of histone deacetylase 2, thus causing cognitive impairment. It was found that sevoflurane may kill neurons by activating microglia, prompting them to produce TNF-α and IL-1β.[5] Others found that sevoflurane directly induced ferroptosis in cortical neurons.[6] However, whether sevoflurane can induce ferroptosis in dopamine neurons has rarely been reported. However, recent studies have found that sevoflurane is capable of inducing neurological damage in the central nervous system, a process that has been associated with a variety of mechanisms that cause oxidative stress in neuronal cells, apoptosis in neuronal cells, neurotransmitter disruption, and altered synaptic plasticity.[7] General anesthesia may have neurological effects, including short-term postoperative cognitive impairment (POCD) and potential long-term effects. These effects are influenced by a variety of factors, such as the type of surgery, anesthetic drugs, and patient health. However, in most cases, the benefits of general anesthesia outweigh the potential risks, and medical decisions should be based on the patient's specific circumstances. Research is ongoing to better understand the effects of general anesthesia and to take steps to reduce potential risks. A 2017 FDA study reported that prolonged or repeated exposure to inhalational anesthetics impairs neuronal cellular progression in developmental children. Ferroptosis is an iron-dependent, novel mode of programmed cell death that distinguishes it from other modes of cell death. When the antioxidant capacity of the organism is reduced, a large amount of lipid reactive oxygen species will accumulate in the cell, which in turn will cause cellular ferroptosis.[8] Therefore oxidative stress may be a potential upstream mechanism of ferroptosis. Ferroptosis is a novel form of cell death discovered in 2012. Unlike autophagy, pyroptosis, apoptosis, and other forms of cell death, the main feature of ferroptosis is iron-dependent lipid peroxidation.[9] The process of ferroptosis is mainly accompanied by an increase in intracellular free Fe^{2+}, the accumulation of lipid peroxides, and the dysfunction of the cystine/glutamate inverse transporter. Intracellular and extracellular stresses lead to an increase in intracellular free Fe^{2+} enrichment, and intracellularly overloaded Fe^{2+} contributes to the transformation of lipids into lipid peroxides through the Fenton reaction, which in turn leads to the impairment of the integrity of the cellular membrane, and induces the cells to undergo ferroptosis. Corresponding mechanisms exist within the cell itself to resist ferroptosis.[9-11] The cystine/glutamate inverse transporter is localized in the cell membrane, and its main function is to exchange extracellular cystine and intracellular glutamate at a ratio of 1:1. After cystine enters the cell, it generates glutathione in a series of redox and enzymatic reactions, and glutathione reduces the lipid peroxides accumulated in the cell under the guidance of glutathione peroxidase 4 (GPX4), which in turn inhibits ferroptosis,[12] GPX4 plays a crucial role in the regulation of cellular ferroptosis. Previous studies have confirmed that GPX4 inactivation induces cells to undergo ferroptosis, while Fe^{2+}-induced ferroptosis is also closely involved in the selective death process of dopamine neurons.[13]

Studies have shown that sevoflurane enhances oxidative stress in the neonatal rat brain, inducing ROS production and neuronal cell death.[5] Increased ROS production causes mitochondrial dysfunction and inhibits cellular DNA repair, which in turn promotes neuronal apoptosis and ferroptosis, ultimately leading to neuronal damage.[14] Therefore, our team believes that the ferroptosis mechanism may be one of the potential mechanisms of brain damage induced by sevoflurane anesthesia in patients in the clinic. Reduced glutathione is a commonly used therapeutic modality to regulate oxidative stress in the body in the clinic.[15] Reduced glutathione can participate in cellular redox processes in vivo, acting as an important endogenous detoxifying agent, scavenging peroxides and free radicals, mitigating cellular damage, and anti-fibrotic effects. In addition, it has been shown that supplementation of exogenous reduced glutathione can also effectively reduce oxidative stress in patients.[15]

Numerous studies have shown that the mechanism of ferroptosis is closely linked to oxidative stress. Sevoflurane can inhibit the activity of GSH and promote the generation of ROS by inducing the activation of reductive coenzyme II oxygenase and peroxidase, and ferroptosis is dependent on the accumulation of lipid peroxidation products.[12] A related study showed that Ferrostatin-1, an inhibitor of ferroptosis in neuronal cells pretreated with sevoflurane, was able to effectively inhibit the emergence of nerve injury, suggesting the important role of the ferroptosis mechanism in sevoflurane-induced nerve injury.[16] Meanwhile, the subsequent study of this team also found that up-regulation of peroxidase expression could significantly inhibit the neuronal cell damage caused by sevoflurane.[16] In conclusion, our team expects to confirm the potential mechanism of ferroptosis in sevoflurane inhalation anesthesia-induced neurological injury and observe the mitigating effect of glutathione tablets in this study.

The study aimed to gain insight into the physiological effects of sevoflurane during surgery, particularly its effects on oxidative stress and the nervous system. The results can help guide the safer use of sevoflurane and provide a reference for the development of anesthetic drugs to improve the safety and effectiveness of surgical procedures.

MATERIALS AND METHODS

Research subjects

One hundred and twenty elderly patients admitted to the Xingtai Third Hospital from January 2018 to January 2023 who received surgical treatment were selected, including 57 males and 63 females; aged 37-61 years old; body mass index (BMI) 41-76 kg/m^2; and years of education 7-15 years. Inclusion criteria: (1) age ≥ 60 years; (2) Those who received general anesthesia for surgical treatment; (3) Patients and their families were informed about the study; (4) American Society of Anesthesiologists (ASA) classification I~II.

Exclusion criteria: (1) People with limb dysfunction, refer to individuals who have significant deficits or impairments in limb function that may interfere with the study results and therefore were chosen to be excluded from this study. These

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limb dysfunctions may include muscle paralysis, loss of limb sensation, or limited motor function.; (2) People with central system diseases; (3) People with recent use of psychotropic drugs; (4) History of alcoholism; (5) People with liver and kidney function impairment. The study was approved by the Ethics Committee of Xingtai Third Hospital.

Grouping method: divided into a control group and an observation group, the control group was given conventional treatment, and the patients in the observation group were given oral glutathione tablets (produced by Chongqing Yuyou Pharmaceutical Co., Ltd., State Pharmaceutical License No. H20050667) 2 weeks before anesthesia based on the control group, 2 mg each time, 3 times/d, for 2 weeks in total.

Methods

Non-invasive blood pressure, electrocardiogram, oxygen saturation, and end-expiratory carbon dioxide were routinely monitored in both groups after admission to the room.

Preparation for surgery

Thirty minutes before the operating theatre, 0.1 g of phenobarbital sodium (Harbin Pharmaceutical Group Sanjing Pharmaceutical Co., Ltd, State Drug Certificate: H23021166; specification: 2 mL: 0.2 g) and 0.5 mg of atropine (Shanghai WoFeng Pharmaceutical Co., Ltd, State Drug Certificate: H31021057; specification: 2 mL:10 mg) were injected intramuscularly.

Anesthesia induction

Vital signs monitoring was routinely given after entering the operating room, and before anesthesia induction, the patient was told to take deep breaths and inhale pure oxygen, and anesthesia was induced by: 1.5 mg/kg succinylcholine (Xi'an HANFENG Pharmaceutical Co., Ltd., China National Pharmaceutical Standard: H20054745; specification: 1 mL: 50 mg); 3~4 g/kg fentanyl (Yichang Renfu Pharmaceutical Co., Ltd: H42022076; specification: 2 mL : 0.1 mg); 0.05 mg/kg midazolam (Yichang Renfu Pharmaceutical Co., Ltd, State Drug Licence: H20067040, specification: 3 mL: 15 mg).

Maintenance of anesthesia

Anesthesia maintenance: Sevoflurane inhalation concentration 1% -3%, propofol 2-3 ug/ml, remifentanil 2-4 ng/ml target-controlled infusion in response room, atracurium cisnenenebb benzenesulfonate 0.1 mg/kg/h continuous intravenous pumping, adjust the inhalation concentration of Sevoflurane and the dosage of other drugs according to the vital signs and surgical needs, stop Sevoflurane inhalation 20 minutes before the end of surgery, and then adjust the Narcotic dosage and stop time according to the surgical conditions.

Termination of anesthesia and after surgery

After the end of the surgery, after the patient wakes up, pull out the Tracheal intubation after meeting the conditions for extubation and send it back to the ward.

Table 1. Basic information of patients in two groups

Project	Control group (n = 60)	Observation Group (n = 60)	χ^2/t value	*P* value
Gender (male/female/case)	26/34	31/29	1.828	.3607
Age/($\bar{x} \pm s$, years)	68.91±5.31	69.17±4.63	-0.323	.747
BMI/($\bar{x} \pm s$, kg/m^2)	24.74±2.90	24.47±2.79	0.555	.579
ASA grading (1/II/case)	49/11	54/6	1.713	.1906
Education years/($\bar{x} \pm s$, years)	9.49±3.47	10.45±3.16	-1.750	.082
Anesthesia time/($\bar{x} \pm s$, min)	136.82±18.54	132.45±16.58	1.506	.134
Surgical time/($\bar{x} \pm s$, min)	97.42±13.25	95.33±15.62	0.835	.405
Bleeding volume/($\bar{x} \pm s$, mL)	387.24±74.82	380.54±72.48	0.544	.588
Respiratory recovery time/($\bar{x} \pm s$, min)	7.68±4.14	8.10±4.50	-0.570	.570
Eye-opening time/($\bar{x} \pm s$, min)	12.25±6.64	13.72±7.15	-1.251	.213
Pulling time/($\bar{x} \pm s$, min)	12.95±5.88	14.20±6.28	-1.208	.229
Recovery room dwell time (min)	45.97±21.78	43.75±23.66	0.468	.641

Observation indicators

Collect patient-related basic data before and after treatment, observe surgical-related indicators and postoperative adverse reactions in the two groups of patients, compare the dynamic changes of diastolic blood pressure, systolic blood pressure, heart rate, and SpO_2 in the two groups of patients before induction (T0), 1 minute after induction (T1), 5 minutes after intubation (T2), and 10 minutes after intubation (T3), and measure the oxidative stress indicators in the serum of each group of patients using ELISA technology: SOD, MDA, GSH, Hif-1α. Ferroptosis-related indicators: SIRT3, GPX4. Related inflammatory indicators: IL-1β, TGF-β, IL-33. Neuroinjury-related proteins: MBP, NGF.

Statistical analysis

Statistic Package for Social Science (SPSS) version 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis of the data. The measurement data conforming to Normal distribution were expressed as mean ± standard deviation, and the measurement data not conforming to Normal distribution were expressed as median and interquartile interval. The Chi-squared test or Fisher exact test was used for inter-group comparison of qualitative data, and the *t* test or Mann-Whitney U test was used for quantitative data analysis. The difference was considered statistically significant if all data comparisons were $P < .05$. Use Graphpad Prism version 8.0 (La Jolla, CA, USA) to create charts and display the differences between groups.

RESULTS

Comparison of general condition and operation time of patients in two groups

According to the inclusion criteria and exclusion criteria, a total of 120 patients were included in this experiment, there were 60 patients in each group. Comparison of the gender composition, age, weight, ASA classification, and operation time of the two groups showed no statistically significant difference (P = .3607, .747, .579, .1906, .405) (see Table 1).

Comparison of oxidative stress indicators between the two groups

The differences in the levels of SOD, MDA, GSH and Hif-1α between the two groups of patients at T0 time point were not statistically significant (P = .87, .37, .53, .87); the

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Table 2. Changes in oxidative stress indices during anesthesia in both groups of patients ($\bar{x} \pm s$)

Groups	Time	SOD (ng/ml)	MDA (ng/ml)	GSH (Ug/ml)	Hif-1α (pg/mL)
Control group	T0	89.58±5.48	63.67±27.46	11.53±3.13	52.77±9.97
	T1	63.99±3.79[a]	48.51±26.22[a]	10.14±2.96[a]	53.53±8.31
	T2	25.62±3.28[ab]	46.12±21.34[a]	10.28±2.34[a]	60.64±6.73[ab]
	T3	77.65±2.87[abc]	44.65±20.93[a]	9.43±3.03[a]	61.43±6.95[ab]
Observation group	T0	89.74±5.32	59.67±21.17	11.86±2.66	52.48±8.75
	T1	68.99±3.79[ad]	46.85±26.75[a]	11.1±2.9	52.62±7.06
	T2	45.32±3.29[abd]	41.91±19.95[a]	11.1±2.68	55.69±6.43[abd]
	T3	80.99±3.79[abcd]	36.59±23.46[abcd]	11.41±2.9[d]	56.01±8.56[abcd]

[a]compared with T0 in the group, $P < .05$
[b]compared with T1 in the group, $P < .05$
[c]compared with T2 in the group, $P < .05$
[d]compared with the control group at the same time, $P < .05$.

Figure 1. Changes in oxidative stress indicators in the two groups of patients ($\bar{x} \pm s$)

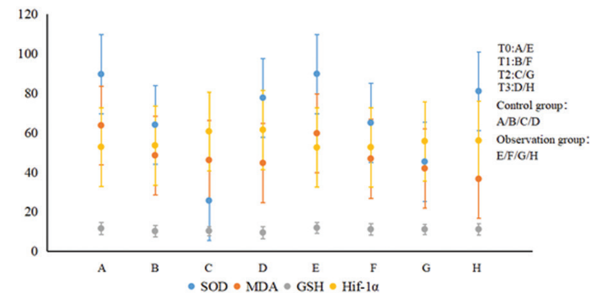


Table 3. Changes in inflammatory factor levels during anesthesia in both groups of patients ($\bar{x} \pm s$)

Groups	Time	IL-1β (pg/ml)	TGF-β (pg/ml)	IL-33 (pg/ml)
Control group (n = 60)	T0	28.6±2.5	43.65±6.81	41.09±6.67
	T1	41.3±3.9[a]	41.26±5.74[a]	41.26±5.78
	T2	86.9±7.9[ab]	40.74±4.78[a]	35.71±5.18[ab]
	T3	94.6±8.7[abc]	37.29±5.17[abc]	34.06±5.27[ab]
Observation group (n = 60)	T0	29.0±1.9	44.75±6.63	40.85±6.79
	T1	37.6±2.9[ad]	40.17±4.15[a]	41.37±6.12
	T2	89.3±7.8[ab]	36.57±6.23[abd]	31.75±5.17[abd]
	T3	78.6±8.6[abcd]	31.45±4.28[abcd]	25.36±4.13[abcd]

[a]compared with T0 in the group, $P < .05$
[b]compared with T1 in the group, $P < .05$
[c]compared with T2 in the group, $P < .05$
[d]compared with the control group at the same time, $P < .05$.

Figure 2. Changes in inflammatory factor levels during anesthesia in both groups of patients ($\bar{x} \pm s$)

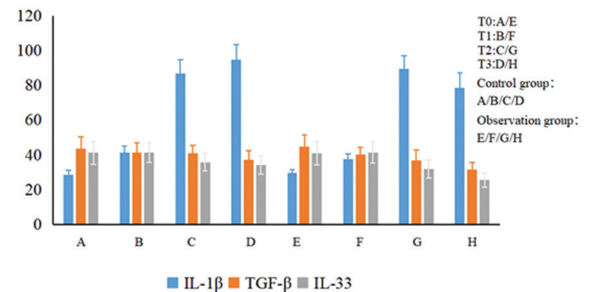
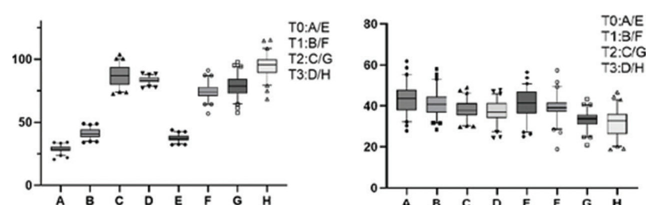


Table 4. Changes in the levels of indicators related to ferroptosis in anesthesia in two groups of patients ($\bar{x} \pm s$)

Groups	Time	SIRT3 (ng/ml)	GPX4 (ng/ml)
Control group (n = 60)	T0	28.6±2.5	43.65±6.81
	T1	41.3±3.9[a]	41.26±5.97[a]
	T2	86.9±7.9[ab]	38.17±4.31[ab]
	T3	83.6±2.5	37.29±5.17[ab]
Observation group (n = 60)	T0	28.6±2.9	41.36±7.13
	T1	74.6±6.5[ad]	39.26±5.68[a]
	T2	78.6±8.6[abd]	33.45±4.28[abd]
	T3	94.6±8.7[abcd]	31.65±6.81[abcd]

[a]compared with T0 in the group, $P < .05$
[b]compared with T1 in the group, $P < .05$
[c]compared with T2 in the group, $P < .05$
[d]compared with the control group at the same time, $P < .05$.

Figure 3. Changes in the levels of indicators related to ferroptosis in anesthesia in two groups of patients ($\bar{x} \pm s$)



differences in the SOD of the patients in the observation group at T1 time point, the SOD, Hif-1α of the patients in the observation group at T2 time point, and the SOD, MDA, GSH and Hif-1α of the patients in the observation group at T3 time point compared with those of the same period as in the control group, were all statistically significant ($P < .001$). Significance ($P < .001$). See Table 2 and Figure 1.

Comparison of inflammatory factor indicators between the two groups

The differences in the levels of IL-1β, TGF-β and IL-33 between the two groups of patients at the T0 time point were not statistically significant ($P = .33, .37, .85$); the differences in IL-1β of the patients in the observation group at the T1 time point, TGF-β and IL-33 of the patients in the observation group at the T2 time point, and IL-1β, TGF-β and IL-33 of the patients in the observation group at the T3 time point compared with the indicators of the opposite control group were all statistically significant ($P < .001$). See Table 3, Figure 2.

Comparison of ferroptosis-related indicators between the two groups

The difference in the levels of SIRT3 and GPX4 between the two groups of patients at the T0 time point was not statistically significant ($P > 0.99$, $P = .07$); the SIRT3 of the patients in the observation group at the T1 time point, the SIRT3 and GPX4 of the patients in the observation group at the T2 time point, and the SIRT3 and GPX4 of the patients in the observation group at the T3 time point were significantly higher than the indexes of the control group during the same period, and the differences were all statistically significant ($P < .001$). See Table 4, Figure 3.

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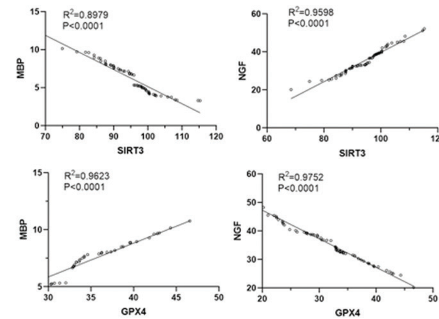
Table 5. Serum levels of nerve injury-related proteins MBP and NGF in two groups of patients ($\bar{x} \pm s$)

Groups	Time	MBP(ng/mL)	NGF(ng/mL)
Control group (n = 60)	T0	6.35±2.06	35.61±6.9
	T1	7.79±1.56[a]	30.5±6.14[a]
	T2	8.67±3.14[a]	29.16±4.35[ab]
	T3	9.1±2.06a[b]	28.29±4.32[ab]
Observation group (n = 60)	T0	6.47±1.85	34.74±6.13
	T1	6.91±1.87	32.19±5.13[ad]
	T2	10.02±1.15[abd]	31.82±5.06[abd]
	T3	12.35±2.06[abcd]	35.61±6.9[abcd]

[a]compared with T0 in the group, $P < .05$
[b]compared with T1 in the group, $P < .05$
[c]compared with T2 in the group, $P < .05$
[d]compared with the control group at the same time, $P < .05$.

Figure 4. Correlation analysis of nerve damage proteins MBP, NGF with ferroptosis SIRT3, GPX4



Relationship between serum nerve damage-related protein MBP and NGF levels and ferroptosis-related indexes SIRT3 and GPX4 in the two groups of patients

The difference between the MBP and NGF levels of the two groups of patients at the T0 time point is not statistically significant (P = .74, .47); the NGF of the patients in the observation group at the T1 time point, the MBP and NGF of the patients in the observation group at the T2 time point, and the MBP and NGF of the patients in the observation group at the T3 time point are significantly higher than the indicators of the control group during the same period, and the differences are all statistically significant ($P < .001$). Among the patients, serum MBP levels were negatively correlated with SIRT3 (r=-0.8979, $P < .0001$), serum MBP levels were positively correlated with GPX4 (r=0.528, $P < .0001$), serum NGF levels were positively correlated with SIRT3 (r=0.8979, $P < .0001$), serum NGF levels were negatively correlated with GPX4 (r=-0.528, $P < .0001$) are shown in Table 5 and Figure 4.

DISCUSSION

Sevoflurane is currently the most commonly used inhalational general anesthetic drug in clinical practice, and previous studies have suggested that sevoflurane can impair cortical neuronal activity, but its effect on the ferroptosis pathway is yet to be explored, and the related pathological mechanisms are yet to be investigated.[2] Glutathione is one of the most important non-protein sulfhydryl compounds in living organisms, which is divided into reduced glutathione (GSH) and oxidized glutathione (GSSG), and the important functional group of GSH, sulphhydryl (-SH), can bind with and reduce free radicals in the body, and thus has a powerful scavenging effect on free radicals.[13] The results of the present study confirmed that glutathione can inhibit ferroptosis by the specific mechanism of increasing GPX4 protein levels.

Halothane pyruvate may affect neurons through multiple mechanisms, including excessive autophagy, endoplasmic reticulum stress, and inflammatory responses.[14] Specifically, halothane pyruvate may trigger excessive autophagy, leading to an abnormal increase in the number of autophagosomes within neurons, thereby disrupting the normal cellular metabolism and function of neurons.[11] In addition, it may also lead to the activation of the endoplasmic reticulum stress response, trigger the instability of the endoplasmic reticulum, and then trigger a series of stress signaling pathways, which may have adverse effects on neurons.[12] Finally, halothane pyruvate may also induce an inflammatory response, leading to inflammatory cell infiltration and the release of pro-inflammatory factors in the tissues surrounding neurons, further damaging the structure and function of neurons.[13] Further in-depth experiments and studies are needed to understand these potential mechanisms in detail to reveal the effects of halothane pyruvate on the nervous system.[14]

This study explored the effect of glutathione on the ferroptosis pathway and oxidative stress-related indexes in the serum of sevoflurane inhalation general anesthesia patients, which can help to understand the ferroptosis pathway and oxidative stress occurrence mechanism of sevoflurane inhalation general anesthesia patients, and at the same time, excavate the potential interventional drugs for their treatment. Previous studies have found that sevoflurane can induce neuronal apoptosis in young mice, impairing their learning and memory abilities.[17] Mechanistically, sevoflurane induces excessive autophagy and endoplasmic reticulum stress response in neurons, which in turn damages neurons. Previous studies have found that sevoflurane can induce microglia activation, exacerbate inflammatory responses, and then damage neurons.[14]

In this study, glutathione was found to reduce the levels of IL-1β, TGF-β, and IL-33, which are relevant inflammatory indicators after sevoflurane inhalation in patients, confirming the reduced inflammatory effect of glutathione. Sevoflurane is one of the potential risk factors for inducing ferroptosis. Ferroptosis is a new form of cell death different from autophagy, pyroptosis, and apoptosis. Under the interference of external factors and the disturbance of the intracellular environment, the intracellular Fe^{2+} level increases, and the reaction between Fe^{2+} and hydrogen peroxide generates excessive hydroxyl radicals, which leads to the oxidation of cell membrane lipids, the integrity of the cell membrane is destroyed, and the cell death occurs. Among them, the intracellular loaded irons are mainly Fe^{2+}, the body's transferrin binds Fe^{3+} and transports Fe^{3+} to the cytoplasm with the assistance of transferrin receptor (TFR), and the intracellular ferric reductase STEAP3 reduces Fe^{3+} to Fe^{2+}, which is one of the most important sources of intracellular

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Fe^{2+}; in addition, intracellular ferritin releases the Fe^{2+} it binds, which leads to an increase in the level of intracellular Fe^{2+}, which is one of the important sources of intracellular Fe^{2+}; furthermore, intracellular ferritin releases its bound Fe^{2+}, which causes the level of intracellular Fe^{2+} to rise, which is another major source of intracellular Fe^{2+}. These results suggest that a high load of Fe^{2+} may be one of the important triggers of neuronal death.[18] Meanwhile, corresponding antioxidant mechanisms exist in vivo to resist ferroptosis. Cystine/glutamate inverse transporter exists in the cell membrane, which transports cystine from extracellular to intracellular, and by depleting NADPH, cystine is converted to cysteine and further generates glutathione.[19] GPX4 by utilizing glutathione, can reduce peroxyl radicals generated by Fe^{2+} overloading, preventing lipid peroxidation of cell membranes and inhibiting ferroptosis. In this study, we confirmed that glutathione tablets can increase SOD and GSH levels and decrease MDA and Hif-1α levels, which are characteristic changes of ferroptosis, suggesting that glutathione tablets can inhibit ferroptosis triggered by sevoflurane inhalation in patients.

Sevoflurane is a volatile anesthetic drug widely used for anesthesia. It produces anesthetic effects by affecting the activity of neurons.[17] Sevoflurane acts on the central nervous system to produce anesthetic effects by modulating the release of neurotransmitters and the excitability of neurons. Specifically, sevoflurane can increase the effects of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, which produces sedative and anesthetic effects by enhancing the inhibitory effects of GABA and reducing neuronal excitability.[18] The relationship with ferroptosis pathways is also an important area of research. Iron ions are essential in the body, but at high concentrations can have harmful effects on neurons, causing oxidative stress and cell damage.[18] Sevoflurane, as a volatile anesthetic drug, may have effects on oxidative stress and iron metabolism.[18] Some studies have shown that sevoflurane can alleviate oxidative stress and reduce the release and oxidation of iron ions, thereby mitigating the risk of neuronal damage.[18]

Anesthesia is an indispensable and important part of modern medicine. Sevoflurane, as a commonly used inhalation general anesthetic drug, has many unique advantages such as fast induction of anesthesia and awakening, and small hemodynamic effects in clinical practice.[7] However, it is believed that sevoflurane can cause brain damage, and the relatively mature and intervention-specific mechanisms include neuroinflammation, apoptosis, and oxidative stress.[8] Ferroptosis, as a newly discovered mode of cell death, may play an important role in this.[11] Meanwhile, reduced glutathione can participate in cellular redox processes in vivo, and as an important endogenous detoxifying drug, it plays a role in scavenging peroxides and free radicals, mitigating cellular damage, and anti-fibrosis.[12]

The results of this study showed that glutathione tablets could elevate GPX4 protein levels in patients. In the presence of glutathione, GPX4 can reduce toxic lipid ROS to non-toxic lipid alcohols and prevent ferroptosis from occurring. Reducing intracellular free Fe^{2+} levels by inhibiting oxidative stress on the one hand, and attenuating lipid peroxidation by elevating GPX4 protein levels on the other hand, maybe an important potential mechanism for inhibiting ferroptosis by glutathione tablets. Of course, glutathione tablets may also inhibit the occurrence of ferroptosis by regulating more signaling pathways. In conclusion, sevoflurane can induce ferroptosis in patients, and glutathione tablets can elevate GPX4 protein levels to prevent ferroptosis.

Although this study provides initial insights into the effects of halothane pyruvate on oxidative stress and the nervous system, there are some limitations to consider. First, this study had a relatively small sample size and a single-center design, which may affect the external validity and generalizability of the results. Future studies could consider expanding the sample size and conducting multicenter studies to more fully evaluate the effects of halothane pyruvate. Secondly, this study mainly focused on oxidative stress and neurological effects but did not address other potential biological and molecular mechanisms. Future studies can further explore the effects of halothane pyruvate on autophagy, inflammatory pathways, and other possible biological effects to more fully understand its mechanism of action. Additionally, this study was observational and cannot determine cause and effect. Future studies may consider conducting more rigorous experimental studies, such as animal model studies, to verify the effects of halothane pyruvate on oxidative stress and the nervous system. Finally, the follow-up period of this study was relatively short, and long-term effects were not considered. Over time, halothane pyruvate may have longer-term effects on patients' health. Future studies could extend the follow-up period to assess its long-term effects.

In summary, while this study provides us with some important insights into halothane pyruvate, further research is still needed to address limitations and delve deeper into its underlying mechanisms and long-term effects. This will provide a better understanding of the use of halothane pyruvate in clinical practice and the role of patient management.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Xingtai Third Hospital. Signed written informed consents were obtained from the patients and/or guardians.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

HL and ZM designed the study and performed the experiments, LY collected the data, HN analyzed the data, and HL and ZM prepared the manuscript. All authors read and approved the final manuscript.

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