

The effects of erythropoietin, dextran and saline on brain edema and lipid peroxidation in experimental head trauma

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ABSTRACT

BACKGROUND: The aim of this study was to investigate the protective effects of erythropoietin, dextran/saline and erythropoietin in combination with dextran/saline on brain edema and lipid peroxidation following traumatic brain injury in rats.

METHODS: In the study, 40 male 3-month-old albino Wistar rats, weighing 250–340 g, were divided into four groups, each consisting of ten rats. Traumatic brain injury was induced in all rats by the weight-drop method, and erythropoietin (5,000 U/kg) and/or dextran and saline (8 ml/kg) solutions were injected intraperitoneally ten minutes after trauma. Control animals received an equal volume of serum physiologic. All rats were sacrificed 24 hours later. Glutathione peroxidase activity and malondialdehyde levels were measured in the left hemisphere, and edema was quantitated by the wet-dry method.

RESULTS: Brain edema and the levels of malondialdehyde, the last product of lipid peroxidation in tissues, were decreased variably, and the activity of glutathione peroxidase, an antioxidant enzyme, was increased in others compared with the control group.

CONCLUSION: In this study, it was concluded that the brain edema that developed in rats on which head trauma was induced and the secondary brain damage caused by oxidative stress could be decreased using a combination of erythropoietin, dextran, and saline.

Key words: Antioxidants; brain edema; dextran; erythropoietin; saline; oxidative stress; severe head trauma.

INTRODUCTION

Traumatic brain injury (TBI) is a commonly used term to describe brain damage that occurs over a larger area than the one in focal brain injury. It is one of the most devastating health problems since it can result in disabilities requiring long-term treatment and care. It is also the primary cause of death, especially in children and the young generation, throughout the world.^[1,2] TBI occurs as a result of a sudden damage to the brain from an external mechanical force, possibly leading to

permanent or temporary impairment of cognitive, physical, or psychosocial functions as well as a diminished or altered state of consciousness. Accelerated social and technological changes have resulted in a gradual increase in the incidence of head injuries and an accompanying increase in the risk of mortality and morbidity.

The pathology associated with TBI can mainly be divided into two parts: primary and secondary injury. Primary injury results immediately from the initial mechanical trauma; the only “treatment” for primary injury is prevention.^[3] In contrast, secondary injury occurs in the hours and days following the primary injury and plays a marked role in brain damage and death that result from TBI.^[4] Efforts to reduce morbidity and mortality resulting from TBI are best aimed at preventing secondary injury.^[5] Secondary injury is caused by a complex cascade of physiological and biochemical mechanisms that are only partially understood.^[6–8] However, since secondary injury occurs over a period of time, a window of opportunity exists during which measures can be taken to avoid further complications such as hypoxia and edema.^[9] Regardless of the

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cause of brain injury, edema almost always occurs. Edema can result in increased intracranial pressure leading to less brain perfusion, which can then contribute to ischemia exacerbating the original edema. Thus, brain edema is a central part of this vicious cycle of secondary injury in TBI. Therefore, any treatment expected to mitigate secondary injury must alleviate brain edema. The aim of this study was to assess the effect of therapeutic agents against brain edema; edema serves as the principal indicator for efficacy.

Oxygen free radicals and lipid peroxidation are believed to play crucial roles in secondary brain injury. There is extensive experimental support for the pathophysiological importance of early oxygen radical formation and cell membrane lipid peroxidation in the injured nervous system.^[10,11] Previous reports of increased lipid peroxidation end products after head injury and the protective effects of free-radical scavengers are consistent with the proposed role of oxygen free radicals and lipid peroxidation in secondary brain injury.^[11,12] Brain is less tolerant of hypoxia and oxidative stress than other organs. If the injured brain can be protected by antioxidants, it is expected to return to its normal physiology.^[13] Accordingly, a traumatized brain should be supported by a variety of antioxidant mechanisms.

Malondialdehyde (MDA) is a reactive species that occurs naturally, which was used as a biomarker of oxidative stress in this study.^[14] Glutathione peroxidase (GPx) is the general name of an enzyme family with peroxidase activity whose main biological function is to protect organisms from oxidative damage by reducing lipid hydroperoxides and free hydrogen peroxide to water. Its activity is generally accepted as a basic indicator of an antioxidant system.^[15]

In addition to its erythropoietic effects, erythropoietin (EPO) possesses many biological activities.^[16,17] It is produced by astrocytes in response to hypoxia, suggesting that it protects neurons from ischemic damage.^[18] Trials on human subjects are not conclusive regarding its ability to protect against ischemic damage. This study was undertaken as EPO had been detected in the brain as a natural response to primary hypoxic damage and might work synergistically with other agents such as dextran and hypertonic saline.

Dextran (D) is a complex of polysaccharide chains of varying lengths (3 to 2,000 kilo Daltons). It is used for a variety of reasons in intensive care units, such as preventing thrombosis, reducing blood viscosity, and expanding volume.^[19] In addition, D, which can act as a potent osmotic agent, is preferred as an alternative to mannitol for urgent treatment of brain edema. The use of hypertonic saline (S) in experimentally induced brain injury has long been known to reduce the intracranial pressure. It is also used in critical care settings to maintain brain perfusion and severe hyponatremia.^[20]

This study investigated whether brain edema occurring in the early stages of severe head trauma could be reduced by the

administration of a combination of EPO, D and S in rats. If these reagents are demonstrated to reduce brain edema, the study will be expanded to include human subjects.

MATERIALS AND METHODS

The approval of Erciyes University, Experimental Animal Ethics Committee was obtained for all procedure.

Animals

Forty 3-month-old male Wistar albino rats, weighing 250–340 g, were used in this study. They were kept in a windowless room where temperature and light were automatically controlled ($21 \pm 1^\circ\text{C}$; 14 h light/10 h dark cycle, light on at 7 am and off at 9 pm). The humidity ranged from 50 to 54%. The Ethical Committee of Erciyes University approved all animal procedures and the experimental protocol. All animals received proper care according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals as prepared by the National Academy of Sciences and published by the National Institutes of Health.

Surgical Technique

The animals were divided randomly into the following four groups of ten rats each: control, EPO, dextran-hypertonic saline (DS) and EPO+DS. The rats were anesthetized with an intraperitoneal injection of ketamine hydrochloride (70 mg/kg) and xylazine hydrochloride (7 mg/kg). The animals maintained spontaneous breathing. The heads of the animals were fit into the head injury device with the chin resting firmly on the bottom plane. Closed head injury was created as described by Marmarou et al.^[21] The cranial impact was induced at the vertex on the midline, just behind the coronal suture for all treatment groups. The free fall occurred from a height of 150 cm, preferable for producing impact energy of 0.7 J over the skull. Ten minutes after the trauma, the rats were injected intraperitoneally with EPO (5,000 U/kg) (EPO group), DS (8 ml/kg) (DS group), both EPO (5,000 U/kg) and DS (8 ml/kg) (EPO+DS group) or an equal volume of serum physiologic (control group). The rats were decapitated 24 h after the onset of injury, and brain hemispheres were removed for biochemical analysis (left hemisphere) and measurement of water content (edema) (right hemisphere).

Measurement of Brain Edema

The water content of the rat brain tissues were evaluated by estimating the water content using the method described by Hara et al.^[22] Briefly, both cerebral hemispheres were immediately weighed after decapitation and kept in an oven at 70°C for 36 h until a constant weight was reached. The percentage of tissue water content was calculated using the following formula: % water content = $[(\text{wet weight} - \text{dry weight}) / \text{wet weight}] \times 100$.^[23]

Measurement of Malondialdehyde (MDA) Level

A hydroxyl radical, a typical example of free radicals, can easi-

ly react with membrane phospholipids, resulting in the provocation of lipid peroxidation. MDA, as the final product of lipid peroxidation, can be identified via thiobarbituric acid (TBA) reaction. The absorptivity of the color formed by MDA with TBA was used to determine the amount of lipid peroxidation per gram of wet tissue in nmol units. After centrifugation, the color was measured at 532 nm.^[24] Protein levels were measured as described by Lowry et al.

Measurement of Glutathione Peroxidase (GPx) Activity

GPx activity was measured by the method of Paglia and Valentine.^[25] In order to initiate enzymatic reaction, H_2O_2 was added to a tube containing NADPH, reduced glutathione (GSH), sodium azide, and glutathione reductase, and the change in absorbance at 340 nm was determined by spectrophotometry. The activity was reported in units per gram protein.

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (SPSS for Windows, version 10.0). Using the Kolmogorov-Smirnov test, the data was determined to be normally distributed. The differences in the measured parameters among the groups were analyzed using one-way ANOVA. The Scheffe procedure was used to determine which group was significantly different. The measurable (quantitative) data distribution was defined as the average values of the $\bar{x} \pm s.d.$, and significance level was taken as 0.05.

RESULTS

Biochemical Findings

Mean MDA levels and GPx activities for each group are shown in Table 1. TBI significantly increased the tissue MDA

levels and significantly decreased the tissue GPx activities when compared with controls ($p < 0.05$). The administration of a single dose of EPO (5,000 U/kg) 10 min after the trauma resulted in significantly decreased MDA levels and significantly increased GPx activity compared with that observed for the control group (Table 1, Fig. 1).

Mean GPx activity observed in the EPO+DS group was significantly higher than that of the control group. There was also an increase in the mean GPx activity of both the EPO and DS groups compared with the control group; however, the differences were not statistically significant (Table 1, Fig. 2).

Edema Findings

Tissue edema was evaluated as the percentage of water in the tissue (Table 2, Fig. 3). The rats in the DS, EPO and EPO+DS groups experienced significantly less edema than the rats in the control group. Furthermore, the rats in the EPO+DS group experienced significantly less edema than the rats in the EPO only or DS only groups. There was no significant difference between the DS and the EPO groups with respect to edema.

DISCUSSION

Severe head injury, which has become one of the most important health problems worldwide, can be fatal or a disabling trauma that requires long-term treatment and care. Defense mechanism of the brain against oxidative stress has long been known to be less than that of the other organs. A traumatized brain; however, can return to its normal physiology if secondary damage caused by oxidants is prevented. Therefore, brain antioxidant mechanisms should be supported as much and as quick as possible when treating TBI.

Table 1. Tissue GPx activities and MDA levels in control and treated rats

	Control (n=10)	EPO (n=10)	DS (n=10)	EPO+DS (n=10)	F	p
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
GPx ($\bar{U}$ /ml)	287.3 $\pm$ 13.2	311.2 $\pm$ 40.6	338.5 $\pm$ 39.8	373.8 $\pm$ 22.3	13.2	0.00
MDA (μ M)	2.06 $\pm$ 0.28	1.62 $\pm$ 0.22	1.95 $\pm$ 0.29	1.88 $\pm$ 0.44	3.7	0.02

Table 2. Mean Water Percent (Edema) in control and treated rats

	Control (n=10)	EPO (n=10)	DS (n=10)	EPO+DS (n=10)	F	p
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
Wet-weight	0.602 $\pm$ 0.040	0.629 $\pm$ 0.025	0.547 $\pm$ 0.020	0.514 $\pm$ 0.032	28.2	0.00
Dry-weight	0.190 $\pm$ 0.014	0.229 $\pm$ 0.010	0.196 $\pm$ 0.010	0.207 $\pm$ 0.018	15.8	0.00
Water% (Edema)	68.4	63.4	64.1	59.7	76.2	0.00

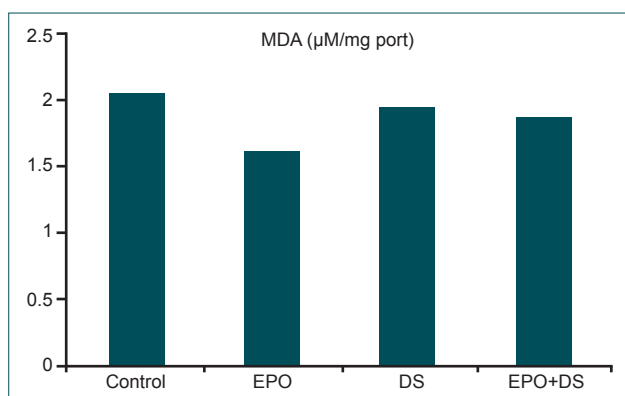


Figure 1. MDA levels in control and treated rats. The reduced MDA levels in the EPO and EPO+DS groups compared with controls suggest that EPO generates a neuroprotective and anti-edema effect by reducing lipid peroxidation.

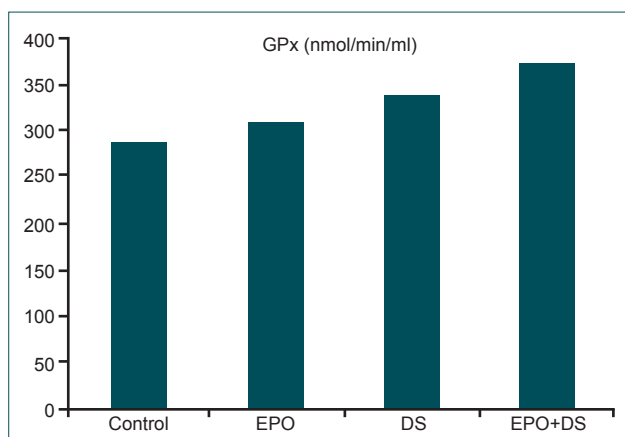


Figure 2. GPx activity in control and treated rats. The EPO, DS and EPO+DS groups show higher GPx activity than the control group; only the difference between the EPO+DS group and the controls was significant.

It has been shown that secondary brain injury negatively affects prognosis. The main approach to treating a traumatized brain has been to protect it from secondary injuries, including ischemia, cerebral hypoxia, cerebral edema, and raised intracranial pressure. Morbidity and mortality can only be reduced if these pathologies are prevented.^[26,27] Rapidly progressive cerebral edema is usually the first step of the pathological process that follows brain trauma. Maintaining reduced brain perfusion pressure by the compression of vascular structures is one of the most important goals of treatment.^[28]

In response to severe trauma, the body tends to develop marked anemia and hypotension, both of which further the susceptibility to hypoxia. In addition to its erythropoietic effects, EPO also possesses many biological activities. The fact that it is produced by astrocytes in response to hypoxia suggests that EPO protects neurons from ischemic damage. Yasuda et al.^[29] have demonstrated that EPO plays an important role in the development of the nervous system, and its absence results in the interruption of neurogenesis in fetal embryos. Brines et al.^[30] have reported that EPO passes through

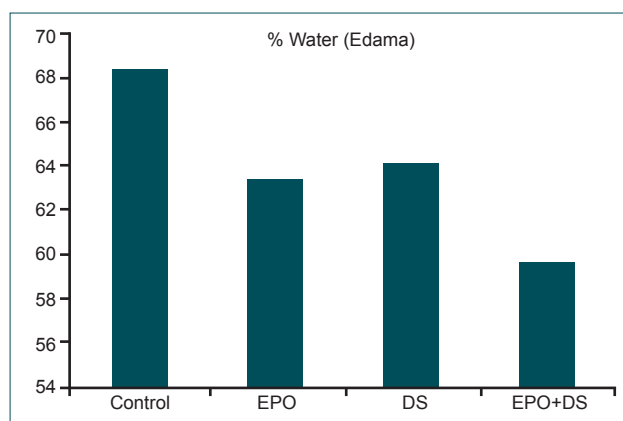


Figure 3. Edema in control and treated rats. The cerebral edema in the EPO, DS and EPO+DS groups was significantly lower than in the control group.

the blood brain barrier by a receptor-mediated mechanism and protects the brain along with the peripheral application. They have concluded that it is a safe therapeutic agent with minimal side effects. Belayev et al.^[31] have histologically investigated the effects of EPO on the hypoxia induced by MCA clipping in rats and reported that EPO-treated rats developed cortical and subcortical infarction at rates that were 58% and 50% lower, respectively, compared with the controls. Ehrenreich^[32] have demonstrated that EPO achieves its protective effects via its antioxidant, anti-apoptotic effects rather than by regulating disease-specific pathological mechanisms. Similarly, Kumral et al.^[33] have reported that EPO increases GPx activity and decreases lipid peroxidation in neonatal rats exposed to hypoxia compared with controls. Kuzugüden et al.^[34] have shown the oxidative stress induced by high doses of thinner can be reduced by EPO via a decrease in the formation of MDA and an increase in GPx activity in rat brain. In another study, Ozturk et al.^[35] have investigated the antioxidant properties of EPO and propofol on closed head injury in a rat model and found that rats treated with EPO or propofol+EPO had lower serum MDA and NO levels compared with the control group. Thus, it was concluded that EPO administration during the early period of trauma caused a significant reduction in the levels of oxidative stress metabolites.

In our study, EPO showed a neuroprotective effect reducing the formation of edema and MDA and increasing the GPx activity. Taken together, these findings suggest that the neuroprotective effect of EPO is achieved by regulating enzyme activities or strengthening the antioxidant defense. It was also demonstrated that there was a significant decrease in MDA levels and a significant increase in GPx activity in the EPO and EPO+DS groups compared with that observed in the controls. These results confirm that EPO has a marked antioxidant effect. So as to take advantage of its neuroprotective effects, it is reported that EPO should be administered within the first 3 to 24 hours after trauma. Hence, EPO was administered intraperitoneally 10 minutes after the trauma occurred.

Verdonck et al.^[36] had investigated the effect of rEPO on brain edema by MRI and gravimetric methods. The model of head trauma described by Marmarou et al. was administered to Wistar albino rats, and rEPO was given 30 min later. The measurements were obtained from the neocortex and kaudaputamen regions of rat brain, and cerebral edema was found to be significantly less in EPO-treated rats than in the controls. This provides further evidence of EPO's positive effect on brain edema. In our study, cerebral edema was decreased in both the EPO and the DS groups compared with the controls. When EPO and DS were co-administered, there was a further decrease in edema, suggesting a synergistic anti-edema effect. These results are consistent with a study by Frei et al.,^[37] in which rEPO was found to significantly increase brain perfusion and improve neurological outcome by reducing cellular apoptosis, tissue inflammation and cerebral edema in rats with closed head injuries.

Thus far, the application of DS hypertonic solution has been limited to studies on hemorrhagic shock recovery. Although the results of these studies indicate that such patients may benefit from treatment with DS hypertonic solution, patients with head injury have not been included into these studies.^[38] It has been shown that DS hypertonic solution reduces intracerebral pressure (ICP) in animals with head injury. Berger et al.^[39] have compared the ability of hypertonic DS with that of hypertonic mannitol to reduce intracranial hypertension that develop due to focal cerebral lesions and intracranial mass and have reported that hypertonic DS provides higher brain perfusion pressure than mannitol. In addition, experimental studies have shown that S also improves cerebral perfusion pressure better than mannitol due to its potential to increase mean arterial blood pressure; in contrast, mannitol reduces mean arterial blood pressure.

Based on our findings in combination with the results of other studies, we believe that EPO should be started in clinical use, and DS might be an alternative to hypertonic mannitol in the treatment of edema in patients with severe head injury.

Based on our results and in light of the above-mentioned studies, we reached the following conclusions:

1. EPO shows a neuroprotective effect reducing the formation of edema and increasing the GPx activity, which has antioxidant effect.
2. EPO alone has an anti-edema effect equivalent to that of hypertonic DS, and this effect is increased when EPO and DS are co-administered.
3. EPO generates its neuroprotective and anti-edema effect reducing lipid peroxidation as evidenced by the reduced MDA level in EPO and EPO+DS rats compared with the controls.
4. In head injuries, lipid peroxidation causes brain edema as evidenced by the fact that brain edema is significant in the rat groups with a high level of MDA.
5. Antioxidant mechanisms play an important role in reduc-

ing brain edema and secondary brain damage as shown by the fact that GPx activity decreases as brain edema increases and vice versa.

6. EPO, DS and EPO+DS groups show higher GPx activity than the control group, but there was only significant difference in EPO+DS the group. This also suggests that the co-administered EPO and DS synergistically reduce brain edema and increase antioxidant activity as evidenced by the fact that the EPO, DS and EPO+DS groups all showed a higher GPx activity than the control group, but the increase was only significant for the EPO+DS.
7. Cerebral edema in the EPO, DS and EPO+DS groups was significantly lower than in the control group.
8. Dextran and saline had no effect on lipid peroxidation.

Conflict of interest: None declared.

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DENEYSSEL ÇALIŞMA - ÖZET

Deneyisel kafa travması oluşturulan sıçanlarda eritropoetin, dekstran ve salin kombinasyonunun lipit peroksidasyonu ve beyin ödemi üzerine etkileri

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AMAÇ: Deneyisel kafa travması oluşturulan sıçanlarda gelişen beyin hasarı ve ödemeine karşı eritropoetin, dekstran ve salin kombinasyonunun koruyucu etkisini araştırmaktır.

GEREÇ VE YÖNTEM: Çalışmada ağırlıkları 250–340 g arasında değişen 40 adet Wistar Albino cinsi erkek sıçan kullanıldı. Her biri 10 adet sıçan içeren dört deney grubu oluşturuldu. Bütün sıçanlara kafa travması oluşturuldu ve ilaçlar intraperitoneal (ip) yolla travmadan 10 dk sonra verildi. Kontrol grubuna (K) diğer gruplarla eşit hacimde serum fizyolojik enjekte edildi. Birinci gruba eritropoetin (EPO) 5000 Ü/kg verildi. İkinci gruba dekstran ve salin (DS) 8 ml/kg verildi. Son gruba da aynı doz ve miktarlarda eritropoetin, dekstran ve salin (EPO+DS) beraberce verildi. Yirmi dört saat sonra sıçanlar sakrifiye edilerek beyin dokuları çıkarıldı. Sağ hemisferde yaş ve kuru ağırlık çalışıldı. Sol hemisferde glutatyon peroksidaz (GPx) aktivitesi ve malondialdehit (MDA) miktarı ölçüldü.

BULGULAR: Kontrol grubuna göre diğer gruplarda beyin ödeminin ve lipit peroksidasyonu son ürünü olan MDA'nın değişik oranlarda azaldığı, antioksidan enzim olan GPx aktivitesinin arttığı tespit edildi.

TARTIŞMA: Bu çalışmada, kafa travması oluşturulan sıçanlarda gelişen beyin ödemi ve oksidatif stresin oluşturduğu sekonder beyin hasarının eritropoetin, dekstran ve salin kombinasyonu kullanılarak azaltılabileceği sonucuna varıldı.

Anahtar sözcükler: Antioksidanlar; beyin ödemi; dekstran; eritropoetin; salin; oksidatif stres; kafa travması.

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