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Propofol Pretreatment Protects Hippocampal CA1 Neurons from Ischemia-reperfusion Injury in Rat

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Abstract

Background: The number of brain strokes induced by ischemia has increased significantly in recent years as a result of brain vascular disorders. Some of these patients will require brain vascular surgery. Brain ischemia, large-scale bleeding, and hypoxia are all severe risks that must be avoided when using an anesthetic medicine that has the best protective benefits for the patient's brain and vascular system during the surgical process. One of the most critical pathogenic events in ischemia-reperfusion is apoptosis, and the CA1 region of the hippocampus is one of the most vulnerable parts of the brain to ischemia. Propofol is a neuroprotective intravenous anesthetic for cerebral ischemia-reperfusion (I/R) injury. Few studies have been conducted on the neuroprotective and neurobehavioral effects of propofol, and the underlying mechanism remains unclear. However, few studies have looked into the dose and injection timing of the drug to achieve neuroprotective effects.

Aim: The purpose of this study was to see if propofol could protect male Wistar rat hippocampal CA1pyramidal cells from ischemia and brief overall reperfusion damage.

Methods: The 18 male Wistar rats were placed into three groups: control, ischemia, and experimental. 1 hour before ischemia, 40 mg/kg propofol was given intraperitoneally. Ischemia was induced by blocking the common carotid arteries on both sides for 20 minutes. For histomorphologic alterations, the Hematoxylin-Eosin, Nissl, and TUNEL techniques were used.

Results: The researchers discovered that 40mg/kg propofol has protective effects on hippocampus pyramidal neurons in ischemia/reperfusion-induced lab rats.

Conclusion: Propofol can drastically reduce neuron death while also protecting them from ischemia damage.

Conflicts of Interest: The Authors declare no conflicts of interest.
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Introduction

Nowadays, brain strokes caused by ischemia threaten the life and health of brain vascular patients at an increasing rate. One of the important factors in the treatment of such patients is to use an anesthetic drug that could provide the highest protective effects on the brain and its vascular system during surgical operations in conditions when there is a risk of brain ischemia, large-scale hemorrhage, and hypoxia. Apoptosis, discharge of cellular energy reserves caused by reduced blood circulation, the release of amino acids, and stimulation in nitric oxide (NO) production are the most important pathological events that might take place in ischemia cases (1-3).

The results of such events could be kinetic-sensory, vision disorders, speech disorders (aphasia), neuropsychiatric defects such as

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cognitive and learning disorders, and disability in performing the tasks that the individual had already learned (4-7). Reperfusion into brain tissues after ischemia leads to inflammation and oxidative lesions caused by oxidative stress. The blood flow return causes the return of oxygen to the cells and lesions caused by the release of free radicals. This could affect signaling and cause programmed cell death (apoptosis). Some specific regions in the brain and particular types of neurons show more sensitivity to brain ischemia such as pyramidal neurons in CA1 of the hippocampus (8-12). Hippocampus plays a key role in different types of learning, memorizing and deleting perceptions and thoughts. The neuroprotective effects of more than 100 substances on cellular planned death have been already proved in experimental models (13); however, unfortunately despite the promising results, which have been obtained from animal models in preventing this type of cell death, no effective pharmacology strategy has been found to confront ischemia so far. This might be due to a deficiency of the effect and/or side effects of the drug. (14, 15).

Recently there have been many researches in connection with the protective effects of propofol (2, 6-diisopropyl phenol) drug. This drug is one of the most common anesthesia medications for inducing and maintaining the anesthesia state. Studies on animals show propofol in transient ischemia-reperfusion model protects the brain cells in rat fetuses against damages caused by brain hypoxia. (16, 18).

In addition, in high doses of propofol, it provides neuroprotection in the internal carotid artery blockage model in rats (19).

According to the need of the anesthesia and surgery team during surgery for a drug for nerve protection, we evaluated the protective effect of propofol on male Wistar rat hippocampal CA1 cells caused by ischemia/ transient overall reperfusion.

Methods

Animal and Experimental Groups

The present research was carried out in empirical-research type on 18 male Wistar rats (supplied by the pharmacology department of Tehran University) at 8 weeks of age, kept in 23-25 centigrade degree temperature, 50 percent humidity, and 12- hours' light-dark cycle.

The rats were divided into three groups, each containing 6 rats:

- Control group: Rats only underwent anesthesia induction by ketamine and xylazine.
- Ischemia group: After anesthesia, ischemia was induced by bilateral common carotid occlusion for 20 minutes followed by reperfusion.
- Experimental group: Rats received 40mg/kg propofol intraperitoneally (IP) one hour before ischemia/reperfusion.

Animals were sacrificed after four days and their brains were removed. The staining was performed by using Hematoxylin-Eosin, Nissl, and Tunel methods.

Surgical Method

After anesthesia, the common carotid arteries of both sides were appeared and closed by microsurgery clamps for 20 minutes. The clamps were then removed and the flow started again. The animal's temperature was measured repeatedly by using anal thermometers and was fixed regularly by a heat lamp at 37± 5o C. The cut was stitched and the animals were monitored until they regained consciousness and stable conditions. After the operation, the animals were kept in separate cages for 24 hours. All animals were induced by anesthesia four days after ischemia and their brains were first fixed through perfusion and then kept in paraformaldehyde 4% for 30 hours after decapitation

Histological Staining

The coronal sections at 5 µ thickness were cut in each group of paraffin blocks by using a

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microtome tool and stained with hematoxylin and eosin (H&E).

Pyramidal cells of the CA1 region in the hippocampus were analyzed at three different regions (100 µm apart), between 2.3- and 5-mm posterior to Bregma fortune. Images were captured at 400× for each section and histopathological changes were observed under an optical microscope.

Nissl staining

After fixation and preparation of paraffin blocks, the coronal sections were prepared from a 2.3- 5 mm distance of the posterior part at 10µ thickness by using a microtome tool and were transferred on gelatin-contained films and were then stained by Nissl method. The specimen was checked by using an optic microscope with × 400 magnitude and only the pyramidal neurons with visible nuclei and nuclides were selected as healthy cells. The photomicrographs were selected at random, the pyramidal cells of the CA1 region of the hippocampus were counted by image tool software (version 2.0) and the mean number was written.

TUNEl staining

The paraffin blocks from coronal sections were cut in 3µ thickness by using a microtome and were placed on fluids containing films. The TUNEL staining was performed as follows for specifying apoptotic cells (Roche, Mannheim, Germany) and following the manufacturer's instructions.

First, the tissue sections were incubated with 20µg/ml proteinase K at 37C temperature for 30 minutes. The films were washed with PBS and incubated in ice for two minutes to increase their penetrability. Then, 50 µl TUNEL reaction mixture solution was added to the films and was incubated at 37C temperature for one hour and was then washed with PBS. It was then placed in 50 µl converter-POD solution for 30 minutes at 37C and was then washed again with PBS solution.

Then, 50-100 µl DAB solution was added to both specimens and they were then incubated at 15-25℃ temperature for 5-20 minutes at the end, the specimen was washed with PBS three times. Five fields were randomly selected from each section at a high magnification (×400) and the number of TUNEL-positive cells in the CA1 region was counted and the average was determined for statistical analysis. All counting procedures were performed randomly.

Statistical Analysis

The results were presented as mean ± standard deviation (SD) observations. The significant difference was determined by a one-way ANOVA, followed by Tukey's Multiple Comparison test and the significant difference was set at 0.05.

Results

The treatment with propofol reduced neurodegeneration in the CA1 region of the hippocampus. The histopathological assessment showed that the control group neurons and neural tissue were intact and had normal structures. These cells had integrity and regular cell arrangement of the pyramidal neurons in the CA1 region. The pyramidal cells had center-positioned nuclei, prominent nucleolus, and clear cytoplasm. Cellular degeneration and necrosis were not seen as shown in Figure 1 (control).

The ischemia group had numerous pyramidal cells with prominent morphological changes such as pyknotic nuclei, lack of nucleolus, and hyperchromatic cytoplasm compared to pyramidal cells of the control group (Figure 1 (Ischemia)). In the treatment (experimental) group, we observed considerably decreased numbers of pyramidal cells with pyknotic nuclei, lack of nucleolus, and hyperchromatic cytoplasm compared to the ischemia group (Figure 1(Experimental)).

Effect of Propofol on the Neuron Survival in the Hippocampus CA1 Area After I/R

Data that were collected from counting viable pyramidal cells in Nissl staining showed that 20 minutes of bilateral common carotid occlusion caused marked CA1 cell loss. In this way, there were statistically significant differences

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between the control group (Figure. 2 (Control)) and the ischemia group (Figure. 2 (Ischemia)); however, this difference was not significant between the control and the experimental groups (p=0.317) (Figure. 2 (Experimental)) (Chart 1).

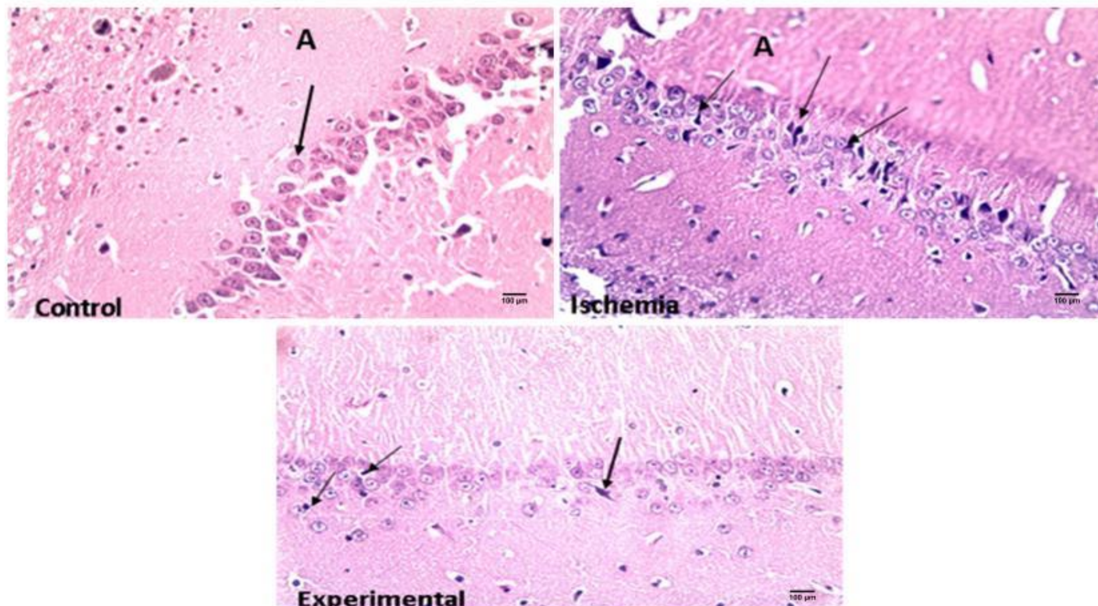

Figure 1. Representative H&E staining photomicrographs of hippocampal sections from Control, Ischemia/reperfusionand experimental rats. A: Alive neuron B: degenerative neuron. (400x).

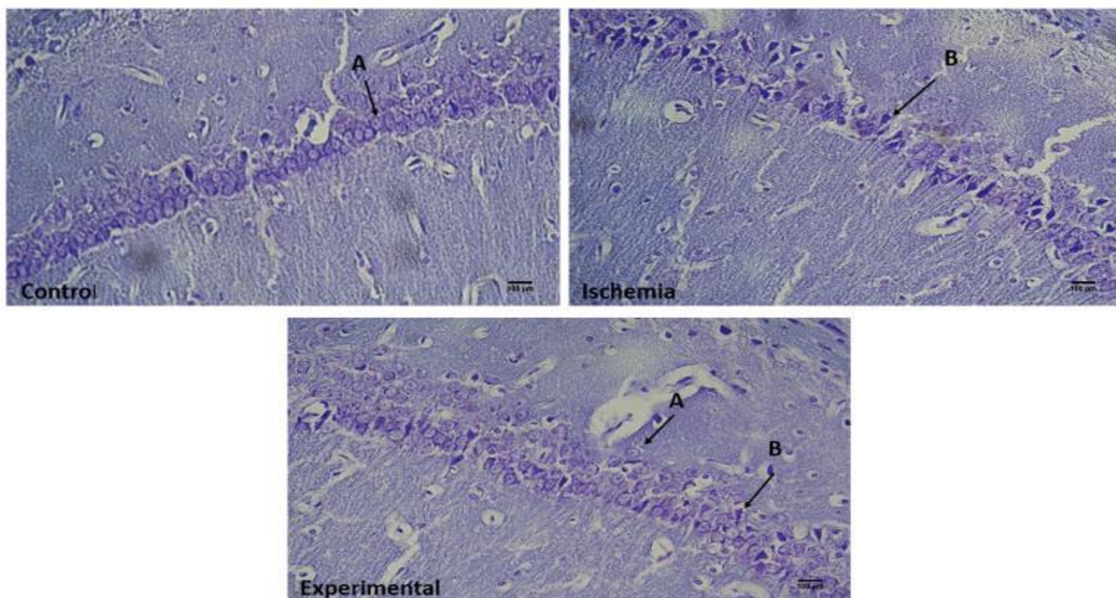

Figure 2. Representative photomicrographs of Nissl-stained hippocampus CA1 region in rat brain from Control, Ischemia/reperfusion, Experimental groups. A: Normal neuron cells B: Degenerated neuron cells. (400x).

Effect of Propofol on Apoptotic Neurodegeneration in the Hippocampus CA1 Area After I/R

Data that were collected from the TUNEL staining method based on DNA damage-induced apoptosis showed that the number of apoptotic cells in the CA1 region of the hippocampus increased after 20 minutes of ischemia/reperfusion; while the number of these cells showed a significant decrease after

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drug injection. There were no statistically significant differences between the control and experimental groups (p=0.339) (Figure 3) (Chart 2).

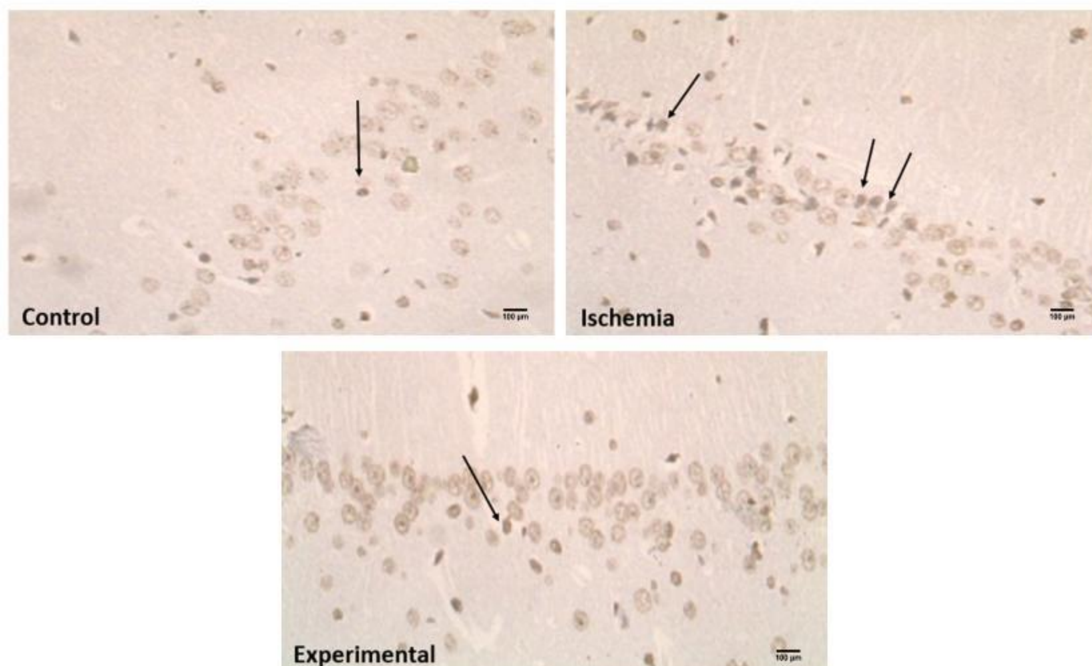

Figure 3. Effects of propofol on transient global I/R-induced apoptotic neurodegeneration. Representative photomicrographs of TUNEL staining and cell counting. (a) Representative images of the TUNEL-positive cell (arrows) were obtained from sections prepared from the animals in control, I/R and I/R+propofol groups. (400x).

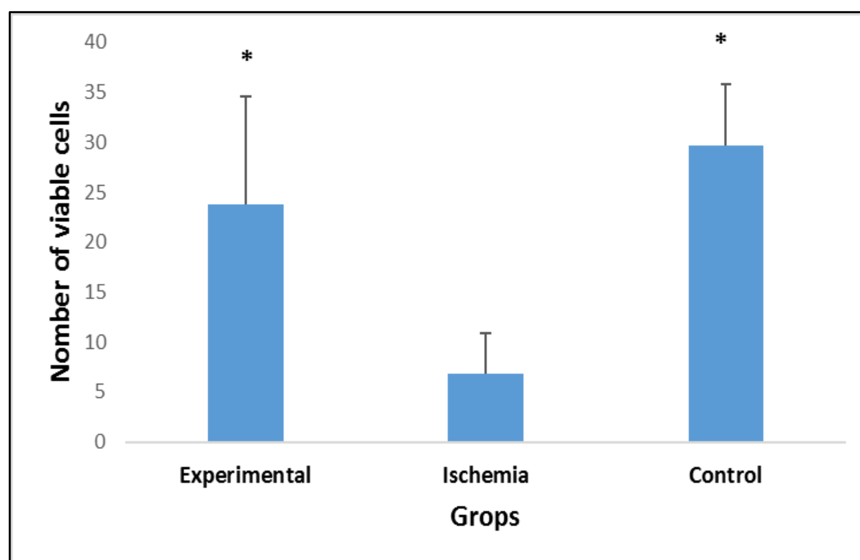

Chart 1. Comparison of the mean number of viable cells in the Control, Ischemia, and Experimental groups according to Nissl staining. The mean number of viable cells significantly decreased in the CA1 region of the hippocampus in the experimental group following propofol treatment in comparison with the ischemia group. However, there was no statistical difference between the number of viable cells in the control and experimental groups. Data are presented as means± SD. *P<0.05 vs. Ischemia group.

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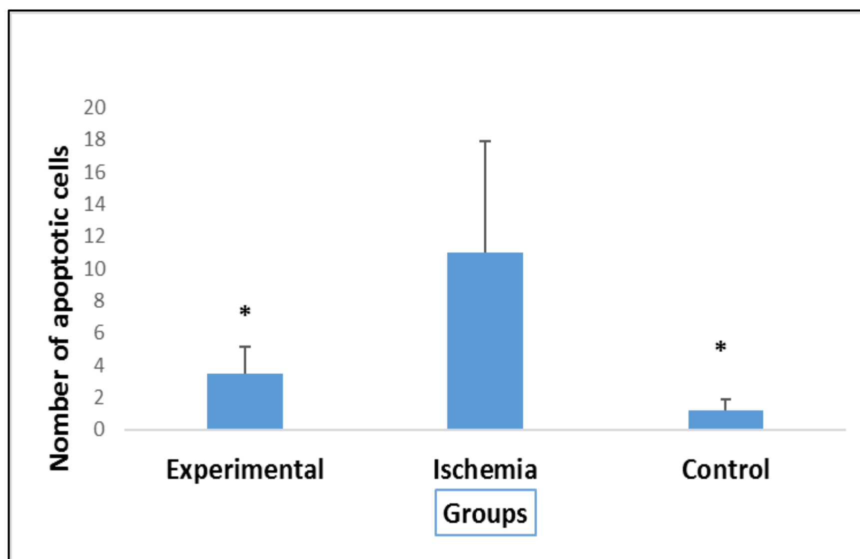

Chart 2. Comparison of the mean number of apoptotic cells in the Control, Ischemia, and Experimental groups according to TUNEL assay. The mean number of apoptotic cells significantly decreased in the CA1 region of hippocampus in the experimental group following propofol treatment in comparison with ischemia group. However, there was no statistical difference between the number of apoptotic cells in the control and experimental groups. Data are presented as means± SD. *P<0.05 vs. Ischemia group.

Discussion

The cerebral transient overall ischemia/reperfusion causes latent death of neurons in the central nervous system such as the CA1 region of the hippocampus (20,21). Using propofol drug as a neuroprotective agent has been recently considered. Propofol has antioxidant activities on one hand and on the other hand, serves as a neuroprotective against neuron toxicology following an increase in glutamate; reduces the number of apoptotic bodies and creates neuro productivity in this manner. This drug is recommended for treating lesions caused by intracerebral hemorrhage and neurologic disease in both operation rooms and ICU (23, 24).

Propofol at the lower dose and highest time interval between injections to ischemia start could provide hopeful results in a fast decrease in neurological damage to the patients.

Our findings in this study showed that transient ischemia-reperfusion in the brain caused latent death of pyramidal cells in the CA1 region of the hippocampus and those cells showed a significant decrease in the number of the mentioned cells after the apoptosis, which was caused by a series of pathophysiological events that were associated with an increase in glutamate concentration and subsequently stimulated the special glutamate receptors, especially NMDA, which increases intracell calcium and the cell's death (25).

Pyramidal cells in the CA1 region of the hippocampus are highly sensitive and show a rapid reaction to overall ischemia. (26). These pyramidal cells play a key role in learning and memory and their destruction might cause disorders in both abilities.

In the present research, it seems that a function similar to the one described above could cause the death of pyramidal cells in the CA1 region. Our studies showed that a 40mg/kg propofol injection 1 hour before ischemia saves the neurons against ischemic damage. Our findings also showed that propofol as a neuroprotective drug could cause a decrease in apoptotic bodies in the damaged hippocampus areas. These findings conform to the previous studies that indicate a decrease in the damage to neurons and apoptosis (27, 29).

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Considerable research has been carried out in connection with the protective capacity of this drug in different ischemic models in large white rats and other mammals (30-33). These studies show that propofol reveals its protective effects on the latent death of hippocampus neurons through inhibiting Aquaporin 4 (AQP4). (34)
Zheng (35) reported that the intraperitoneal injection of propofol 0.1mg/kg/min 30 minutes before ischemia has protective effects that comply with our findings on this subject.
Zhang et al (36) conducted tests on animals and performed clinical studies and reported that propofol as a pretreatment improves the performance of neurons after cardiovascular restitution significantly. However, studies on the protective mechanism of propofol-induced general anesthesia on the brain have revealed that the drug serves as a source and recommends reasonable doses of the drug, as well as being highly effective in the discovery and development of brain-protective drugs. It was recognized as a reference and protects the brain from damage caused by anesthesia and cardiac-pulmonary resuscitation (CPR). The result of this research also showed propofol protects the brain against damage caused by hypoxia (37).
A mechanism that enables propofol to prevent brain ischemic damage is not known thoroughly; however, this mechanism might be more associated with lowering the number of active proteins in the apoptosis path. In the present study, propofol caused an increase in pyramidal cells and a reduction in apoptotic cells significantly which could lead to lowering performance disorders. These findings conform to the opinion of individuals who showed the mentioned drugs cause a reduction in performance damage following acute ischemia in the brain (38, 39).
Propofol has been studied in various doses and injection times on lab animals; however, in this research, the histology studies showed that a 40 mg/kg dose of propofol by injecting 1 hour before ischemia shows protective effects on pyramidal cells in the CA1 region of the hippocampus and if injected 1 hour before ischemia, the damages caused by hypoxic conditions will not appear. Therefore, it seems that due to having protective properties, propofol could be considered as an alternative treatment for brain ischemic and brain vascular diseases. Therefore, more studies are required for confirming this hypothesis (40).

Conclusion

Results shown in this research study reveal propofol treatment before ischemia reduces neuronal death in the hippocampus fowling ischemia /reperfusion injury. It appears to protect the brain against the risk of brain ischemia, large-scale hemorrhage, and hypoxia. Therefore, propofol could be used as a neuroprotective drug in cardiovascular surgeries.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

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