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Original Article

Comparison of cerebral effects of thiopental and propofol infusion in traumatic brain injured rats

Travmatik beyin hasarlı ratlarda tiyopental ve propofol infüzyonunun serebral etkilerinin karşılaştırılması

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ABSTRACT

Objective: Head trauma is a lethal, disabling, and pathological condition requiring long-term treatment and care. Thiopental and propofol infusions are frequently used for sedation in the intensive care unit (ICU). However, we do not have clear data on whether they are neuroprotective or neurotoxic. We aimed to compare the early cerebral effects of propofol and thiopental, which are used for sedation in acute head trauma.
Methods: A total of 30 rats were included in this experimental study, and the animals were randomly divided into three groups; 5 ml/kg/h 0.9% dose NaCl infusion was given in the control group, 30 mg/kg/h dose propofol infusion was given in the propofol group, and 140 mcg/kg/h dose of thiopental infusion was given in the thiopental group. Blood samples were taken 4 hours after infusion. A craniotomy was performed, the brain was removed, and it was placed in 10% neutral formalin for histological examination. The materials were examined biochemically and histologically and then compared between the groups.
Results: The S100B value between the groups was significantly lower in the thiopental group than in the control group (p=0.018). Tau protein levels were significantly lower in the propofol group than in the control group (p=0.07). In histological examinations, the number of apoptotic cells in the propofol and thiopental groups were significantly lower than in the control group (p=0.02). There was no significant difference between the propofol and thiopental groups in apoptotic cell numbers (p=0.3).
Conclusion: Our study demonstrated that thiopental and propofol infusions following a head trauma reduced apoptotic cell death and caused a decrease in trauma markers.

Keywords: Head trauma, thiopental, propofol

ÖZ

Giriş ve Amaç: Kafa travması, uzun süreli tedavi ve bakım gerektiren ölümcül, sakat bırakan, patolojik bir durumdur. Yoğun bakımda sedasyon için sıklıkla tiyopental ve propofol infüzyonları kullanılmaktadır. Ancak nöroprotektif mi yoksa nörotoksik mi oldukları konusunda net bir veriye sahip değiliz. Akut kafa travmasında sedasyon amaçlı kullanılan propofol ve tiyopentalin erken serebral etkilerini karşılaştırmayı amaçladık.
Yöntem ve Gereçler: Bu deneysel çalışmaya toplam 30 sıçan dahil edildi ve hayvanlar rastgele 3 gruba ayrıldı; Kontrol grubuna 5 ml/kg/saat %0.9 NaCl infüzyonu, propofol grubuna 30 mg/kg/saat doz propofol infüzyonu, tiyopental grubuna 140 mcg/kg/saat doz tiyopental infüzyonu verildi. İnfüzyondan 4 saat sonra kan örnekleri alındı. Kraniyotomi yapıldı, beyin çıkarıldı ve histolojik inceleme için %10 nötral formalin içine yerleştirildi. Materyaller biyokimyasal ve histolojik olarak incelendi ve ardından gruplar arasında karşılaştırıldı.
Bulgular: Gruplar arası S100B değeri tiyopental grubunda kontrol grubuna göre anlamlı derecede düşüktü (p=0.018). Propofol grubunda tau protein düzeyleri kontrol grubuna göre anlamlı derecede düşüktü (p=0.07). Histolojik incelemelerde propofol ve tiyopental gruplarındaki apoptotik hücre sayıları kontrol grubuna göre anlamlı derecede düşüktü

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(p=0.02). Apoptotik hücre sayıları açısından propofol ve tiyopental grupları arasında anlamlı fark yoktu (p=0,3).
Tartışma ve Sonuç: Çalışmamız kafa travması sonrası tiyopental ve propofol infüzyonlarının apoptotik hücre ölümünü azalttığını ve travma belirteçlerinde azalmaya neden olduğunu göstermiştir.

Anahtar kelimeler: Kafa travması, tiyopental, propofol

INTRODUCTION

One of the most important causes of childhood and young adult deaths worldwide is head trauma due to accidents, both inside and outside vehicles. Deaths due to head traumas are responsible for approximately 50% of overall deaths. Head trauma is the fourth most common (37%) cause of death in adults and the leading cause of permanent disability in patients under 40 years of age (1). Permanent disabilities caused by head trauma affect patients and their families and cause an increase in medical costs and economic burden. Thus, it is essential to prevent head traumas or provide fast and effective treatments after they occur (2). The first stages of brain injury resulting from a head trauma include primary cellular damage in the brain tissues. Secondary brain damage occurs if the damage progresses and early and effective management cannot be provided. The risk of permanent disability due to secondary brain damage can be minimized if some factors that cause brain damage, such as bleeding, edema, and increased intracranial pressure, can be prevented in the early period (3). Inhibition of free oxygen radicals, which lead to secondary damage, positively affects the poor neurological outcome picture after trauma or ischemia in the central nervous system (4).

Sedation is the first-line treatment of increased intracranial hypertension and pressure to avoid the extension of the lesions and preserve the neurons. The hypnotic and opioid combination is often used for this. Propofol is widely used as a sedative in neurosurgical and neurologic intensive care units apart from its general use. Propofol provides its neuroprotective effect by preventing lipid peroxidation, decreasing intracranial pressure (ICP), and maintaining coupling with the cerebral metabolic rate of oxygen (5). Propofol administration after acute brain lesions can have a deleterious impact because of its role in the pro-brain-derived neurotrophic factor-p75 neurotrophin receptor pathway (6). It is also thought to indirectly induce apoptosis by increasing the expression of caspase-3 and TUNEL-positive cells. The dose-dependent neuroprotective effects of propofol after head injury are not well known (7). Thiopental is an effective anticonvulsant that decreases the brain's oxygen consumption and reduces cerebral blood flow and metabolic rate. The cerebral metabolic rate balances oxygen delivery and consumption in the brain. Thiopental has a role in treating refractory elevated ICP and refractory status epilepticus if hypotension is not already a problem in traumatic brain injury (TBI) (8).

This experimental study aimed to compare the early cerebral effects of propofol and thiopental, which are used for sedation in acute head trauma.

METHODS

After receiving approval from the Bolu Abant Izzet Baysal University local ethics committee (decision number: 2017/04), 30 rats weighing 250–300g were included in the study and randomly and blindly divided into three groups. Rats were sedated by intramuscular (IM) route with 90 mg/kg ketamine and 10 mg/kg xylazine. Vascular access was provided from the tail vein with a 24 G cannula. Since endotracheal intubation was a more difficult and relatively longer procedure, sacrification would be performed on the animals after the study. Trachea exploration was performed before trauma to prevent hypoxia and provide rapid ventilation. For this reason, the neck area was sterilized before the trauma. Soft tissues in the trachea region were dissected after the skin incision. The trachea was explored. After cannulation, a 3/0 suture was passed around the trachea and prepared to bind. A stainless-

steel metal disc was placed on the vertex of the rat to cause diffuse cranial damage by the falling weight. Head trauma was created by modifying the trauma model developed by Marmarou et al.[13] in 1994. Two hundred gr metal weight was dropped free fall from a height of 50 cm with the effect of gravity to the metal disc on the head. After head trauma, the trachea was cannulated with a 16 G venous cannula, and rats were connected to the mechanical ventilator device (SAR-830 series Small Animal Ventilator CWE, Inc. 25 St. Paul's Road Ardmore PA 19003 USA). Ventilator settings were made following the user manual of the device. The time from tracheal cannulation to mechanical ventilation was 30 seconds. The drug infusion doses were prepared before the trauma and were given immediately by the infusion pump after the trauma. 5 ml/kg/h 0.9% NaCl infusion was given in the control group (n=10). 30 mg/kg/h dose of propofol infusion (Propofol Lipuro %1, B. Braun Irengun, Istanbul, Turkey) was given in the propofol group (n=10). 140 mcg/kg/h dose of thiopental infusion (Pental Sodium 0.5 g. İ.E. Ulugay Istanbul, Turkey) was given in the thiopental group (n=10). Equal amounts of fluid were infused into all groups. A heated table was used for temperature management. The table was kept at a constant temperature of 37 °C and the room temperature at 25 °C. Blood samples were taken at the end of the 4th hour. 0.1 mg/kg of vecuronium was administered intravenously to provide the necessary muscle relaxation after the blood samples. Ventilation was terminated, and the head was dissected between the atlas and axis at the end of the study. The brain was removed with a temporal craniotomy, and the rats were sacrificed. This process took a maximum of 2 minutes.

Biochemical analysis: The phospho tau protein (pτ), glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), Serum Total Antioxidant Level (TAL), and Total Oxidant Level (TOL) were analyzed. Blood samples were taken into tubes containing a clot activator. Samples were centrifuged at 1500g for 10 minutes, and the sera were separated. Alkalinized serums were stored at -80 ° C until biochemical analysis. Samples were gradually thawed before analysis. TAL and TOL, Rel commercial assay kit (Rel Assay Diagnostics, Gaziantep, Turkey) C8000 using Architect (Abbott, Chicago, IL, USA) were measured following the manufacturer's instructions autoanalyzer. The oxidative stress index (OSI) was calculated using the (TOL / TAL x100) formula. The phospho tau protein, GFAP, NSE, and S100B were measured using commercial enzyme-linked immunosorbent measuring kits (Elabscience Biotech, Wuhan, China) according to the manufacturer's instructions.

Histological examination: Brain tissues were fixed in 10% neutral formalin. Routine histological follow-up was performed, and paraffin blocks were prepared. Coronal sections (5 mm) were prepared from the frontal cortex (1.8 mm anterior and 2.8 mm posterior to Bregma) to the hippocampus (2.3 mm posterior and 4.3 mm posterior to Bregma) and stained with Hematoxylin-Eosin (9). For Hematoxylin-Eosin staining, sections were deparaffinized and passed through graded ethanol series. After the ethanol series, sections were washed with distilled water and then stained with hematoxylin for 3 minutes. Then sections were rinsed within distilled water and passed through 80% ethanol. Sections were stained with eosin for 40 seconds. Following eosin stain, sections were passed through ethanol to remove water, then rinsed in xylene for transparent tissues. The slides were covered with a coverslip.

Immunohistochemical staining of the terminal deoxynucleotidyl transferase dUTP nick-end-labeling (TUNEL) (Roche Cat. No: 11684817910, Germany) was performed to evaluate apoptotic cells. TUNEL positive cells (cells with dark-brown nuclei) were counted in 5 different areas of the frontal cortex and hippocampus regions with x40 objective magnification. The apoptotic index was calculated by counting TUNEL (+) stained cells in 100 cells in each field.

Statistical analysis: Statistical Package for Social Sciences (SPSS) program version 21 was used for statistical analysis. Data were expressed as mean ± standard deviation. The One-Way ANOVA test was conducted, followed by the post-hoc Games-Howell test to compare the biochemical markers across three groups. P <0.05 was considered statistically significant.

RESULTS

No skull fracture or subsequent death was observed in any animal in our study. The study was completed as planned with 30 animals. The cortical areas of the control group and the cortical areas of the propofol and thiopental groups were examined with light microscopy after trauma. In the control group, tissue integrity was impaired in the area of trauma, hemorrhage, capillary congestion, and edema (Figure 1a). It was found that congestion was evident in the pia mater and cortex capillaries in the areas around the trauma and edema in the molecular layer. It was found that congestion was prominent in the pia mater and cortex capillaries in the areas around the trauma, and there was edema in the molecular layer (Figure 1b). Edema in the peritraumatic areas and cortical capillary congestion decreased in the groups treated with propofol (Figure 1c) and thiopental (Figure 1d) in trauma compared to the control group. The hippocampus region was found to have a normal structure in the experimental groups.

TUNEL immunohistochemical staining showed that apoptotic cells significantly increased in the propofol (p=0,01) and thiopental groups (p=0,02) compared to the control group's peritraumatic

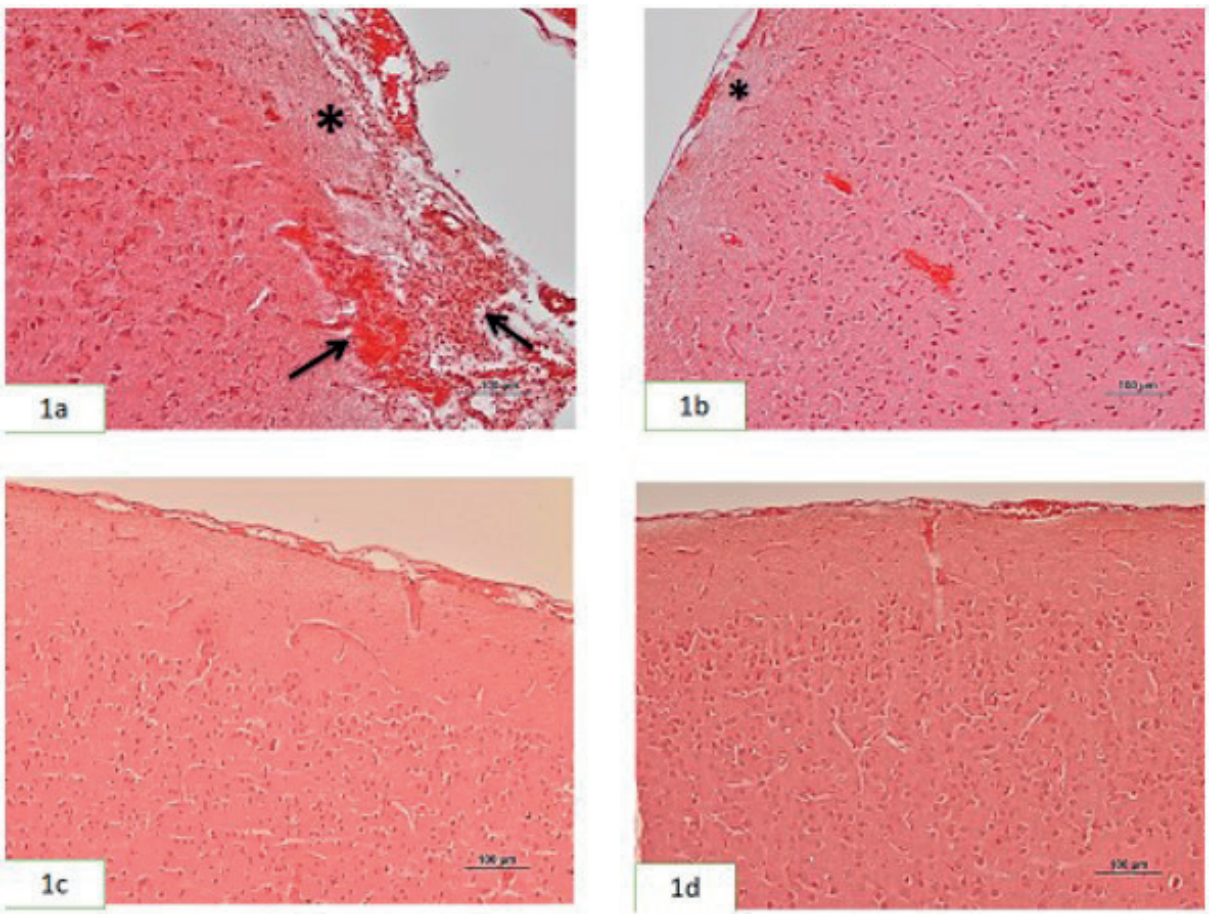

Figure 1. Congestion, hemorrhage (→) and edema (*) are seen in the trauma area of the control group (1a). It is seen that edema in the peritrauma area, congestion in capillaries of piamater and cortical in the control group (1b), cortical congestion and edema are decreased in propofol (1c) and thiopental (1d) groups. X10 original magnification, Hematoxylin Eosin staining. Bar 100 µm.

frontal cortex. There was no significant difference between propofol and thiopental groups (Figure 2 a, b, and c). The intensity of TUNEL (+) staining in the propofol and thiopental groups in the hippocampus region was decreased compared to the control group (Figure 3 a, b, and c), but it was not statistically significant (control p=0,12; propofol p= 0,14; thiopental p= 0,14).

S100B was significantly lower in the thiopental group in our study (p=0.018). Tau protein was significantly lower in the propofol group (p=0.007). There was no significant difference in NSE and GFAP values between the groups (Table 1).

DISCUSSION

This experimental study showed that propofol and thiopental prevented the increase of brain injury in the acute period after head trauma. Amounts of congestion, edema, and the number

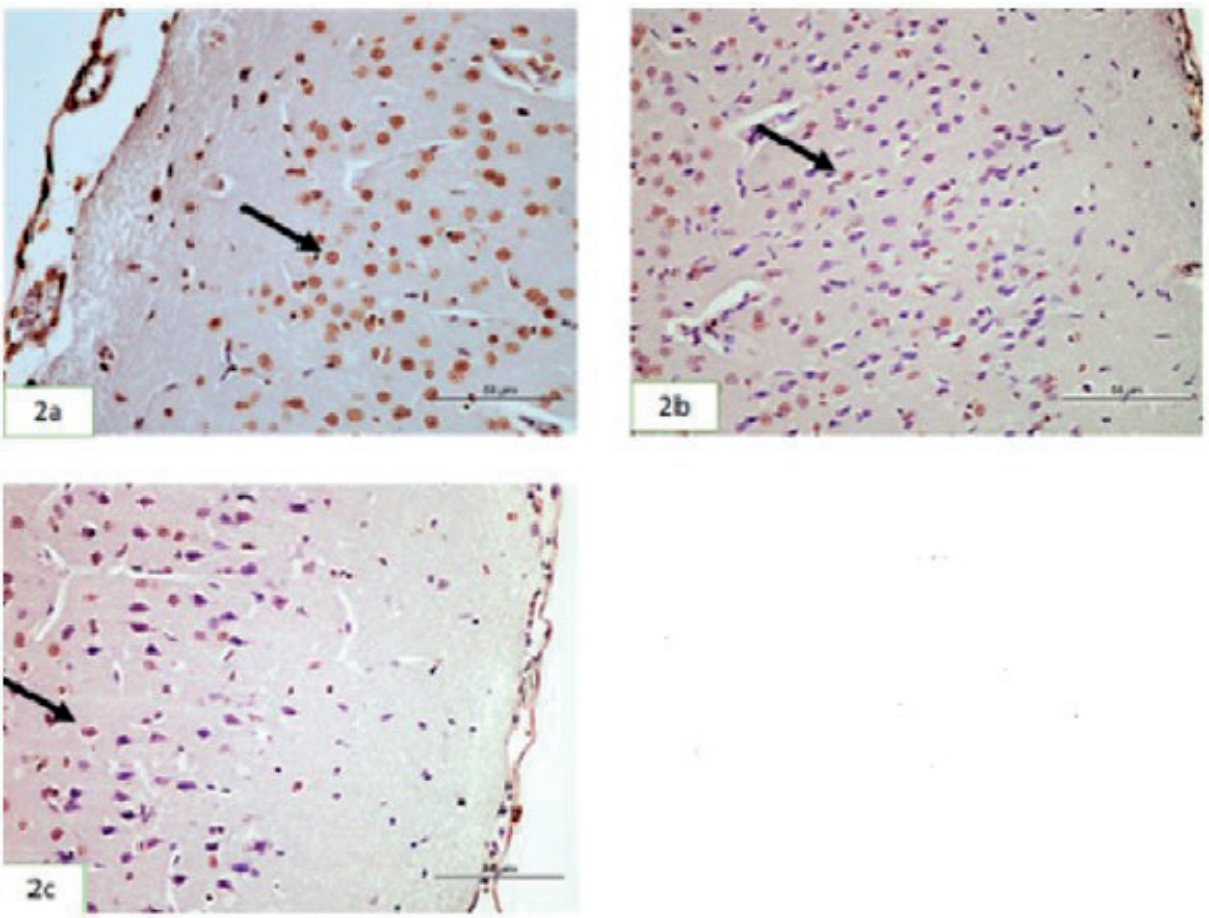

Figure 2. In the control (2a), propofol (2b) and thiopental (2c) groups, apoptotic cells (arrows) are observed in the frontal cortex areas in the periphery of the trauma induced area. x20 original magnification, TUNEL staining. Bar 50 µm.

Table 1. Biochemical markers of the groups.

	Propofol	Tiyopental	Control	p value*
NSE (ng/ml)	18.1±8.6	27±14.9	20.2±11.0	0.200
S100B (pg/ml)	688.3±282.3	501.6±331.4[a]	1171.8±759.4[a]	**0.018**
GFAP (ng/ml)	3.9±1.4	6.2±3.5	4.1±1.3	0.060
TAU Protein (pg/ml)	145.1±54.8[a]	178.9±143.3	359.8±208.2[a]	**0.007**
TAL (umol/l)	1.75±0.18	1.84±0.24	1.77±0.21	0.601
TOL (umol/l)	3.99±2.64	5.88±5.35	5.71±5.32	0.607

*mean±sd. *One-way ANOVA. NSE: Neuron specific enolase, GFAP: Glial fibrillary acidic protein, TAL: Total antioxidant level, TOL: Total oxidant level. Same superscript letters show statistically significant difference between groups based on Games-Howell test.*

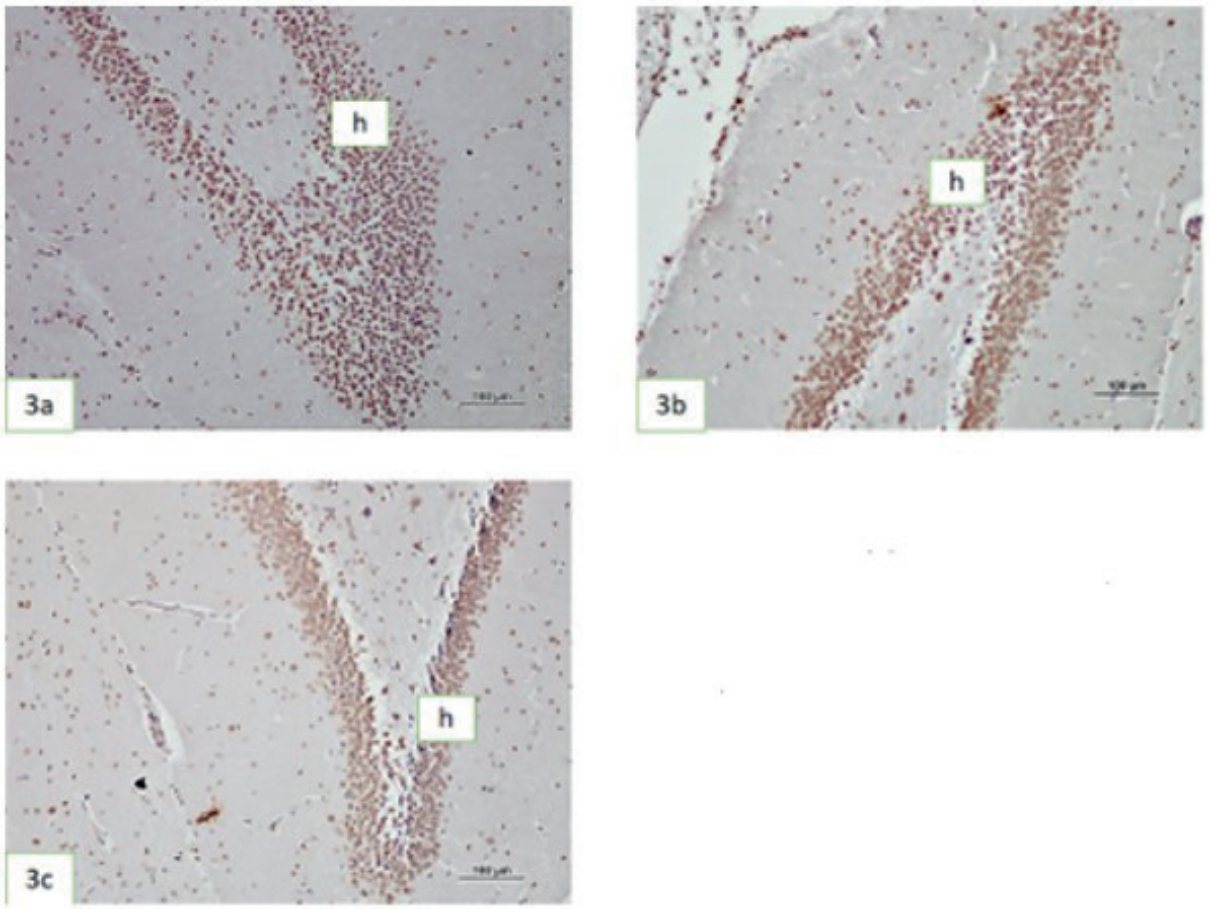

Figure 3. TUNEL (+) stained cells are seen in the hippocampus region (h) of the control (3a), propofol (3b) and thiopental (3c) groups. X10 original magnification. TUNEL staining. Bar 100 µm.

of atypical cells decreased in the histopathological examination. In addition, it also prevented the increase in some trauma markers. However, no superiorities were identified between propofol and thiopental. Vascular and hemodynamic mechanisms deteriorate after traumatic brain injury. The intracranial compartment expands with increased tissue edema and increased blood count. Cerebral ischemia causes cerebral edema, neuronal damage, and increased intracranial pressure. An imbalance occurs between cerebral oxygen consumption and the amount of oxygen delivery to the brain. The incidence, duration, and extent of tissue hypoxia are associated with poor prognosis (10). Therefore, early diagnosis and treatment are important. Anti-inflammatory agents, glutamate antagonists, cation homeostasis modulators, endocannabinoids, free radical scavengers, immunosuppressants, apoptosis, and caspase inhibitors have a role in the pharmacological treatment of traumatic brain injuries (11). Diffuse head trauma is a common finding in patients with severe brain damage for whom the computer tomography (CT) scan does not show mass lesions. Since the rodents have a relatively small size and cost that allows repetitious biochemical and histopathological examinations, many researchers have preferred rodent models as the most appropriate option in brain trauma investigations despite many different ideas concerning the model type (12). We used a modified trauma model developed by Marmarou et al. among various animal models of head trauma. This model has been widely used and accepted universally (13).

In many studies, the neuroprotective effect of propofol has been investigated (14). It has been found to reduce postischemic injury in transient focal ischemia by different mechanisms (5).

On the other hand, evidence suggests that propofol may be neurotoxic. Propofol can cause neuronal cell death in healthy immature brains via p75NTR receptor signaling. p75NTR receptor becomes down-regulated in adulthood, and propofol loses its neurotoxic effect. However, p75NTR receptor expression increases in traumatic brain injury. This can stimulate reparative processes and sensitize the brain to propofol-mediated neurotoxicity (6,15). Recent studies suggest that proNGF, the precursor form of nerve growth factor (NGF), is more active than mature NGF in inducing apoptosis after binding to p75NTR and a coreceptor sortilin (15). Reactive oxygen and nitrogen species after TBI cause lipid peroxidation (LP) mediated oxidative damage. This causes increased permeability of membranes, decreased membrane adenosine triphosphatase activity, mitochondrial dysfunction, and cell damage. Collapsin response mediator protein-2 (CRMP2) is a multifunctional cytosolic protein. LP is involved in triggering postinjury CRMP2 proteolysis, possibly inhibiting post-traumatic neurite regeneration. Propofol could attenuate LP, calpain-induced CRMP2 degradation, and brain injury after TBI. Yu et al.[16] investigated the effect of propofol on rats after cortical trauma. They administered 40 mg/kg/h propofol by iv infusion for 2 hours after 12.5 mg/kg propofol injection. They found that propofol in the acute post-traumatic period (initiated within 4 h after TBI) attenuates calpain-mediated CRMP2 proteolysis and provides a neuroprotective effect by reducing calpain activation and inactivating LP. LP levels increase significantly at 3 hours, and the peak level is seen even 48 hours after trauma. Their results indicated that propofol provides evident neuroprotection even when the onset is delayed up to 4 h post-trauma. We determined the infusion time as 4 hours based on the time that the LP level significantly increased. We obtained similar results to Yu et al.'s study by administering propofol infusion in the early post-traumatic period. In addition, we determined the duration of infusion as 4 hours, considering the presence of trauma markers in the rats' serum (17).

Benzodiazepines are commonly used as sedative agents with anxiolytic, amnesic, and anticonvulsant properties. However, its use is limited to the most severe cases of TBI because subanesthetic or anesthetic doses of thiopental suppress catecholamine release and decrease adrenaline amount. Suppressed adrenaline production leads to hypotension and oxidative stress in the brain striatum. For all these reasons, the effect of early thiopental use for sedation in traumatic brain injury is not clear (8). The guidelines for TBI management recommend using high doses of thiopental to lower intracranial pressure in patients with traumatic brain injury and refractory intracranial hypertension. Majdan et al. investigated barbiturates and the effects of barbiturates on ICP, vasopressor use, and short and long-term effects. They accepted the use of thiopental> 2g/24h as high and <2g as a low dose. They reported that while high-dose barbiturate treatment caused a decrease in ICP in 69% of the patients, it also caused hemodynamic instability and that low-dose thiopental and methohexital were used to sedate patients without side effects (18). We used low-dose thiopental in the early period treatment of TBI and saw that it has beneficial effects.

The oxidative stress index (OSI) can be calculated as a result of Total Antioxidant Level and Total Oxidant Level measurements. A high oxidative stress index (OSI) increases oxidative stress (19). Kaptanoğlu et al.[20] investigated the antioxidant effects of propofol and thiopental in experimental spinal cord trauma. They found that malondialdehyde levels increased as an indicator of lipid peroxidation in rats treated with contusion injury. They showed that thiopental and propofol decreased lipid peroxidation. In our study, we could not find any difference between the antioxidant properties of thiopental and propofol. But the oxidative stress index value was significantly lower in the propofol group compared to the thiopental and control groups.

Biochemical markers such as S100B, NSE, GFAP, and phospho tau protein are important for evaluating post-traumatic damage. The S100B has a half-life of 60 minutes and is the best predictor of brain damage. Studies suggest that NSE peaks after 24 hours rather than the acute period (21,22). Pelinka et al.[23] looked at GFAP and S100B in a 12-hour period in patients with traumatic brain injury and compared them with Glasgow Coma Scale (GCS) scores. They did not deviate from the significant differences in these markers and indicated that they could be used in prognosis. Olczak et al.[24] studied tau protein as a possible biochemical marker of traumatic brain injury in postmortem examination. They revealed that tau protein levels were significantly higher in patients with head trauma. The authors finally concluded that an increase in tau protein levels could be due to axonal injury. In our study, we could not find a significant difference in GFAP values seen at the end of the 4th hour. S100B was found to be significantly lower in rats given thiopental. Tau protein was significantly lower in the propofol group. TUNEL staining was performed to determine apoptotic cells in histological sections. Schwer et al.[25] investigated the basic neuroprotective molecular mechanisms mediated by thiopental in their study. They concluded that therapeutic inhibition of global protein synthesis protects neurons from hypoxic damage by preserving energy balance in oxygen-deprived cells. We similarly determined that propofol or thiopental treatment reduced apoptotic cell death in the early post-traumatic period.

The present study has several limitations. Firstly, the short infusion time of anesthetic agents was one of the study's major limitations. Different studies are needed to increase infusion times to understand the antioxidant effects of thiopental and propofol and their effects on brain trauma markers. Secondly, we did not measure some physiologic variables such as pH, oxygen saturation, heart rate, and blood pressure, and these variables could affect intracranial pressure. Thirdly, another major limitation was the lack of monitoring of neurologic outcomes and intracranial pressure. Monitoring the intracranial pressure parameters has been recommended in some weight-drop model studies in rats. In addition, quantification of motoric, functional, cognitive, and behavioral performance by a battery of neurologic assessments could improve the quality of our study. However, since we did not have enough resources and equipment for the relevant experiment, we could not examine the neurologic status and detect intracranial pressure parameters between thiopental and propofol. Finally, the effects of ketamine and xylazine administrations on results were ignored since these agents were administrated to all groups.

In conclusion, we suggest that thiopental and propofol infusion after head trauma reduces apoptotic cell death, decreases congestion and edema, and causes a significant decrease in trauma markers. Further prospective randomized large-scale studies with different infusion doses are required to better understand the effects of thiopental and propofol on brain trauma and markers.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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