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Original Investigation

The Protective Effects of Propofol and Citicoline Combination in Experimental Head Injury in Rats

Propofol ve Sitikolin Kombinasyonunun Deneysel Kafa Travması Üzerindeki Koruyucu Etkileri

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ABSTRACT

AIM: Lipid peroxidation (LP) is an important factor in tissue damage following head injury. Reactive oxygen radicals which damage cellular components play an important role in ischemic or hypoxic tissue. They initiate the lipid peroxidation process after head trauma. However, antioxidant agents may protect brain tissue against oxidative damage

MATERIAL and METHODS: 39 male Swiss Albino rats (200-250 g) were used in this experimental study. These animals were divided into 3 groups: 1) control group, 2) propofol group (100 mg/kg) and, 3) citicoline (250 mg/kg) and propofol (100 mg/kg) combination group. Oxidant effect in brain tissue content was assessed by measuring the Malonyldialdehyde (MDA), Superoxide Dismutase (SOD) and Gluthatione Peroxidase (GPx) activities.

RESULTS: There was no statistically meaningful difference among the groups regarding GPx levels. MDA levels were significantly lower in the citicoline and combination group than those of the control group. As for the levels of SOD, there was an increase both in the propofol and combination groups.

CONCLUSION: A therapeutic benefit of the propofol and citicolin combination in head trauma has not been previously demonstrated. We examined the possible potential protective effect of propofol and citicolin against oxidative damage in experimental head trauma in the present study.

KEYWORDS: Antioxidant, Citicoline, Head injury, Lipid peroxidation, Propofol

ÖZ

AMAÇ: Lipid peroksidasyonu kafa travmasında hasar oluşturan önemli bir faktördür. Hücresel yapılara zarar veren reaktif oksijen radikalleri iskemik ve hipoksik dokuda önemli rol oynar. Kafa travması sonrası lipid peroksidasyon sürecini başlatırlar. Bununla birlikte antioksidan ajanlar beyni oksidatif hasardan korurlar.

YÖNTEM ve GEREÇ: Bu deneysel çalışmada, 39 erkek Swiss Albino tipi rat (200-250 g) kullanıldı. Bu hayvanlar 3 gruba ayrıldı: 1) kontrol grubu, 2) propofol grubu (100 mg/kg) ve 3) Sitikolin (250 mg/kg) ve propofol (100 mg/kg) kombinasyon grubu. Beyin dokusundaki antioksidan etki, Malonildialdehit (MDA), Süperoksit Dismutaz (SOD) and Glutatyon Peroksidaz (GPx) aktiviteleri ölçülerek değerlendirildi..

BULGULAR: GPx seviyelerinde gruplar arasında istatistiksel olarak anlamlı bir fark yoktu. MDA seviyeleri sitikolin ve propofol kombinasyon grubunda, kontrol grubuna göre anlamlı bir şekilde düşüktü. SOD seviyeleri ise, propofol ve kombinasyon grubunda yüksekti.

SONUÇ: Propofol ve sitikolin kombinasyon grubunun kafa travmasındaki tedavi edici etkileri şu ana kadar gösterilemedi. Bu çalışmada, propofol ve sitikolin kombinasyonunun, deneysel kafa travmasındaki oksidatif hasara karşı, potansiyel koruyucu etkileri olduğunu gösterdik.

ANAHTAR SÖZCÜKLER: Antioksidan, Sitikolin, Kafa travması, Lipid peroksidasyonu, Propofol

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INTRODUCTION

The morbidity and mortality after traumatic brain injury depends on primary damage, such as contusion, laceration, diffuse axonal injury and intracerebral haematoma, and secondary damage that occurs at the moment of injury due to raised intracranial pressure, swelling and hypoxia/ ischemia (17, 24, 30). Preventing and reducing secondary brain damage after head trauma have been the focus of recent research on central nervous system (CNS) trauma. It has been suggested that one of the most important factors precipitating posttraumatic degeneration in the brain is free oxygen radical-induced lipid peroxidation (4, 5)

Propofol (2, 6-diisopropylphenol) is a potent intravenous hypnotic agent which is widely used for the induction and maintenance of anesthesia and for sedation in the intensive care unit (8).

Propofol decreases cerebral oxygen consumption, reduces intracranial pressure and has potent anti-convulsant properties. In addition, propofol contains a phenolic hydroxyl group that donates electrons to free radicals and therefore may complement endogenous antioxidants (25). The antioxidant characteristics of propofol may provide protection against ischemia of the central nervous system (7, 20, 27). Propofol may restore excitatory amino acid transport after peroxide-induced oxidative stress (31)

Citicoline is classified as an acetylcholine precursor. It is a pyrimidine 5-nucleotide prodrug that dissociates into choline and cytidine (6). Citicoline is a complex organic molecule that functions as an intermediate in the biosynthesis of cell membrane phospholipids.

Citicoline appears to reverse neuronal membrane pathology that occurs in cerebral ischemia. Depletion of ATP causes cytidine 5′-monophosphate to accumulate within the membrane, which in turn increases bioconversion of phosphatidylcholine to diacylglycerol and free fatty acids. These breakdown products can become toxic to the membrane due to excess levels of free radicals, lipid peroxides, and arachidonic acid and its metabolites such as leukotrienes (13).

The inhibition of lipid peroxidation by many agents, such as antioxidants or free radical scavengers, may be useful in the treatment of head injury. The purpose of this study was to investigate the effect of propofol, and the propofol-citicoline combination on LP after head trauma.

MATERIAL and METHODS

The experimental procedure was approved by the Animal Experimentation Committee of Erciyes University at Kayseri, Turkey. Thirty nine adult, male, Swiss Albino rats, each weighing between 250-300 g were used in this study. Moderate diffuse head injury in rats was performed as described by Marmarou e t al. (23). A simple head injury device was designed to induce blunt trauma to the protected skull of the rat. A cylindrical column of brass weighing 450 g was allowed to fall through a 1m Plexiglas tube onto a small rounded stainless-steel disc fixed to the central portion of the skull vault of the rat. The animals were anesthetized by a mixture of ketamine (60 mg/kg) and diazepam (6 mg/kg) injected i.p. Rats breathed spontaneously throughout the experiment. A midline scalp incision was performed followed by periosteal elevation to expose the central area of the skull vault between the coronal and lambdoid sutures. A stainless steel disc 1 cm in diameter was firmly fixed by dental acrylic to this central portion of the skull vault. When the trauma device was ready, the rat was placed in the prone position on a foam bed with the disc centered immediately under the lower end of the Plexiglass tube of the trauma device. The weight was allowed to drop freely from the 1 m height through the Plexiglass tube onto the disc. The cranial vault was inspected for the presence of any fracture. The scalp was sutured. Rats that died on impact and those with skull fractures were excluded from the study.

The rats were divided randomly and blindly to one of three groups (thirteen animals in each): (1) the control group rats received equal volumes of saline solution; (2) the propofol group rats received injections of 100 mg/kg propofol (3) the citicoline plus propofol group rats received injections of 250 mg/kg citicoline and 100 mg/kg propofol intraperitoneally at 10 minute after trauma.

After 24 h, each rat was killed with intracardiac KCl. The brains were rapidly removed. The left and right hemispheres were separated and weighed. The left hemisphere was immersed in liquid nitrogen for freezing fixation of brain to quantitatively assess MDA as a product of LP. Using this method, we were able to standardize the sampling procedure so that equal amounts were obtained from each animal. After washing with 0.9% NaCl, tissue homogenates were

prepared in a ratio of 1 g of wet tissue to 9 ml of 1.15% KCl by using Teflon homogenizer. MDA was measured by the thiobarbituric acid (TBA) test in order to calculate the levels of LP by means of a method described by Ohkawa et al. (26). Malondialdehyd-bis-(dimethylacetal) (Merck) was used as a standard. The level of LP is expressed in terms of nmol MDA/g wet tissue.

Statistical analysis: ANOVA variant analysis was used for statistical analysis. All results were presented as mean ± standard deviation. A p value less than 0.05 was considered statistically significant.

RESULTS

Physiological parameters are shown in (Table I). There was no significant difference in HR, MABP, Hct, pH, pCO2 or pO2 values before and after head trauma.

Three rats that died on impact and two rats with skull fractures were excluded from the study.

As a result of the weight drop, both hemispheres were affected symmetrically in all animals. The contused area and subarachnoid hemorrhage were easily recognized and well defined.

MDA levels were significantly lower in the propofol and citicoline combination group than the control and the propofol groups ($p<0.05$) (Table II) (Figure 1). As for the level of SOD, there was an increase both in the combination and propofol groups ($p<0.05$) (Table III) (Figure 2).

Table II: MDA levels were significantly lower in the propofol and citicolin combination group* than control and propofol groups ($p<0.05$)

Groups	n	MDA nmol MDA/g wet tissue
Control	13	207.41 ± 30.72
Propofol	13	163.25 ± 23.60
Propofol + Citicoline	13	32.02 ± 8.76*

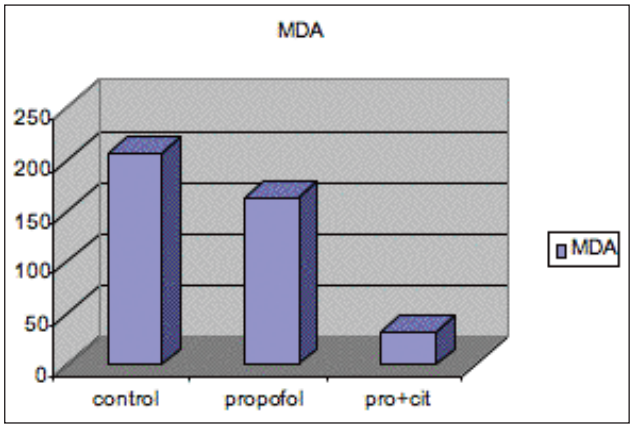

Figure 1: *MDA levels were significantly lower in propofol and citicoline combination group ($p<0.05$).*

There was no statistically meaningful difference among the groups for GPx levels ($p>0.05$) (Table IV) (Figure 3).

Table I: Physiological parameters in the control, propofol and citicoline plus propofol groups.

Groups	*n*	*HR* (beats/min)	*MABP* (mmHg)	*Hct %*	*pH*	*pCO_2* (mmHg)	*pO_2* (mmHg)
Control	*13*						
Before trauma		*309 ± 10*	*93 ± 5*	*37.5 ± 0.6*	*7.42 ± 0.04*	*36 ± 4*	*206 ± 20*
After trauma 1st h		*320 ± 12*	*88 ± 6*	*37.8 ± 0.4*	*7.41 ± 0.03*	*42 ± 3*	*196 ± 16*
After trauma 24th h		*315 ± 8*	*92 ± 8*	*36.9 ± 0.7*	*7.41 ± 0.02*	*40 ± 6*	*204 ± 18*
Propofol	*13*						
Before trauma		*305 ±12*	*96 ± 5*	*36.8 ± 0.6*	*7.41 ± 0.03*	*38 ± 5*	*212 ± 26*
After trauma 1st h		*315 ± 8*	*88 ± 6*	*37.4 ± 0.8*	*7.40 ± 0.03*	*42 ± 6*	*202 ± 22*
After trauma 24th h		*296 ±12*	*92 ± 4*	*37.5 ± 0.6*	*7.42 ± 0.04*	*40 ± 4*	*214 ± 24*
Citicoline+propofol	*13*						
Before trauma		*296 ±16*	*90 ± 5*	*37.5 ± 0.6*	*7.39 ± 0.03*	*38 ± 5*	*208 ± 20*
After trauma 1st h		*316 ± 14*	*85 ± 4*	*37.8 ± 0.4*	*7.41 ± 0.03*	*40 ± 3*	*192 ± 12*
After trauma 24th h		*305 ± 8*	*90 ± 8*	*36.8 ± 0.7*	*7.40 ± 0.03*	*35 ± 4*	*214 ± 15*

Data are mean ± standard deviation of the mean. **Hct:** Hematocrit, **HR:** Heart rate, **MABP:** Mean arterial blood pressure. All physiological parameters of the animals were normal and not significantly different from each other during the experimental course.

Table III: SOD levels were significantly higher in both combination* and propofol* groups (p<0.05)

Groups	n	SOD U/g prot
Control	13	21.5 ± 5.7
Propofol	13	37.6 ± 17.4*
Propofol + Citicoline	13	35.8 ± 11.03*

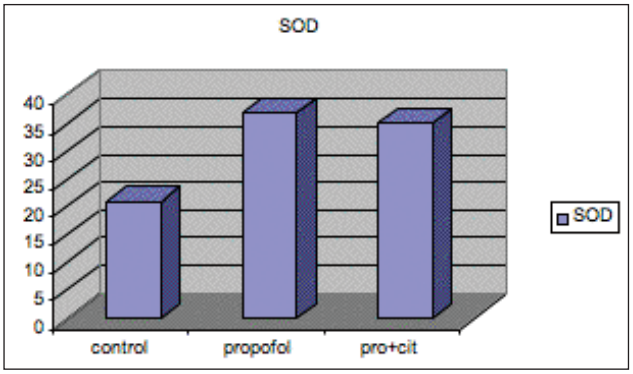

Figure 2: SOD levels were significantly higher in both combination and propofol groups (p<0.05).

Table IV: There was no statistically meaningful difference among the groups for GPx levels (p>0.05)

Groups	n	GPx U/g prot
Control	13	4.26 ± 1.2
Propofol	13	4.81 ± 2.2
Propofol + Citicoline	13	4.72 ± 1.6

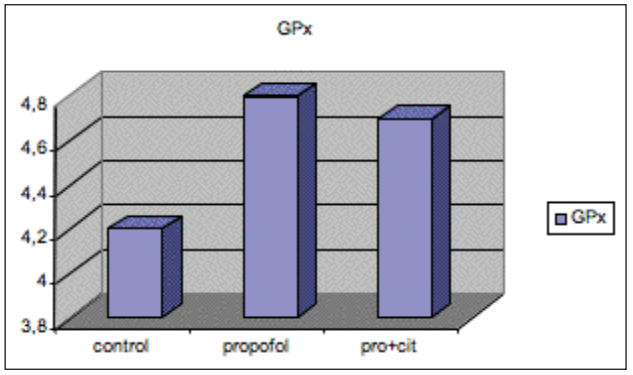

Figure 3: In the levels of GPx, there was no statistically meaningful difference among the groups (p>0.05).

DISCUSSION

Cerebral damage after CNS trauma can be categorized as primary neuronal damage from the trauma itself or secondary damage caused by a cascade of events. Traumatic injury damages the brain in numerous ways, including cell death due to edema, disruption of the blood-brain barrier, ischemia, and shear stress. Three underlying pathologies are thought to be at work at the site of brain injury: (1) breakdown of phospholipids in the cell membrane, resulting in decreased phosphatidylcholine content; (2) release of free fatty acids from the degraded membrane, which causes local edema due to accumulation of inflammatory arachidonic acid metabolites such as prostaglandins and leukotrienes; and (3) decreased release of acetylcholine, resulting in impaired cholinergic nerve transmission (13).

There is no surgical and medical treatment for primary damage, but it is possible to influence the injury generated by cascade of biochemical events that occur secondarily.

Preventing and reducing secondary brain injury after head trauma have been the focus of recent research on central nervous system trauma. Although the precise mechanism of delayed injury after mechanical trauma is unclear, several investigators have reported that free radical production after head trauma plays an important role in secondary injury (14,18).

There are enough experimental supports for the early occurrence and pathophysiological importance of oxygen radical formation and cell membrane LP in the injured CNS (15,19). LP is a geometrically progressing process that will spread over the surface of the cell membrane causing impairment to phospholipid-dependent enzyme, disruption of ionic gradients, and if severe enough, membrane lysis (19). MDA is a main breakdown product of LP in CNS (29).

Free oxygen radicals damage phospholipids of the neural membranes, and it has been proposed that in situ myelin proteins in the membrane are highly susceptible to the attack of reactive oxygen species as well (21).

In an animal study, citicoline was found to decrease the formation of hydroxyl radicals following ischemia and perfusion, again suggesting that citicoline acts to decrease phospholipase stimulation (3).

Chiu et al. (12) demonstrated that propofol improved the recovery phase in patients with head injury. Propofol decreased ICP to less than 20 mm Hg and maintained CPP above 70 mm Hg. The survival rate in the propofol group was significantly higher than that in the nonpropofol group. It was stated that

Propofol can be recommended for use in the treatment of head-injured patients because of the beneficial clinical outcomes and unique pharmacokinetic/ pharmacodynamic characteristics.

The effect of propofol on CBF, cerebral metabolism, and ICP reduction has been reliably proven in a number of studies (28). Propofol also reduced lipid peroxidation by decreasing NO synthesis.

Sun et al. (32) demonstrated that propofol was also a good anesthetic for travmatic brain injury. Propofol not only had neuroprotective effect such as reducing cerebral metabolism and decreasing intracranial pressure, it could also relieve the gastro-intestinal inflammatory response following traumatic brain injury. It should reduce perioperative gastro-intestinal complications.

Citicoline injected experimentally into the cerebrum of gerbils shortly before artificially-induced ischemia has demonstrated an ability to partially restore phosphatidylcholine levels while inhibiting free fatty acid release, suggesting stabilization of the neuronal membrane (2).

In another gerbil study, citicoline restored ischemia-depleted levels of phosphatidylcholine, sphingomyelin, and cardiolipin after one day of reperfusion. In addition, this study found that citicoline increased both glutathione levels and glutathione reductase activity after three days of reperfusion, suggesting that citicoline may contribute to the reduction of oxidative stress (1).

A large single-blind study on Citicoline was conducted by Calatayud-Maldonado et al. (10) in moderate-to-severe head injury over a 3-month period and showed that all measures, including the clinical impression, improved and the treatment group was significantly more likely to end in the Glasgow Outcome Scale (GOS) 'Good Recovery Group'.

Cholinomimetics represent a new option for the management and amelioration of cognitive and behavioral problems after brain injury. One study has shown that citicoline facilitates memory rehabilitation in brain trauma patients by restoring blood flow to the lesion site (22)

Citicoline restored Na+/K+-ATPase activity via inhibition of the release of arachidonic acid, which inhibits Na+/K+-ATPase activity (11). Restoration of this activity could be mediated through the prevention of phospholipase A2 activation and the subsequent decrease in arachidonic acid release (9).

We therefore conclude that Citicoline and propofol, administered alone or in combination, have neuroprotective effects on head injury through different physiological pathways, but administration of these agents in combination does not have any superiority over the administration of either drug alone (27).

It is not yet possible to conclude whether citicoline works better with milder injuries, more severe injuries or equally well with the whole spectrum of severity. Further randomized controlled trials are urgently required for clinical use of citicoline on moderate or severe head injury.

Products of lipid peroxidation, e.g., MDA levels, together with SOD and GPx activity levels, can be measured in monitoring the degree of lipid peroxidation (33).

The present study demonstrated that SOD levels are decreased compared to the preinjury levels, which indicates that the propofol probably works like a scavenger instead of, or together with GPx.

One of the antioxidant defense systems is SOD, which eliminates superoxides by converting them to hydrogen peroxide (H2O2). H2O2 is reduced to water by cytosolic antioxidants, catalase, and GPx (16).

In spite of experimental evidence of the neuroprotective effects of citicoline in cerebral ischemia and head injury, there are limited reports about its effects in head injury. In this experimental study, MDA levels were lowest in the combination group and highest in the trauma group. The mean MDA value of the propofol group was lower than the trauma group. However, the difference was not statistically significant.

We believe that the propofol and citicoline combination protect the injured brain by inhibiting posttraumatic lipid peroxidation. Therefore, systemic administration of this combination may provide protection to the brain from secondary injury after trauma. Lastly, the combinated use of these therapeutic agents will be more useful due to their synergetic effects.

CONCLUSION

The effects of propofol on the activity of

antioxidant enzyme system were more meaningful than its effect on lipid peroxidation. Whereas we found that citicoline was not effective on the activities of enzymatic antioxidants. Instead it was found to be highly effective on the lipid peroxidation positively. However, head injury involves multiple pathological mechanisms and biochemical responses, thus no single agent is likely to provide complete neuroprotection from secondary injury. Combination drug therapy may become a feasible option for future treatment of head injury.

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