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The Role of Captopril on Pentylenetetrazole-Induced Seizures in Rats

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ABSTRACT:
Purpose: In recent years, experimental studies have shown that some angiotensin-converting enzyme (ACE) inhibitors with antihypertensive effects have anticonvulsant effects against seizures. After the seizure, the process of inflammation begins in the brain and body, with the production of free radicals. Renin has some effects on the central nervous system of the angiotensin system. The current study's objective was to examine how captopril, an ACE inhibitor, affects neuroinflammation in the hippocampus and cortical areas in acute epileptic seizures and post-seizures induced by pentylenetetrazole (PTZ).
Material and Methods: Eighteen Wistar Albino rats were separated into three groups: control, PTZ (serum physiologic 1 ml/kg as solvent), and captopril (50 mg/kg/day for 7days). To produce epileptic seizures, PTZ (45 mg/kg) was delivered thirty minutes after the drug was administered. The animals were monitored during 30 minutes to record seizures scoring scale and the onset time of first myoclonic jerk (FMJ). In the brain tissue, the activity of TNF- α, IL-1 β, NF-kB, COX-1, and COX-2 were examined.
Results: Captopril increased FMJ onset time and reduced seizure stage as compared to the PTZ group ($p<0.05$). Additionally, captopril treatment dramatically decreased the expression of TNF- α, IL-1 β, COX-2 and NF-kB in the hippocampus and cortex, while, it enhanced the level of COX-1.
Conclusion: Captopril improves epileptic seizure parameters and attenuated its effect on neuroinflammatory damage caused by PTZ. In epileptic patients with hypertension, captopril may be a supportive drug.
Keywords: *Captopril, Epilepsy, Pentylenetetrazole, Neuroinflammation, Rat*

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INTRODUCTION

Epilepsy is a chronic brain disease characterized by excessive synchronous and spontaneous seizures A seizure is a short brain malfunction caused by abnormal and excessive cortical neuron firing (Karabulut and Taşkıran, 2021). Patients suffering from epilepsy frequently experience spontaneous seizures, which are characterized by synchronous and excessive cortical neuron discharges (Chen et al., 2018). Over the last two decades, various researches have been handled to uncover the mechanisms underlying causes of the epileptogenesis process. It has been found that apoptosis, inflammation, and oxidative stress play a significant role in the mechanisms underlying epilepsy (Vezzani et al., 2011). The goal of developing experimental epilepsy models is to better understand and reveal the underlying mechanisms that cause epileptic seizures. To generate experimental seizures, the pharmacological drug pentylenetetrazole is a selectively inhibits the GABAA receptor. PTZ damages neuronal membranes, closes potassium channels, opens calcium channels, activates intracellular calcium ion storage, and inhibits opening of Cl^- channels (Kandratavicius et al., 2014). The conversion of circulating angiotensin I to

angiotensin II, a strong vasoconstrictor and one of the key actors in remodeling processes, is carried out by angiotensin-converting enzyme (ACE) (Johnston, 1990). As an ACE inhibitor, captopril is a routinely used as antihypertensive drug that selectively inhibits ACE. Furthermore, it has been hypothesized that ACE inhibitors, such as captopril, improve human learning processes (Braszko et al., 2003). Neuroinflammation is a reaction of pro-inflammatory or anti-inflammatory mediators (Taşkıran and Taştemur, 2020) triggered by microglia, astrocytes, activation of the blood-brain barrier endothelial cells, infiltration of plasma proteins and immune cells. It is widely accepted that pathways in the neuroinflammation process cause the development of some brain diseases (Glass et al., 2010). Increasing evidence suggests an association between inflammation and epilepsy in line with the outcomes of both epileptogenesis and epileptic seizures (Vezzani et al., 2011). Reactive oxygen species (ROS) buildup has been linked to the development and progression of inflammatory diseases by either oxidizing biomolecules or altering the structural makeup of proteins and genes. The activation of transcription factors and pro-inflammatory genes called ROS results in inflammation. Captopril has been shown to scavenge free radicals in several tissues (Karimani et al., 2018; Mowry and Biancardi, 2019). Captopril has also been demonstrated to boost enzymatic and nonenzymatic defenses in a variety of tissues (de Cavanagh et al., 2000). Captopril has been demonstrated to reduce oxidative/nitrosative stress in the brain, hence preventing neuronal damage (Abbassi et al., 2016). However, ameliorative effects of captopril on neuroinflammation in PTZ-induced acut epileptic seizures have yet to be study. Therefore the purpose of currrent research was to examine the protective effects of captopril on PTZ-induced acut epileptic seizures in rats.

MATERIAL and METHODS

Animals

The research was carried out in the Laboratory of Experimental Animals of the Faculty of Medicine of Sivas Cumhuriyet University. Eighteen male Wistar Albino rats (230–250 g) used in the study were procured from the Experimental Animals Application and Research Center of the Republic University of Sivas. All rats were housed on a 12-h light/dark cycle and standard ambient conditions at 21-23°C. Rats were fed with water and standard food. Prior to the experiment, the rats were acclimated to laboratory conditions. All work was carried out from 09:00 to 16:00. The light and sound levels of the experimental environment were kept constant. All experimental programs have been approved by the Sivas Cumhuriyet University Animal Experiments Local Ethics Committee (2020/326).

Chemicals

Pentylenetetrazole and captopril (Sigma-Aldrich Co., St. Louis, MO, USA) were dissolved in physiological saline and prepared freshly on the day of the experiment.

Experimental Design

The rats were randomly classified control, PTZ, and captopril (n=6). 1 ml/kg physiological saline was given to the control group and PTZ group, and 50 mg/kg captopril was given to the captopril group intraperitoneally (i.p) for 7 days. Excluding the control group, PTZ and captopril groups were given 45 mg/kg PTZ i.p to induce seizures.The captopril and PTZ doses were determined based on the results of a prior study (Abareshi et al., 2016; Taskıran et al., 2021). The intensity of the seizure was determined using Racine's Convulsion Scale (RCS), which has the following seizure stages: 0. No seizure response, 1. No motion, eye closure, ear twitching, whisker trembling, sniffing motion; 2. Nodding added to more severe fascial clonus; 3. Clonus of one of the anterior extremities, myoclonic jerk no rearing-up; 4. Clonus of bilateral anterior extremity, rearing-up; 5. Falling on one side due to rearing-up and generalized clonic seizure; 6. Lethal seizure (Ciltas¸ et al., 2022). The rats were monitored during 30 minutes after receiving PTZ to determine the onset time of first myoclonic jerk (FMJ)and to score their behavior according to the RCS. The animals were decapitated 24 h after receiving PTZ injection. Animal brain tissue was taken for biochemical analysis, and the cortex and hippocampus were separated. Figure 1 illustrates the detailed experimental design.

Biochemical Assays

Nuclear Factor kappa B (NF-kB), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) levels of brain supernatants were measured with Rat ELISA kits (BT LAB, Shanghai, China). After cervical dislocation was applied to the animals, their brain tissue was removed under cold chain conditions. The cortex and hippocampus were separated. Brain tissues taken into the ependorf under cold chain conditions were weighed and homogenized with the help of a manual blade homogenizer in a 1:9 phosphate buffer solution (PBS, pH: 7,4). The obtained homogenates were placed in 15 ml falcon tubes and centrifuged at 4000 rpm for 10 minutes. Levels of NF-kB, TNF-α, IL-1β, COX-1 and COX-2 from the obtained brain supernatates were measured using specific rat ELISA commercial kits. According to the manufacturer's instructions. The standard and tissue samples in the kit were loaded and incubated at 37 °C for 60 min. Then the washing process was done and the dyeing solutions were added and left to incubate again for 15 min at 37 °C. The stop solution was added and scanned at a wavelength of 450 nm. A linear graph was created according to the absorbance of the standards. The values of the samples were calculated with the help of the equation obtained with this graph. Total protein determination was performed in the samples to standardize the results obtained. For this purpose, the Bradford protein assay kit (Biosciences, Beltsville, ABD) was used (Ernst and Zor, 2010). Parameter levels were presented as pg/g and ng/g tissue.

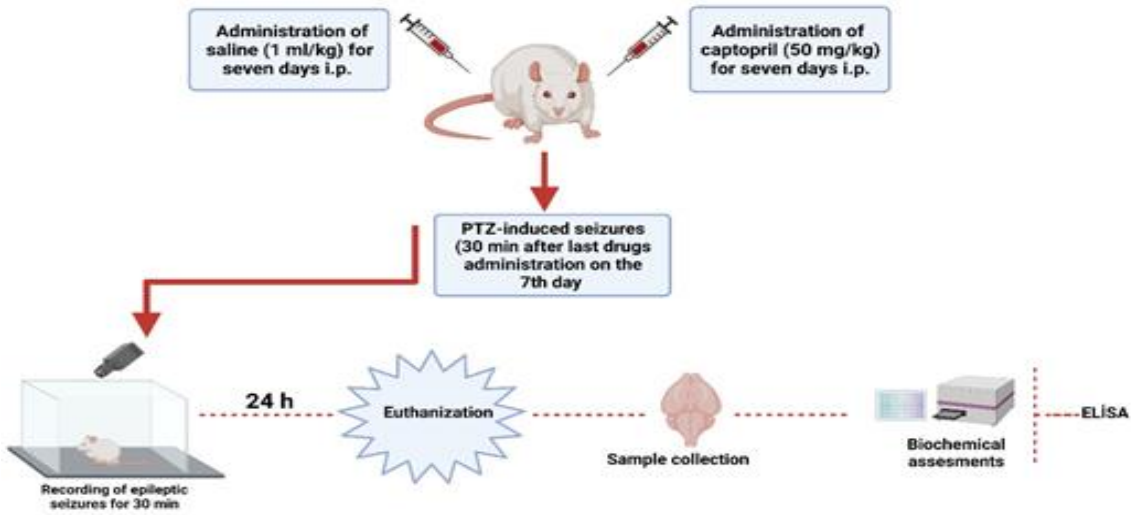

Figure 1. The experimental protocol is presented as a diagram (formed by BioRender).

Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Since the data showed a normal distribution, they were evaluated by Shapiro Wilk's test and analysis of variance (One-way ANOVA) was used in the comparison between the groups, followed by Tukey test (post-hoc test). P values ($p<0.05$) were regarded as significant. Statistical analyses were performed using GraphPad Prism software version 7 (GraphPad Software, San Diego, CA, USA).

RESULTS

Seizure Stage and First Myoclonic Jerk Status

Captopril showed significantly decrease the seizure stage compared to the PTZ group, while significantly increasing the FMJ (Table 1).

Effect of Captopril on Proinflammatory Cytokines in Acute PTZ Models

As shown in Figures 2A-B-C-D treating the rat with 50 mg/kg doses of captopril significantly reduced both hippocampus and cortex TNF-α and IL-1 β expression compared to the PTZ group rats.

Table 1: Effect of captopril on Seizure Stage and FMJ in PTZ-induced seizures in rat

Groups	Seizure stage	Onset time of FMJ (sec)
Control	None	None
Saline +PTZ	5,23±0,16	35,09±6,23
Captopril + PTZ	3,66±0,20*	53,16±10,73*

Data are reported as mean SEM; *p < 0.05 in compared to the PTZ group

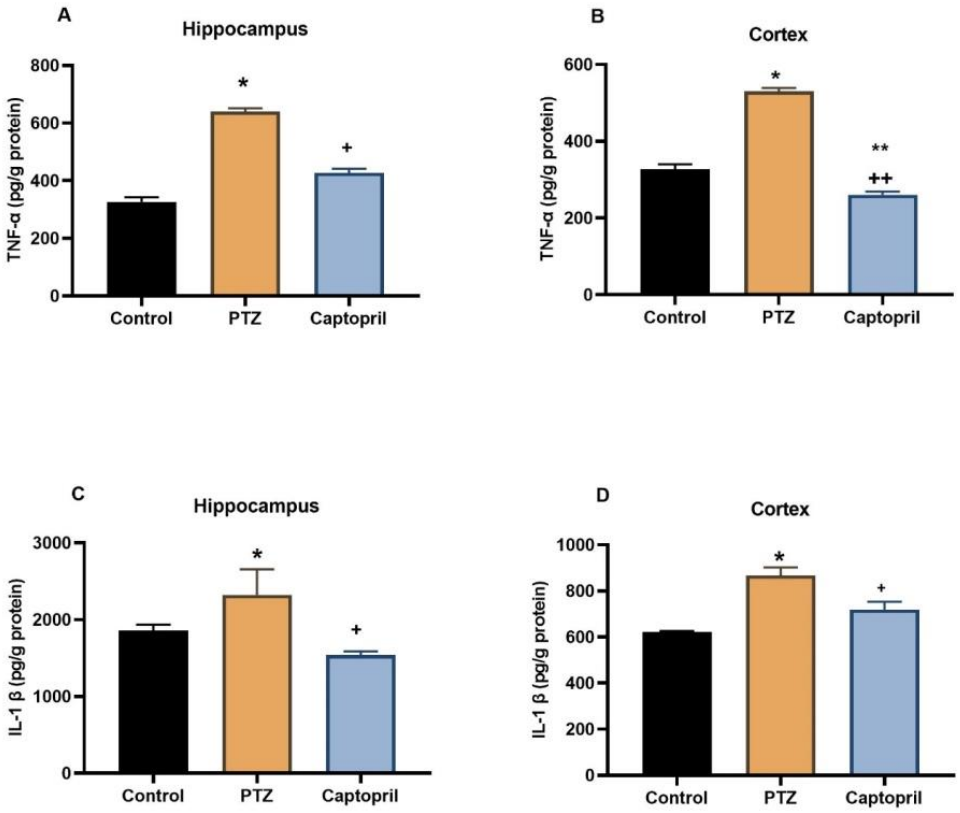

Figure 2. Effects of captopril on proinflammatory cytokines levels in the hippocampus (**A, C**) and cortex (**B, D)** after PTZ-induced seizure in rats (*n*=6). Values are presented as mean ± SEM; *p<0.05 compared to cntrl; $^{+}$p<0.05 compared to PTZ.

Effect of Captopril on inflammatory enzyme in Acute PTZ Models

Inflammatory enzyme levels in the hippocampal and cortex are displayed in Figure 3. There was a significant decrease in the levels of COX-1 in the hippocampal and cortex of the PTZ group in comparison to the control group (Figure 3A, 3B). However, COX-1 levels significantly enhanced in hippocampal and cortex of the captopril group as compared to the PTZ group (Figure 3A, 3B). COX-2 levels of the PTZ group significantly enhanced as compared to the control group in hippocampal and cortex (Figure 3C, 3D). Moreover, COX-2 levels of the captopril group were found to be lower in both the cortex and hippocampal than in the PTZ group (Figure 3C, 3D).

Effect of Captopril on NF-kB in Acute PTZ Models

Measurement of NF-kB levels in brain tissues revealed that animals treated with PTZ had higher level of this enzyme compared to the control group (Figure 4A, 4B). In the Captopril group, NF-kB levels significantly decreased in both the hippocampal and cortex in compare to the control and PTZ group (Figure 4A, 4B).

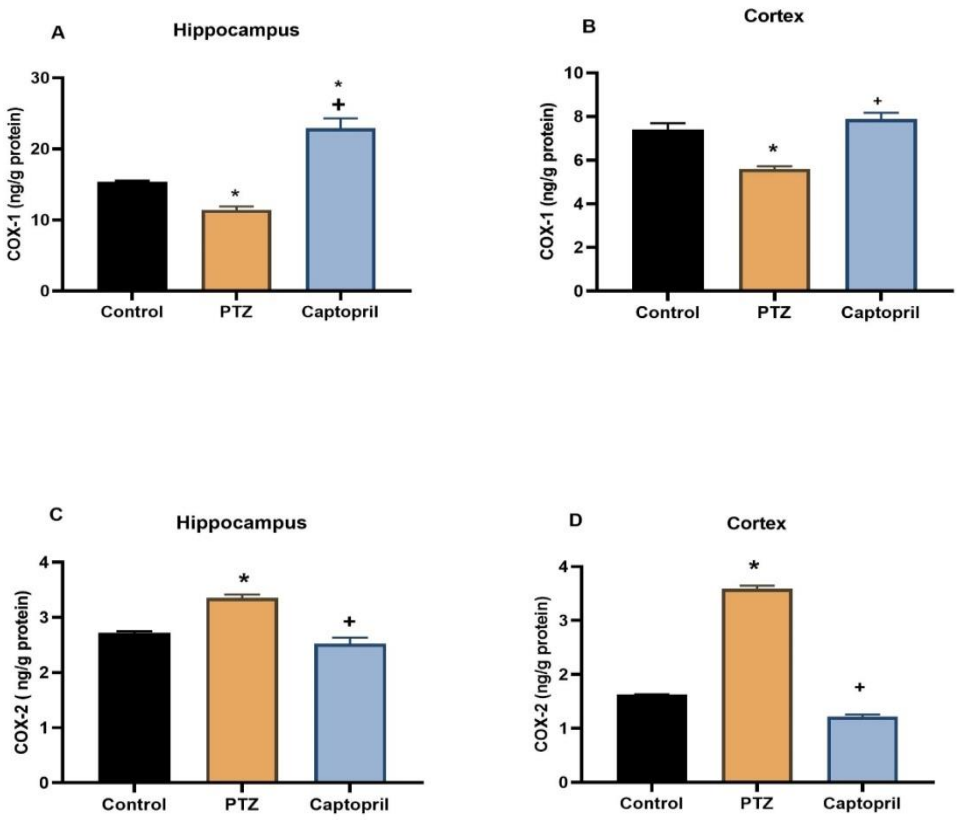

Figure 3. Effects of captopril on inflammatory enzymes levels in the hippocampus (**A, C**) and cortex (**B, D)** after PTZ-induced seizure in rats (*n*=6). Values are presented as mean ± SEM; *p<0.05 compared to ctrl; +p<0.05 and compared to PTZ.

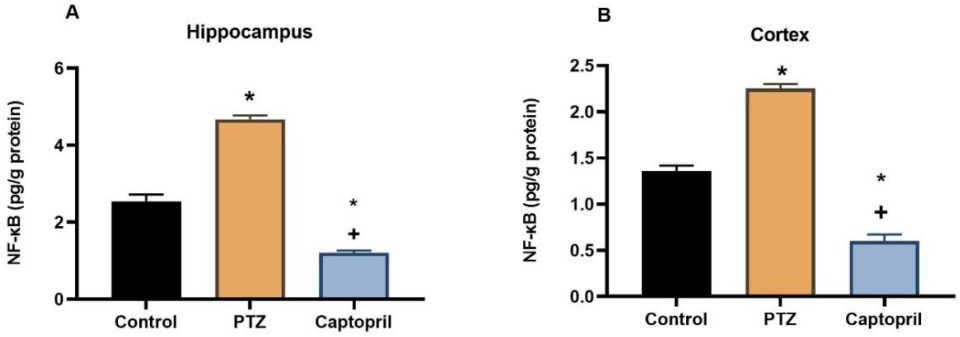

Figure 4. Effects of captopril on NF-kB levels in the hippocampus (**A**) and cortex (**B**) after PTZ-induced seizure in rats (*n*=6). Values are presented as mean ± SEM *p<0.05 compared to ctrl; +p<0.05 compared to PTZ.

DISCUSSION

The findings of the study revealed that captopril reduced the levels of cortex IL-1 β and TNF-α, COX-2 and NF-kB in a PTZ-induced epilepsy model, while enhanced the COX-1 levels in both the hippocampal and cortex. There are signs of neuroinflammation under various diseases of the central nervous system. It has been proven in studies that neuroinflammation triggers the formation of epilepsy. Clinical and experimental studies have shown that neuroinflammation increases the frequency and severity of seizures (Vezzani et al., 2011). In the process of persistence of inflammation, IL-6, IL-1β, TNF-α are secreted from microglial cells

and astrocytes and cause a detrimental effect (Kruger, 1992). Additionally, experimental studies have shown that NF-kB is associated with various diseases (Dingledine et al., 2014), myocardial infarction (Campolo et al., 2017), atherosclerosis, and experimental autoimmune encephalomyelitis (Meili-Butz et al., 2008). In the hippocampus, the brain region most affected in the epileptogenesis process according to the studies, the changes such as hippocampal sclerosis, neuronal cell death, short- and long-term synaptic plasticity have occurred (Singh et al., 2018; Vezzani et al., 2013). Activity of COX-2, one of the inflammatory enzymes, has been found to increase in humans and experimental animals after seizures of epilepsy (Pitkanen et al., 2015). It has been shown in experimental studies that neuronal over-induction of COX-2 simplifies kainate-triggered convulsions and enhances seizure-related mortality in mice (Desjardins et al., 2003). The threshold for seizures enhanced in COX-2 knockout mice and the severity of seizures decreased suggesting role of COX-2 in the pathogenesis of epilepsy (Takemiya et al., 2003). In another study, nimesulide, a COX-2 inhibitor, has been shown to provide protect against PTZ-induced toxicity in mice (Dhir et al., 2007). COX-inhibitors have been demonstrated to be neuroprotective after brain damage in experimental studies of localized ischemia in rats, concussive brain injury in cats, preconcussion-induced neurotrauma in rats, and clinical neurosurgery (Cernak et al., 2011). In our study, captopril, an ACE inhibitor, reduced hippocampal and cortex COX-2 levels while causing a significant enhance in COX-1 levels compared to PTZ group.

Several studies have recently revealed that inflammation and oxidative stress play a key role in epilepsy pathophysiology. In many studies, angiotensin-converting enzyme (ACE) inhibitors were shown to have antioxidant activities (Vahidirad et al., 2018). Captopril's ability to prevent PTZ-induced seizures in the current study may be related, at least in part, to the antioxidant defense system being enhanced and oxidative stress and inflammation in the brain being reduced (Gurer et al., 1999; Ciobica et al., 2011). As a result of various studies, it has been suggested that captopril therapy may protect neurons from neuroinflammation caused by the gathering of β amyloid plaque in the brain (de Cavanagh et al., 2000). Another study reported its protective effects on dopaminergic neurons in the nigrostriatal pathway in Parkinson-like rats (Sonsalla et al., 2013). According to past research, our data showed that captopril decreased cortex TNF-α and IL-1 β levels, but also reduced both hippocampus and cortex COX-2 and NF-kB levels. Similarly, captopril has been reported to reduce oxidative stress and inflammation levels in tissues and significantly increase the epileptic seizure threshold (Abraham et al., 2012). Taştemur et al. (2020) showed that captopril prevented dark neuron formation in the hippocampal tissue after PTZ, relieving brain oxidative stress. In addition, it has been shown to protect hippocampal neurons by increasing GABA influx to neurons. In a study, captopril was shown to positively affect memory function by reducing oxidative stress in the hippocampus (Bild et al., 2012). Asgharzadeh et al. (2019) reported that captopril (50 and 100 mg/kg) reduced malondialdehyde in PTZ-induced hippocampus and cortex tissues in mice, and enhanced the activity of superoxide dismutase, and catalase. In this study, captopril at 50 mg/kg i.p. dose reduced inflammation markers, and COX-2 levels compared to the PTZ group, while enhanced COX-1 level in comparison to the PTZ group.

A study carried out on diabetic patients revealed that captopril prevented oxidative stress by reducing level of lipid peroxidation (Ha and Kim, 1992). Captopril has also been shown to protect hepatocytes against oxidative stress induced by paraquat (Pourahmad et al., 2011; Mansoor et al., 2018). Abareshi et al. (2016) showed that captopril reduced levels of IL-6, TNF-α, malondialdehyde (MDA), and nitric oxide (NO) in rats, improving learning and memory deficits. The changes in the expression of inflammation markers in different parts of the brain have been demonstrated in induced seizure models with PTZ (Vezzani et al., 1999), kainate, and lithium-pilocarpine, in epilepsy types such as the WAG/RIJ rat and the electroshock model. Inflammation markers levels enhanced with the damage caused after this seizure (De Luca et al., 2004). Consistent with other studies, a significant

increase was observed in the hippocampus and cortex IL-1β, TNF-α levels of rats given PTZ in our study.

CONCLUSION

As a result, captopril treatment, known as an ACE inhibitor, may have a protective effect on neurons by reducing IL-1β, TNF-α, NF-kB, COX-2 levels in different brain tissues (hippocampus, cortex) of rats.

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Conflict of Interest

The authors declare no conflicts of interest.

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